Hillsboro Airport Roundtable Exchange Lead Discussion Working Group
November 19, 2013: Hillsboro Airport Conference Room, 5:30 – 7:00 p.m.

Meeting Summary

MEMBERS PRESENT
Bob Flansberg, Aircraft Owners and Pilots Association (Oregon Chapter)
Henry Oberhelman, CPO 8/Chair of Lead Discussion Working Group
Mike Gallagher, Citizen At Large

MEMBERS ABSENT
Tom Black, CPO 9
Fred Hostetler, Chair of HARE
Jack Lettieri, Citizen At Large

PORT STAFF
Brooke Berglund, Community Affairs Outreach Manager
David Breen, Air Quality Manager
Sam Hartsfield, Environmental Specialist
Steve Nagy, General Aviation Manager

AUDIENCE
Miki Barnes
Jeff Lewis
Debrorah Lockwood
Jim Lubischer
Vernon Mock
Staff Representative from State Representative Joe Gallegos' Office
Staff Representative from State Representative Ben Unger's Office

SUMMARY
Introductions
Henry started the meeting at 5:30 p.m. Everyone introduced themselves and what their role was/why they were on the committee. The group then went on to provide updates on the assigned areas for further research.

Leaded Fuel Replacement Schedule (Assigned to the Port of Portland)
Sam provided information on what the replacement schedule is for leaded fuel. The program is being spearheaded by the FAA. The project is broken into two different phases. The first phase involved an RFP for fuel companies to be selected to look at developing alternative fuels. Those ten companies will then submit 100 gallons of fuel to be tested at the FAA's laboratory to determine which best meet the requirements for the drop-in fuel alternative. The FAA will then select the companies that will go on to the second phase.

The second phase of the program will select two candidate fuels from the initial pool of ten. These fuels will be tested in aircraft engines. . Based on the aircraft engine testing, the FAA will certify the replacement fuel for use by the aviation community at large. The FAA will also determine which aircraft cannot use the replacement fuel as a drop-in and determine what modifications to engines will need to be made in order for the fuel to be used in these aircraft. Finally, FAA will develop engine modification and subsequent engine certification procedures for these engines. During Phase II, FAA will also develop a fuel deployment plan. The timeline for the replacement fuel is to have a certified product available for use by 2018. After that 2018 date, FAA then has four years to implement the deployment plan for the transition of aircraft to the use of nonleaded fuel. How the program will be rolled out is unknown at this time, as the plan will depend on a variety of factors that have not been identified or vetted yet.

Bob said that there is an alternative form of fuel that is automotive fuel without ethanol in it called mogas. Some of the smaller aircraft can use this fuel without any modifications. The challenge is the availability of the fuel. The state of Oregon has a mandate that requires all vehicle fuel to have a certain percentage of ethanol in it. He said that he knows there are two gas stations off of TV Highway that do sell it.

Cost Impacts of Leaded Fuel Alternatives (Assigned to Mike Gallagher)
Mike suggested there be an informal meeting with Hillsboro Aviation to ask what their plan is for looking at replacing their aircraft as they age with aircraft that don't use leaded fuel. He also is curious to know if they have looked at converting some of their aircraft to use alternative fuels. There is a company in Texas that has identified a way to convert training aircraft to use diesel fuel instead of leaded fuel. Henry said he thinks it would be beneficial to see a matrix that outlines the different types of fuel available now and what the costs associated with using them are.

Henry asked if the Port has the infrastructure to add additional fueling facilities when the new fuel is available. Steve stated that the Port is not the fuel distributer at HIO. It is all the responsibility of our tenants. The FAA says either the airport sells the fuel in a monopoly situation or the tenants/FBOs are responsible for the fueling. At HIO, there are four fuel retailers. They all have individual tank systems that they manage that are their own. Mike suggested that possibly there be a discussion with the fueling suppliers at HIO to see if one of them would be willing to sell mogas as an alternative fuel. Steve suggested that if the subcommittee is interested in exploring this further, they look at using the resources on the HARE committee (AOPA, HABA, etc.) to survey pilots to see if they could use mogas now. Bob offered to go to AOPA to see how many aircraft currently could use mogas. Steve offered to have the Port explore how Independence Airport (the only airport in Oregon that has mogas available) gets their fuel and their distribution model. Steve said it is important to show the businesses on the airfield that sell fuel that there is a market for mogas.

Health Impacts on Individuals (Assigned to Henry Oberhelman)
Henry asked how to determine what blood lead levels would occur in people exposed to particular blood lead levels. He would like to be able to correlate the two pieces of information together: if the level of lead in the air is x amount near the airport, what does that translate into for a blood lead level. David said the EPA is currently updating national ambient air quality standard that looks at maximum levels for a certain level of acceptable risk. The information looks at a variety of sources including toxicological data. Bob said that nothing he has read shows where the level of lead is coming from. Steve suggested that it could be worth following up with the Oregon Health Authority and the Washington County Health Authority, who were on the CPO 9 discussion panel on lead, to see if they could assist Henry in accomplishing his goal. Mike said that none of the research that he has seen that shows there is a direct connection between living next to an airport and elevated blood levels. Brooke said that she would check to make sure the EPA Federal Register information on the reduced national ambient air quality standard maximum level from the last revision done by EPA is on the SharePoint site for the committee to review.

Lead Level Measurements and Modeling at HIO (Assigned to the Port of Portland)
Sam gave an overview of the modeling that has been done on lead emissions for the airport. Sam said one of the key things to keep in mind is that just because there is the amount of pollutants emitted does not directly translate to an ambient concentration of that pollutant in a given location. There are a variety of factors that affect the way that pollutants move around in the atmosphere, including where the pollutants are emitted, meteorology, and topography. When DEQ first did their Portland Air Toxics analysis for 2005, they used the emission inventory at the airport and considered all the pollutants to be emitted on the airport, at ground level, without taking into consideration that aircraft are moving both vertically and horizontally. In other words, they assumed all the lead emissions would be concentrated at the airport without being dispersed anywhere else. They then worked with the Port to figure out how to model emissions more accurately based on a more realistic placement of aircraft in the airshed, but still using their own dispersion model to predict the resulting ambient concentrations of lead. DEQ used a conservative approach to determine if there was a potential exceedance of the benchmark, using 2017 operational forecast numbers. The results of DEQ's refined modeling indicated that the maximum ambient lead concentrations would be well below the benchmark.

The Port also did an analysis using a consultant, CDM. CDM is an expert on air quality dispersion modeling to predict ambient pollutant concentrations from airport sources. When CDM did their study, they found that the maximum predicted lead concentration at the fence line was 37 times below the EPA standard of .15 micrograms per cubic meter. The modeling used by CDM is the FAA's required model for developing emissions inventories and conducting dispersion modeling.

The results of the DEQ refined modeling effort and CDM's modeling effort were very similar. Based on this information, DEQ decided not to address lead emissions as part of their action plan, as there were not any indicators that the emissions would exceed the EPA's national air ambient quality standard or DEQ's health protective benchmark.

Mike asked if you could deduce that because the modeling shows that the airport is within compliance with the standards for EPA, there is not a human health risk from leaded fuel. David said that while the airport is significantly lower than the ambient air quality standard, the EPA notes that the standard was developed with acceptable risk, not no risk. They do include their documentation that there is no identified safe level of blood lead concentration for humans. Mike asked if the group could take the modeling information from the airport to one of the health authorities to determine if kids that have

higher exposure levels in Hillsboro can be attributed to the leaded fuel at Hillsboro. Sam said that one would want to talk to a toxicologist to analyze the data. Mike said that the Port should pay for a study to analyze the two data sets of the health effects and the ambient air quality information to show whether or not the issue can be correlated.

Public Comment
Henry asked the audience if they had anything they would like to contribute to the discussion. Vernon Mock said to get rid of Hillsboro Aviation.

Miki Barnes said that the Oregon Health Authority did a great disservice at the meeting last week. She and Jim talked with the Oregon Health Authority last year and they said their data is not valid. The airport does need to do blood level testing of kids around the airport. There are studies that show living next to the airport does increase lead levels. Dr. Denny's comment at the forum was dismissive and she followed up with him afterward. She got an email from him in writing that there is no safe level of lead and they are committed to removing all lead level sources from the environment.

Jeff Lewis said that the Port needs to take ownership of the airport and pay for the blood level testing.

Jim Lubischer said that the report from the CDC says that there is no safe level of lead. The EPA study of the 17 airports shows that all the airports do have lead, which is bad. It is a terrible neurotoxin. To rely on benchmarks of .15, we can do better than that.

HARE Leaded Fuel Subcommittee

LEADED AVIATION GASOLINE (AvGas) REPLACEMENT

SCHEDULE PHASES I and II and SUPPORTING DOCUMENTS

October 28, 2013

Attachments:

1) **Leaded AvGas Replacement Schedule – Phase I and Phase II (Port of Portland)**
2) **Request for Proposals for AvGas Unleaded Fuel Replacement, June 10, 2013 (FAA)**
3) **Unleaded AVGAS Transition Aviation Rulemaking Committee FAA UAT ARC Final Report – Part I – Body: Unleaded AVGAS Findings & Recommendations, February 17, 2012 (FAA)**

Leaded AvGas Replacement Schedule – Phase I and Phase II

(Port of Portland)

Leaded Avgas Replacement Schedule

The Unleaded Avgas Transition (UAT) Plan is FAA's long term mitigation strategy to find a replacement for leaded fuels. FAA developed a roadmap for Avgas readiness levels that identifies milestones in the aviation gasoline development process. FAA established centralized testing of candidate unleaded fuels which would generate standardized qualification and certification data and a solicitation and selection process for candidate unleaded aviation gasoline for the centralized testing program. In Phase 1 of the testing program, up to 10 fuels will be selected for rig and property testing. In Phase 2, two fuels will be tested in engines and aircraft.

FAA established a collaborative industry-government initiative called the Piston Aviation Fuels Initiative (PAFI) to implement the UAT PAFI recommendations to facilitate the development and deployment of an unleaded avgas with the least impact on the existing piston engine aircraft fleet.

Phase I

Laboratory testing of candidate replacement fuels

Components

- FAA developed ASTM specifications for replacement fuel
- 10 suppliers to participate in developing candidate fuels
- Each will submit 100 gallons of fuel for Phase I testing at FAA's William J Hughes Technical Center laboratory

Dates:

June 10, 2013: FAA issued a request for candidate fuel producers to submit unleaded fuel formulations to be evaluated as replacements for 100L

July 1, 2014: Prospective fuel suppliers to submit data packages for candidate replacement unleaded fuel formulations to FAA for evaluation.

September 1, 2014: FAA will select up to 10 suppliers to participate in Phase 1 testing

Mid 2014: FAA will establish testing protocols and methods

2014: Laboratory testing of fuels

Early 2015: FAA will determine which fuels will go on to Phase II

2015: FAA will establish testing vehicles

Phase II

Engine and aircraft testing of candidate replacement fuels

Components

- Test 2 candidate replacement fuels, selected from initial pool of 10, in aircraft engines
- Determine aircraft that cannot use replacement fuel as a drop-in, and conduct engine modification and testing with new fuel
- FAA certification of replacement fuel
- Deployment of replacement fuel

Date

Mid 2015 – Late 2016: Conduct aircraft engine testing

2017: Review data and publish reports from Phase II

2018: Conduct engine modification testing

2018 – 2022: Implement deployment plan for replacement fuel

References

Unleaded AVGAS Transition Aviation Rulemaking Committee Final Report. February 17, 2012

Request for Proposals for AvGas Unleaded Fuel Replacement, June 10, 2013

(FAA)

49SOLICITATION, OFFER AND AWARD	1. THIS CONTRACT IS A RATED ORDER ☐ Yes ☒ No	RATING	PAGE 1	OF PAGES 42

2. CONTRACT NO.	3. SOLICITATION NO.	4. THIS IS A: Small Business Set-Aside ☐ YES ☒ NO	5. DATE ISSUED	6. REQUISITION/PURCHASE NO.
	DTFACT-13-R-00015		06/10/2013	N/A

7. ISSUED BY:	8. ADDRESS OFFER TO (*If other than Block 7*)
FAA William J. Hughes Technical Center Acquisition Services Sub-Team, AAQ-620/LM Atlantic City International Airport, NJ 08405	Same as block no. 7.

SOLICITATION

9. Offers in original and * copies for furnishing the supplies or services in the Schedule will be received at the place in the depository specified in Item 8, or if hand-carried located in FAA Wm. J. Hughes Technical Center, Contracts Branch, Tech Bldg., 4th floor,, Atlantic City Int'l Airport, NJ 08405 Until 4 p.m. (Hour) local time 7/1/2014 (Date)

*See Section L for detailed submission requirements

CAUTION - LATE Submissions, Modifications, and Withdrawals: See Section L.

10. FOR INFORMATION CALL:	A. NAME	B. TELEPHONE NO. (*Include area cod) (NO COLLECT CALLS*)
	LORI MCLAUGHLIN	(609) 485-5174

11. TABLE OF CONTENTS

(X)	SEC	DESCRIPTION	PAGE(S)	(X)	SEC	DESCRIPTION	PAGE(S)
		PART I - THE SCHEDULE				PART II - CONTRACT CLAUSES	
X	A	SOLICITATION/CONTRACT FORM	1	X	I	CONTRACT CLAUSES	13-17
X	B	SUPPLIES OR SERVICES AND PRICES/COSTS	2				
X	C	DESCRIPTION/SPECS/WORK STATEMENT	3-4	X	J	LIST OF ATTACHMENTS	18
X	D	PACKAGING AND MARKING	5				
X	E	INSPECTION AND ACCEPTANCE	6	X	K	REPRESENTATIONS, CERTIFICATIONS AND	
X	F	DELIVERIES OR PERFORMANCE	7			OTHER STATEMENTS OF OFFERORS	19-27
X	G	CONTRACT ADMINISTRATION DATA	8-9	X	L	INSTRS., CONDS., AND NOTICES TO OFFERORS	28-35
X	H	SPECIAL CONTRACT REQUIREMENTS	10-12	X	M	EVALUATION FACTORS FOR AWARD	36-42

OFFER *(must be fully completed by Offeror)*

12. In compliance with the above, the undersigned agree, if this offer is accepted within _____ calendar days (60 calendar days unless a different period is inserted by the Offeror) from the date for receipt of offers specified above, to furnish any or all items upon which prices are offered at the price set opposite each item, delivered at the designated point(s), within the time specified in the schedule.

13. DISCOUNT FOR PROMPT PAYMENT *(See Section I, Clause No. 3.3.1-6)*	10 CALENDAR DAYS %	20 CALENDAR DAYS %	30 CALENDAR DAYS %	_____CALENDAR DAYS %

14. ACKNOWLEDGMENT OF AMENDMENTS (The Offeror acknowledges receipt of amendments to the SOLICITATION for Offerors and related documents numbered and dated)	AMENDMENT NO.	DATE	AMENDMENT NO.	DATE

15A. NAME AND ADDRESS OF OFFEROR		16. NAME AND TITLE OF PERSON AUTHORIZED TO SIGN OFFER *(Type or print)*	
15B. TELEPHONE NO. *(Include area code)*	15C. ☐ CHECK IF REMITTANCE ADDRESS IS DIFFERENT FROM ABOVE - ENTER SUCH ADDRESS IN SCHEDULE	17. SIGNATURE	18. OFFER DATE

AWARD *(To be completed by Government)*

19. ACCEPTED AS TO ITEMS NUMBERED	20. AMOUNT	21. ACCOUNTING AND APPROPRIATION DATA	
22. RESERVED		23. SUBMIT INVOICES TO ADDRESS SHOWN IN *(4 copies unless otherwise specified)*	ITEM
24. ADMINISTERED BY *(if other than item 7)*		25. PAYMENT WILL BE MADE BY	
26. NAME OF CONTRACTING OFFICER *(Type or print)*		27. UNITED STATES OF AMERICA	28. AWARD DATE

PART I - SECTION B
SUPPLIES OR SERVICES AND PRICES/COSTS

This page is intentionally left blank

PART I - SECTION C
STATEMENT OF WORK

1. Background

Aviation gasoline (avgas) is a vital element of the piston engine aircraft safety system. Approximately 167,000 aircraft in the United States and 230,000 worldwide rely on 100 low lead (100LL) avgas for safe operation. 100LL is the only remaining transportation fuel in the United States that contains the additive tetraethyl lead (TEL). The avgas used today has its origins in the development of the high power aircraft engines necessary to enable reliable and economical military and commercial flight. TEL has been used as an avgas additive for decades to create the very high octane levels required to prevent detonation (engine knock) in high power aircraft engines. Operation with inadequate fuel octane can result in engine failure and aircraft accidents.

The US Environmental Protection Agency (EPA) regularly updates the national ambient air quality standards for lead and is currently measuring lead levels near airports which will help determine whether new standards are necessary for general aviation aircraft lead emissions. Petitions and litigation from environmental organizations have called for the EPA to consider regulatory actions to eliminate or reduce lead emissions from aircraft. Similar regulatory actions are under consideration globally. These activities raise concerns about the continued availability and use of leaded avgas. Worldwide uncertainty and concern exists amongst piston aircraft equipment manufacturers, avgas producers, avgas distributors, fixed base operators, aircraft owners and aircraft operators regarding:

(a) Future utility and value of existing aircraft
(b) Availability and cost of aviation gasoline to maintain viable business operations
(c) Justification of new aviation product development
(d) Justification of new aircraft purchases.

With the current number of piston aircraft in the US alone more than 200 times larger than annual new aircraft production, the turnover rate of the existing fleet is very low. This low turnover rate leaves existing piston engine aircraft owners particularly vulnerable to devaluation of their aircraft should an unleaded replacement avgas be incompatible with the existing fleet. This vulnerability, combined with the stagnation of new aircraft sales and an overall deteriorating economic condition within the aviation industry, has created a sense of urgency regarding the development and deployment of an unleaded avgas that meets the performance demands of the current fleet.

In response to the rapidly increasing concerns expressed by the General Aviation community, the Unleaded AVGAS Transition Aviation Rulemaking Committee (UAT ARC) was chartered on January 31, 2011, by the Federal Aviation Administration (FAA) Administrator to investigate, prioritize, and summarize the current issues relating to the transition to an unleaded avgas; and to recommend the tasks necessary to investigate and resolve these issues. The final report of the UAT ARC can be found on the FAA Avgas website at the following URL:

http://www.faa.gov/about/initiatives/avgas/

in the Archived Articles section.

2. Purpose

The ultimate purpose of this requirement is to solicit candidate unleaded avgas formulations for testing to identify the most viable replacements for the existing 100LL avgas with the least impact on the existing fleet of piston aircraft and fuel availability. The FAA will continue to support certification projects relating to aviation fuel that are being conducted independently of this OTA. This process is described in detail in the UAT ARC Final Report referenced above. This data will be used to support the evaluation of candidate unleaded avgas fuels by industry and regulatory agencies for the potential approval and deployment of these fuels. A final report including all data acquired or generated during the course of the research shall be prepared by the FAA for use in industry qualification and FAA certification activities.

Fuel sponsors, planning on responding to this Solicitation with a candidate unleaded avgas are highly encouraged to review the extensive literature from past testing at the FAA Technical Center on proposed additives. Candidates should utilize the research previously done at the FAA Technical Center to make the best use of the current state of fuel technology and to prevent duplicating past efforts. This research covered many different topics in the search for a drop-in unleaded replacement fuel, including use of specific fuel components, relationship of performance differences between leaded and unleaded fuels, effects of stoichiometry on fuel performance, specific testing procedures, potential fit-for-purpose and engine performance issues, antagonistic and synergistic fuel responses, and applicability of specific fuel tests. This research also addressed the detonation and engine performance in full-scale engines of many different fuel components, such as ethanol, autogas, aviation alkylate, super alkylate, motor alkylate, xylenes, amines, metallic additives, and ethers. Research publications can be found at the following links:

http://www.faa.gov/about/office_org/headquarters_offices/ang/offices/tc/library/

http://207.67.203.68/F10011Staff/OPAC/index.asp

www.crcao.com

www.astm.org

PART I - SECTION D
PACKAGING AND MARKING

This page intentionally left blank

PART I - SECTION E
INSPECTION AND ACCEPTANCE

`This page is intentionally blank

PART I - SECTION F
Deliveries or Performance

3.1-1 Clauses and Provisions Incorporated by reference (July 2011)

This screening information request (SIR) or OTA, as applicable, incorporates by reference the provisions or clauses listed below with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make the full text available, or offerors and contractors may obtain the full text via Internet at: http://conwrite.faa.gov.

(End of clause)

3.10.1-9 **Stop-Work Order** (October 1996)
3.10.1-11 **Government Delay of Work** (April 1996)

F.2 WJHTC 3.2.2.8-1 – Period of Performance (June 2002)

The period of performance for this requirement shall not exceed five years from date of issuance of OTA.

PART I - SECTION G
CONTRACT/OTA ADMINISTRATION DATA

3.1-1 Clauses and Provisions Incorporated by reference (July 2011)

This screening information request (SIR) or "OTA", as applicable, incorporates by reference the provisions or clauses listed below with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make the full text available, or offerors and contractors may obtain the full text via Internet at: http://conwrite.faa.gov.

(End of clause)

3.10.1-22 Contracting Officer's Representative (April 2012)

G.1 WJHTC 3.6.2-1 - Observance of Legal Holidays and Excused Absence (June 2002)
Clause provided for informational purposes, only.

a. Government personnel observe the following listed days as holidays:

New Year's Day
Martin Luther King's Birthday
President's Birthday
Memorial Day
Independence Day
Labor Day
Columbus Day
Veteran's Day
Thanksgiving Day
Christmas

b. In addition to the days designated as holidays, the Government observes the following days:

Any other day designated by Federal Statute
Any other day designated by Executive Order
Any other day designated by the President's Proclamation
Any other day designed by the Center Director

c. It is understood and agreed between the Government and the Contractor that observance of such days by Government personnel shall not otherwise be a reason for an additional period of performance. In the event the Contractor's personnel work during the holiday, no form of holiday or other premium compensation will be reimbursed, other than their normal compensation for the time worked.

d. When the Federal, State, Local and other governmental entities grant excused absence to its employees, assigned Contractor personnel may also be dismissed; however, they will not be directly reimbursed for the excused absence.

e. Information about Center delayed openings or closings may be obtained by calling (609) 485-6100.

G.4 Responsibility for OTA Administration

The Contracting Officer (CO) identified below, has the overall responsibility of this OTA. The CO is authorized to take actions on behalf of the Government to amend, modify, or deviate from the OTA terms, conditions, and requirements. The CO may delegate certain other responsibilities to his/her authorized representatives or Contracting Officer's Representative (COR). The CO for this OTA is:

FAA William J. Hughes Technical Center
Acquisition Service Group, AAQ-620
Attn: Lori McLaughlin
Atlantic City International Airport, NJ 08405

A COR will be appointed for the OTA. Changes to the COR may only be made by the CO and will be transmitted via electronic mail direction or modification (changes directed by electronic mail will be confirmed in the next subsequent modification as applicable).

The COR has the authority to monitor the technical progress of the services that are to be delivered under the OTA. This includes visits to the place of performance, meetings and telephone conversations with contractor personnel, acceptance, or rejection of the contracted items and other duties that may be authorized by the CO.

The COR cannot authorize or order the cessation of OTA work, nor delete, change, or waive any of the technical requirements or other terms and conditions of the OTA.

Whenever a difference of opinion between the contractor and the COR occurs, the contractor shall notify the CO immediately for resolution.

G.6 Interpretation or Modification

No oral statement of any person, and no written statement of anyone other than the Contracting Officer, or his/her authorized representative, shall modify or otherwise affect the terms or meaning of the schedule or statement of work. All requests for interpretation or modifications shall be made in writing to the Contracting Officer.

PART I - SECTION H
SPECIAL OTA REQUIREMENTS

H.1 Personnel Security Program

Consistent with Appendix 9 and 10 of FAA Order 1600.1D and the Security Requirements clause, the contractor shall implement a personnel security program for contractor employees, subcontractors, or consultants who have access to FAA facilities, and/or classified or sensitive information, or resources. See clauses 3.14-2, 3.14-3 and 3.14-4 in Section I.

H.2 Relationship Between Government, Contractor and Contractor Personnel

a. The Government and the contractor understands and agrees that the services to be delivered under this OTA by the contractor to the Government are non-personal services and the parties recognize and agree that no employer-employee or master-servant relationship exist or will exist under the contract between the Government and the contractor and/or between the Government and the contractor's personnel. The contractor personnel shall be responsible, not to the Government, but solely to the contractor, who in turn, shall be accountable to the Government.

b. The Government will not exercise any direct or continuing supervision or control over the contractor personnel performing services under this OTA. Contractor personnel shall not be placed under the supervision, direction, or evaluation of a Federal officer, manager, or employee in connection with performance under this OTA. Likewise, contractor personnel shall not be placed in a position of supervision, administration, or evaluation over WJHTC civilian personnel, or personnel of other prime contractors, or become an integrated part of the Government organization in connection with performance under this contractor, nor shall contractor personnel be used in administration or supervision of FAA procurement activities.

c. The contractor shall be responsible for selecting personnel who are well qualified to perform the required services, for supervising techniques used in their work and for keeping them informed of all improvements, changes, and methods of operation.

d. Rules, regulations, directives and requirements which are issued during the OTA during the OTA term by William J. Hughes Technical Center authorities, under their responsibility for law and order, administration, and security on the installation shall be applicable to all contractor personnel or representatives who enter the installation, or who travel on Government transportation. This requirement shall not be construed or interpreted to establish any degree of Government control that is inconsistent with the intent of a non-personal services contract/OTA. Contractor personnel or representatives shall be subject to such checks as may be deemed necessary to assure that their presence on the Center or airport property does not violate these requirements. No employees will be permitted on this property when such a check reveals that the employee presence would be detrimental to the security of the Center or airport. When directed by the Contracting Officer, the contractor shall remove any employee from an assignment to perform services under this OTA for reasons of misconduct or breach of security in connection with his or her employment. Under such circumstances, replacement cost will be a contractor expense and will not be reimbursable by the Government. In other instances, the contractor shall take appropriate personnel action as required in the event of employee misconduct in connection with his or her employment.

e. The services to be performed under this OTA shall not require the contractor or his/her employees to exercise personal judgment and discretion on behalf of the Government, but rather, the contractor's employees shall act and exercise personal judgment and discretion on behalf of the contractor.

f. Contractor and contractor personnel shall not be considered employees of the Federal Government and shall not be eligible, by virtue of performance under this OTA, for payment by the Government of entitlement and benefits accorded to Federal employees.

H.3 Organizational Conflicts of Interest

(a) The Contractor warrants that, to the best of the Contractor's knowledge and belief, there are no relevant facts or circumstances that could give rise to an organizational conflict of interest (OCI) or that the Contractor has disclosed all such relevant information.

(b) The Contractor agrees that if an actual or potential OCI is discovered after award, the Contractor shall make a full disclosure in writing to the Contracting Officer. This disclosure shall include a description of actions that the Contractor has taken or proposes to take, after consultation with the Contracting Officer, to avoid, mitigate, or neutralize the actual or potential conflict.

(c) The Contracting Officer may terminate this OTA for convenience, in whole or in part, if it deems such termination necessary to avoid an OCI. If the Contractor was aware of a potential OCI prior to award or discovered an actual or potential conflict after award and did not disclose or misrepresented relevant information to the Contacting Officer, the Government may terminate the OTA for default, debar the Contractor from Government contracting, or pursue such other remedies as may be permitted by law or this OTA.

(d) The Contractor shall include this clause in all subcontracts and in lower tier subcontracts unless a waiver is requested from, and granted by, the Contracting Officer.

(e) In the event that a contract or OTA is issued to the Contractor requiring activity that would create a potential conflict of interest, the Contractor shall:

(1) Notify the Contracting Officer of a potential conflict, and;

(2) Recommend to the Government an alternate tasking approach which would avoid the potential conflict, or

(3) Present for approval a conflict of interest mitigation plan that will:

a. Describe in detail the requirement that creates the potential conflict of interest; and

b. Outline in detail the actions to be taken by the Contractor or the Government in the performance of the task to mitigate the conflict, division of subcontractor effort, and limited access to information, or other acceptable means.

(4) The Contractor shall not commence work on a requirement related to a potential conflict of interest until specifically notified by the Contracting Officer to proceed.

(5) If the Contracting Officer determines that it is in the best interest of the Government to issue a requirement, notwithstanding a conflict of interest, a request for waiver shall be submitted in accordance with AMS 3.1.7.

H.4 Contractor Responsibilities

(a) The Contractor shall provide all management, administrative, clerical, and supervisory functions required for the effective and efficient performance of this OTA.

(b) The Contractor shall save and hold harmless and indemnify the Government against any and all liability, claims, and costs of whatever kind and nature for injury to or death of any person or persons and for loss or damage to any property occurring in connection with, or in any way incident to, or arising out of, the occupancy, use, service, operations, or performance of work under the terms of this OTA, to the extent resulting from the negligent acts or omissions of the Contractor.

(c) The Government shall not be liable for any injury to the Contractor's personnel or damage to the Contractor's property unless such injury or damage is due to negligence on the part of the Government and is recoverable under the Federal Torts Claims Act, or pursuant to another Federal statutory authority.

(d) A smooth and orderly transition between the Contractor and a predecessor or successor Contractor is necessary to ensure minimum disruption to vital Government business. The Contractor shall cooperate fully in the transition.

(e) The Contractor shall adhere to the same professional and ethical standards of conduct required of Government personnel. The Contractor shall not:

(1) Discuss with unauthorized persons any information obtained in the performance of work under this OTA;

(2) Conduct business not directly related to this OTA on Government premises;

(3) Use computer systems and/or other Government facilities for company or personal business other than work related to the OTA requirement; or

(4) Recruit on Government premises or otherwise act to disrupt official Government business.

H.5 Contractor Staff Training

The contractor shall provide fully trained and experienced technical personnel required for the performance of all terms and conditions outlined in the SOW and/or OTA. This includes training necessary for keeping personnel abreast of industry advances and for maintaining proficiency on aircraft instrumentation, equipment, computers, applications that are available on the commercial market. The Contractor, at its own expense, shall provide all training of personnel required for successful performance of OTA.

PART II - SECTION I
OTA CLAUSES

I.1 3.1-1 Clauses and Provisions Incorporated by reference (July 2011)

This screening information request (SIR) or OTA, as applicable, incorporates by reference the provisions or clauses listed below with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make the full text available, or offerors and contractors may obtain the full text via Internet at: http://conwrite.faa.gov.

(End of clause)

3.1.7-5	Disclosure of Conflicts of Interest (March 2009)
3.1.8-1	Cancellation, Rescission, and Recovery of Funds for Illegal or Improper Activity (October 2009)
3.1.8-2	Price or Fee Adjustment for Illegal or Improper Activity (April 2010)
3.2.2.3-67	Special Precautions for Working at Operating Airports (July 2004)
3.2.2.7-6	Protecting the Government's Interest when Subcontracting with Contractors Debarred, Suspended, or Proposed for Debarment (April 2011)
3.2.5-1	Officials Not to Benefit (April 1996)
3.2.5-3	Gratuities or Gifts (January 1999)
3.2.5-4	Contingent Fees (October 1996)
3.2.5-5	Anti-Kickback Procedures (October 2010)
3.2.5-7	Disclosure Regarding Payments to Influence Certain Federal Transactions (Oct 2010)
3.2.5-8	Whistleblower Protection for Contractor Employees (April 1996)
3.3.1-6	Discounts for Prompt Payment (May 1997)
3.3.1-8	Extras (May 1997
3.4.1-10	Insurance--Work on a Government Installation (July 1996)
3.4.1-13	Errors and Omissions (July 1996)
3.4.2-6	Taxes--Contracts Performed in U.S. Possessions or Puerto Rico (October 1996)
3.4.2-8	Federal, State, and Local Taxes--Fixed Price Contract (April 1996)
3.6.2-2	Convict Labor (April 1996)
3.6.2-9	Equal Opportunity (August 1998)
3.6.2-12	Equal Opportunity for Veterans (January 2011)
3.6.2-13	Affirmative Action for Workers with Disabilities (October 2010)
3.6.2-14	Employment Reports on Veterans (January 2011)
3.6.2-35	Prevention of Sexual Harassment (August 1998)
3.6.3-16	Drug Free Workplace (March 2009)
3.6.4-10	Restrictions on Certain Foreign Purchases (January 2010)
3.8.2-10	Protection of Government buildings, Equipment, and Vegetation (April 1996)
3.8.2-11	Continuity of Services (October 1998)
3.10.1-7	Bankruptcy (April 1996)
3.10.1-12	Changes - Fixed-Price (April 1996)
3.10.1-25	Novation and Change-Of-Name Agreements (October 2007)
3.10.2-1	Subcontracts (Fixed Price Contracts) (April 1996)
3.10.6-1	Termination for Convenience of the Government (Fixed Price) (October 1996)
3.10.6-4	Default (Fixed-Price Supply and Service) (October 1996)
3.11-21	Contractor Liability for Personal Injury and/or Property Damage (April 1999)
3.13-5	Seat Belt Use by Contractor Employees (October 2001)
3.13-11	Plain Language (July 2006)
3.14-3	Foreign Nationals as Contractor Employees (April 2008)

3.1.7-6 Disclosure of Certain Employee Relationships (July 2009)

(a) The policy of the FAA is to avoid doing business with contractors, subcontractors, and consultants who have a conflict of interest or an appearance of a conflict of interest. The purpose of this policy is to maintain the highest level of integrity within its workforce and to ensure that the award of procurement awards is based upon fairness and merit.

(b) The contractor must provide to the Contracting Officer the following information with its proposal and must provide an information update within 30 days of the award of a contract or OTA, any subcontract, or any consultant agreement, or within 30 days of the retention of a Subject Individual or former FAA employee subject to this clause:

(1) The names of all Subject Individuals who:

(i) participated in preparation of proposals for award; or
(ii) are planned to be used during performance; or
(iii) are used during performance; and

(2) The names of all former FAA employees, retained by the contractor who were employed by FAA during the two year period immediately prior to the date of:

(i) the award; or
(ii) their retention by the contractor; and

(3) The date on which the initial expression of interest in a future financial arrangement was discussed with the contractor by any former FAA employee whose name is required to be provided by the contractor pursuant to subparagraph (2); and

(4) The location where any Subject Individual or former FAA employee whose name is required to be provided by the contractor pursuant to subparagraphs (1) and (2), are expected to be assigned.

(c) "Subject Individual" means a current FAA employee's father, mother, son, daughter, brother, sister, uncle, aunt, first cousin, nephew, niece, husband, wife, father-in-law, mother-in-law, son-in-law, daughter-in-law, brother-in-law, sister-in-law, stepfather, stepmother, stepson, stepdaughter, stepbrother, stepsister, half brother, half sister, spouse of an in-law, or a member of his/her household.

(d) The contractor must incorporate this clause into all subcontracts or consultant agreements awarded under this OTA and must further require that each such subcontractor or consultant incorporate this clause into all subcontracts or consultant agreements at any tier awarded under this OTA unless the Contracting Officer determines otherwise.

(e) The information as it is submitted, must be certified as being true and correct. If there is no such information, the certification must so state.

(f) Remedies for nondisclosure: The following are possible remedies available to the FAA should a contractor misrepresent or refuse to disclose or misrepresent any information required by this clause:

(1) Termination of the OTA.
(2) Exclusion from subsequent FAA contracts/OTAs.

(3) Other remedial action as may be permitted or provided by law or regulation or policy or by the terms of the OTA.

(g) Annual Certification. The contractor must provide annually, based on the anniversary date of award, the following certification in writing to the Contracting Officer:

ANNUAL CERTIFICATION OF DISCLOSURE OF CERTAIN EMPLOYEE RELATIONSHIPS

The contractor represents and certifies that to the best of its knowledge and belief that during the prior 12 month period:

[ ] A former FAA employee(s) or Subject Individual(s) has been retained to work under the OTA or subcontract or consultant agreement and complete disclosure has been made in accordance with subparagraph (b) of AMS Clause 3.1.7-6.

[ ] No former FAA employee(s) or Subject Individual(s) has been retained to work under the OTA or subcontract or consultant agreement, and disclosure required by AMS Clause 3.1.7-6 is not applicable.

_____
Authorized Representative

_____
Company Name

_____
Date

(End of clause)

3.3.1-33 System for Award Management (August 2012)

(a) Definitions. As used in this clause

"Data Universal Numbering System (DUNS) number" means the 9-digit number assigned by Dun and Bradstreet, Inc. (D&B) to identify unique business entities.

"Data Universal Numbering System +4 (DUNS+4) number" means the DUNS number assigned by D&B plus a 4-character suffix that may be assigned by a business concern. (D&B has no affiliation with this 4-character suffix.) This 4-character suffix may be assigned at the discretion of the business concern to establish additional SAM records for identifying alternative Electronic Funds Transfer (EFT) accounts for the same parent concern.

"Registered in the SAM database" means that the Contractor has entered all mandatory information, including the DUNS number or the DUNS+4 number, into the SAM database.

"System for Award Management (SAM) Database" means the primary Government repository for Contractor information required for the conduct of business with the Government.

(b)(1) By submission of an offer, the offeror acknowledges the requirement that a prospective awardee

shall be registered in the SAM database prior to award, during performance, and through final payment of any contract, OTA, basic agreement, basic ordering agreement, or blanket purchasing agreement resulting from this solicitation.

(2) The offeror shall enter, in Representations, Certifications and Other Statements of Offerors Section of the solicitation, the DUNS or DUNS +4 number that identifies the offeror's name and address exactly as stated in the offer. The DUNS number will be used by the Contracting Officer to verify that the offeror is registered in the SAM database.

(c) If the offeror does not have a DUNS number, it should contact Dun and Bradstreet directly to obtain one.

(1) An offeror may obtain a DUNS number
(i) If located within the United States, by calling Dun and Bradstreet at 1-866-705-5711 or via the Internet at http://fedgov.dnb.com/webform; or
(ii) If located outside the United States, by contacting the local Dun and Bradstreet office.

(2) The offeror should be prepared to provide the following information:
(i) Company legal business.
(ii) Tradestyle, doing business, or other name by which your entity is commonly recognized.
(iii) Company Physical Street Address, City, State, and ZIP Code.
(iv) Company Mailing Address, City, State and ZIP Code (if different from physical street address).
(v) Company Telephone Number.
(vi) Date the company was started.
(vii) Number of employees at your location.
(viii) Chief executive officer/key manager.
(ix) Line of business (industry).
(x) Company Headquarters name and address (reporting relationship within your entity).

(d) If the offeror does not become registered in the SAM database in the time prescribed by the Contracting Officer, the Contracting Officer may proceed to award to the next otherwise successful registered offeror.

(e) Processing time, which normally takes 48 hours, should be taken into consideration when registering. Offerors who are not registered should consider applying for registration immediately upon receipt of this solicitation.

(f) The Contractor is responsible for the accuracy and completeness of the data within the SAM database, and for any liability resulting from the Government's reliance on inaccurate or incomplete data. To remain registered in the SAM database after the initial registration, the Contractor is required to review and update on an annual basis from the date of initial registration or subsequent updates its information in the SAM database to ensure it is current, accurate and complete. Updating information in the SAM does not alter the terms and conditions of this OTA and is not a substitute for a properly executed contractual document.

(g)(1)(i) If a Contractor has legally changed its existing business name, "doing business as" name, or division name (whichever is shown on the OTA), or has transferred the assets used in performing the contract, but has not completed the necessary requirements regarding novation and change-of-name agreements in AMS Procurement Guidance, the Contractor shall provide the responsible Contracting Officer a minimum of one business day's written notification of its intention to:

(A) change the name in the SAM database;
(B) comply with the requirements of AMS regarding novation and change-of-name agreements; and
(C) agree in writing to the timeline and procedures specified by the responsible Contracting Officer. The Contractor must provide the Contracting Officer with the notification, sufficient documentation to support the legally changed name.

(ii) If the Contractor fails to comply with the requirements of paragraph (g)(1)(i) of this clause, or fails to perform the agreement at paragraph (g)(1)(i)(C) of this clause, and, in the absence of a properly executed novation or change-of-name agreement, the SAM information that shows the Contractor to be other than the Contractor indicated in the OTA will be considered to be incorrect information within the meaning of the "Suspension of Payment" paragraph of the electronic funds transfer (EFT) clause of this OTA.

(2) The Contractor shall not change the name or address for EFT payments or manual payments, as appropriate, in the SAM record to reflect an assignee for the purpose of assignment of claims. Assignees shall be separately registered in the SAM database. Information provided to the Contractor's SAM record that indicates payments, including those made by EFT, to an ultimate recipient other than that Contractor will be considered to be incorrect information within the meaning of the "Suspension of payment" paragraph of the EFT clause of this OTA.

(h) Offerors and Contractors may obtain information on registration and annual confirmation requirements via the internet at https://www.sam.gov/portal/public/SAM/ or by calling 1-888-227-2423, or 269-961-5757.

(End of Clause)

PART III - SECTION J
LIST OF DOCUMENTS, EXHIBITS, AND OTHER ATTACHMENTS

ATTACHMENT	TITLE	PAGES
I	Appendix I (Alternative Data in lieu of ASTM International Test Specification and Research Report)	1
II	Business Declaration Form	1

PART IV - SECTION K
REPRESENTATIONS, CERTIFICATIONS, AND OTHER STATEMENTS OF OFFERORS

K.1 3.1-1 3.1-1 Clauses and Provisions Incorporated by reference (July 2011)

This screening information request (SIR) or OTA, as applicable, incorporates by reference the provisions or clauses listed below with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make the full text available, or offerors and contractors may obtain the full text via Internet at: http://conwrite.faa.gov.

(End of clause)

K.1 NORTH AMERICAN INDUSTRY CLASSIFICATION SYSTEM (NAICS)

The services required are determined to be within North American Industry Classification System (NAICS) code 324110 Jet Fuels manufacturing. The size standard for this code is less than 1500 employees.

Note: The competition designation for this OTA is **full and open**. The NAICS code is used strictly to determine business size for statistical purposes.

K.2 3.2.2.3-70 Taxpayer Identification (July 2004)

(a) Definitions.

(1) "Common parent," as used in this clause, means a corporate entity that owns or controls an affiliated group of corporations that files an offeror's (you, your) Federal income tax returns on a consolidated basis, and of which you are a member.

(2) "Corporate status," as used in this clause, means a designation as to whether you are a corporate entity, an unincorporated entity (for example, sole proprietorship or partnership), or a corporation providing medical and health care services.

(3) "Taxpayer Identification Number (TIN)," as used in this clause, means the number the Internal Revenue Service (IRS) requires you use in reporting income tax and other returns.

(b) All offerors must submit the information required in paragraphs (c) through (e) of this provision to comply with reporting requirements of 26 U.S.C. 6041, 6041A, and 6050M and implementing regulations issued by IRS. The FAA will use this information to collect and report on any delinquent amounts arising out of your relation with the Federal Government, under Public Law 104 -134, the Debt Collection Improvement Act of 1996, Section 31001(I)(3). If the resulting contract or OTA is subject to the reporting requirements and you refuse or fail to provide the information, the Contracting Officer (CO) may reduce your payments 31 percent under the contract or OTA.

(c) Taxpayer Identification Number (TIN).

[ ] TIN: _____
[ ] TIN has been applied for.
[ ] TIN is not required because:

[ ] Offeror is a nonresident alien, foreign corporation, or foreign partnership that does not leave income effectively connected with the conduct of a trade or business in the U.S. and does not have an office or place of business or a fiscal paying agent in the U.S.;
[ ] Offeror is an agency or instrumentality of a foreign government;
[ ] Offeror is an agency or instrumentality of a Federal, state, or local government;
[ ] Other--State basis. _____.

(d) Corporate Status.

[ ] Corporation providing medical and health care services, or engaged in the billing and collecting of payments for such services;
[ ] Other corporate entity
[ ] Not a corporate entity
[ ] Sole proprietorship
[ ] Partnership
[ ] Hospital or extended care facility described in 26 CFR 501(c)(3) that is exempt from taxation under 26 CFR 501(a).

(e) Common Parent.

[ ] A common parent does not own or control the offeror as defined in paragraph (a).
[ ] Name and TIN of common parent:

Name _____TIN _____

(End of provision)

K.3 3.2.2.3-2 Minimum Offer Acceptance Period (July 2004)

(a) 'Acceptance period,' as used in this provision, means the number of calendar days the FAA (we, us) has to award an OTA from the date the SIR specifies for receiving Phase 2 submissions.

(b) This provision supersedes any language about the acceptance period appearing elsewhere in this SIR.

(c) We require a minimum acceptance period of ninety (90) **calendar days** from the end date of Phase 2 submissions.

(d) The offeror (you) may specify a longer acceptance period than the period shown in paragraph (c). To specify a longer period, fill in the blank: The offeror allows the following acceptance period: _____ calendar days.

(e) We may reject an offer allowing less than the FAA's minimum acceptance period.

(f) You agree to fulfill your offer completely if the FAA accepts your offer in writing within:

(1) The acceptance period stated in paragraph (c) of this provision; or
(2) Any longer acceptance period stated in paragraph (d) of this provision.

(End of provision)

K.4 3.2.2.3-10 Type of Business Organization (July 2004)

By checking the applicable box, the offeror (you) represents that--

(a) You operate as [ ] a corporation incorporated under the laws of the State of _____ , [ ] an individual, [ ] a partnership, [ ] a nonprofit organization, [ ] a joint venture or [ ] other _____[specify what type of organization].

(b) If you are a foreign entity, you operate as [ ] an individual, [ ] a partnership, [ ] a nonprofit organization, [ ] a joint venture, or [ ] a corporation, registered for business in_____ .
(country)

K.5 3.2.2.3-15 Authorized Negotiators (July 2004)

The offeror states that the following persons are authorized to negotiate on your behalf with the FAA in connection with this offer:

Name:_____

Title:_____

Phone number:_____

(End of provision)

K.6 3.2.2.7-7 Certification Regarding Responsibility Matters (January 2010)

(a)(1) The Offeror certifies, to the best of its knowledge and belief, that
(i) The Offeror and/or any of its Principals-
A) Are [ ] are not [ ] presently debarred, suspended, proposed for debarment, or declared ineligible for the award of contracts or OTAs by any Federal agency;
(B) Have [ ] have not [ ] within a three-year period preceding this offer, been convicted of or had a civil judgment rendered against them for: commission of fraud or a criminal offense in connection with obtaining, attempting to obtain, or performing a public
(Federal, state, or local) contract /OTA or subcontract; violation of Federal or state antitrust statutes relating to the submission of offers; or commission of embezzlement, theft, forgery, bribery, falsification or destruction of records, making false statements, tax evasion, violating Federal criminal tax laws or receiving stolen property; and
(C) Are [ ] are not [ ] presently indicted for, or otherwise criminally or civilly charged by a governmental entity with, commission of any of the offenses enumerated in subdivision a)(1)
(i)(B) of this provision.
(D) Have [ ], have not [ ], within a three-year period preceding this offer, been notified of any delinquent Federal taxes in an amount that exceeds $3,000 for which the liability remains unsatisfied.
(1) Federal taxes are considered delinquent if both of the following criteria apply:
(i) The tax liability is finally determined. The liability is finally determined if it has been assessed. A liability is not finally determined if there is a pending administrative or judicial challenge. In the case of a

judicial challenge to the liability, the liability is not finally determined until all judicial appeal rights have been exhausted.
(ii) The taxpayer is delinquent in making payment. A taxpayer is delinquent if the taxpayer has failed to pay the tax liability when full payment was due and required. A taxpayer is not delinquent in cases where enforced collection action is precluded.
(2) Examples-
(i) The taxpayer has received a statutory notice of deficiency, under I.R.C. Sec. 6212, which entitles the taxpayer to seek Tax Court review of a proposed tax deficiency. This is not a delinquent tax because it is not a final tax liability. Should the taxpayer seek Tax Court review, this will not be a final tax liability until the taxpayer has exercised all judicial appeal rights.
(ii) The IRS has filed a notice of Federal tax lien with respect to an assessed tax liability, and the taxpayer has been issued a notice under I.R.C. Sec. 6320 entitling the taxpayer to request a hearing with the IRS Office of Appeals contesting the lien filing, and to further appeal to the Tax Court if the IRS determines to sustain the lien filing. In the course of the hearing, the taxpayer is entitled to contest the underlying tax liability because the taxpayer has had no prior opportunity to contest the liability. This is not a delinquent tax because it is not a final tax liability. Should the taxpayer seek tax court review, this will not be a final tax liability until the taxpayer has exercised all judicial appeal rights.
(iii) The taxpayer has entered into an installment agreement pursuant to I.R.C. Sec. 6159. The taxpayer is making timely payments and is in full compliance with the agreement terms. The taxpayer is not delinquent because the taxpayer is not currently
required to make full payment.
(iv) The taxpayer has filed for bankruptcy protection. The taxpayer is not delinquent because enforced collection action is stayed under 11 U.S.C. 362 (the Bankruptcy Code).
(b) The Offeror has [ ] has not [ ] within a three-year period preceding this offer, had one or more contracts or OTAs terminated for default by any Federal agency.
(2) 'Principals,' for the purposes of this certification, means officers; directors; owners; partners; and, persons having primary management or supervisory responsibilities within a business entity (e.g., general manager; plant manager; head of a subsidiary, division, or business segment, and similar positions). THIS CERTIFICATION CONCERNS A MATTER WITHIN THE JURISDICTION OF AN AGENCY OF THE UNITED STATES AND THE MAKING OF A FALSE, FICTITIOUS, OR FRAUDULENT CERTIFICATION MAY RENDER THE MAKER SUBJECT TO PROSECUTION UNDER SECTION 1001, TITLE 18, UNITED STATES CODE.
(c) The Offeror shall provide immediate written notice to the Contracting Officer if, at any time prior to OTA award, the Offeror learns that its certification was erroneous when submitted or has become erroneous by reason of changed circumstances.
(d) A certification that any of the items in paragraph (a) of this provision exists will not necessarily result in withholding of an award under this SIR. However, the certification will be considered in connection with a determination of the Offeror's responsibility. Failure of the Offeror to furnish a certification or provide such
additional information as requested by the Contracting Officer may render the Offeror nonresponsible.
(e) Nothing contained in the foregoing shall be construed to require establishment of a system of records in order to render, in good faith, the certification required by paragraph (a) of this provision. The knowledge and information of an Offeror is not
required to exceed that which is normally possessed by a prudent person in the ordinary course of business dealings.
(f) The certification in paragraph (a) of this provision is a material representation of fact upon which reliance was placed when making award. If it is later determined that the Offeror knowingly rendered an erroneous certification, in addition to other remedies available to the Government, the Contracting Officer may terminate the OTA resulting from this SIR for default.

(End of provision)

K.7 3.2.5-13 Contractor Code of Business Ethics and Conduct (April 2010)

(a) Definition.
"Agent" means any individual, including a director, an officer, an employee, or an independent Contractor, authorized to act on behalf of the organization.
"Full cooperation"
(1) Means disclosure to the Government of the information sufficient for law enforcement to identify the nature and extent of the offense and the individuals responsible for the conduct. It includes providing timely and complete response to Government auditors' and investigators' request for documents and access to employees with information;
(2) Does not foreclose any Contractor rights arising in law, the AMS, or the terms of the OTA. It does not require:
(i) A Contractor to waive its attorney-client privilege or the protections afforded by the attorney work product doctrine; or
(ii) Any officer, director, owner, or employee of the Contractor, including a sole proprietor, to waive his or her attorney client privilege or Fifth Amendment rights; and (3) Does not restrict a Contractor from
(i) Conducting an internal investigation; or
(ii) Defending a proceeding or dispute arising under the OTA or related to a potential or disclosed violation.
"Outlying areas," as used in this clause means: (1) Commonwealths. (i) Puerto Rico. (ii) The Northern Mariana Islands; (2) Territories. (i) American Samoa. (ii) Guam. (iii) U.S. Virgin Islands; and (3) Minor outlying islands. (i) Baker Island. (ii) Howland Island. (iii) Jarvis Island. (iv) Johnston Atoll. (v) Kingman Reef. (vi) Midway Islands. (vii) Navassa Island. (viii) Palmyra Atoll. (ix) Wake Atoll.
"Principal" means an officer, director, owner, partner, or a person having primary management or supervisory responsibilities within a business entity (e.g., general manager; plant manager; head of a subsidiary, division, or business segment; and similar positions).
"Subcontract" means any contract entered into by a subcontractor to furnish supplies or services for performance of a prime contract/OTA or a subcontract.
"Subcontractor" means any supplier, distributor, vendor, or firm that furnished supplies or services to or for a prime contractor or another subcontractor. "United States," as used in this clause, means the 50 States, the District of Columbia, and outlying areas.
(b) Code of business ethics and conduct.
(1) Within 30 days after OTA award, unless the Contracting Officer establishes a longer time period, the Contractor must:
(i) Have a written code of business ethics and conduct; and
(ii) Provide a copy of the code to each employee engaged in performance of the contract.
(2) The Contractor must-
(i) Exercise due diligence to prevent and detect criminal conduct; and
(ii) Otherwise promote an organizational culture that encourages ethical conduct and a commitment to compliance with the law.
(3)(i) The Contractor must timely disclose, in writing, to the agency Office of the Inspector General (OIG), with a copy to the Contracting Officer, whenever, in connection with the award, performance, or closeout of this contract or any subcontract thereunder, the Contractor has credible evidence that a principal, employee, agent, or subcontractor of the Contractor has committed:

(A) A violation of Federal criminal law involving fraud, conflict of interest, bribery, or gratuity violations found in Title 18 of the United States Code; or
(B) A violation of the civil False Claims Act (31 U.S.C. 3729-3733).
(ii) The Government, to the extent permitted by law and regulation, will safeguard and treat information obtained pursuant to the Contractor's disclosure as confidential where the information has been marked 'confidential' or 'proprietary' by the company. To the extent permitted by law and regulation, such information will not be released by the Government to the public pursuant to a Freedom of Information Act request, 5 U.S.C. Section 552, without prior notification to the Contractor. The Government may transfer documents provided by the Contractor to any department or agency within the Executive Branch if the information relates to matters within the organization's jurisdiction.
(iii) If the violation relates to an order against a Government wide acquisition contract, a multi-agency contract, a multiple-award schedule contract such as the Federal Supply Schedule, or any other procurement instrument intended for use by multiple agencies, the Contractor must notify the OIG of the ordering agency and the IG of the agency responsible for the basic contract. (c) Business ethics awareness and compliance program and internal control system. This paragraph (c) does not apply if the Contractor has represented itself as a small business concern pursuant to the award of this OTA. All other Contractors must establish within 90 days after award, unless the Contracting Officer establishes a longer time period:
(1) An ongoing business ethics and business conduct awareness program.
(i) This program must include reasonable steps to communicate periodically and in a practical manner the Contractor's standards and procedures and other aspects of the Contractor's business ethics awareness and compliance program and internal control system, by conducting effective training programs and otherwise disseminating information appropriate to an individual's respective roles and responsibilities.
(ii) The training conducted under this program must be provided to the Contractor's principals and employees, and as appropriate, the Contractor's agents and subcontractors. (2) An internal control system.
(i) The Contractor's internal control system must:
(A) Establish standards and procedures to facilitate timely discovery of improper conduct in connection with FAA contracts or OTAs; and
(B) Ensure corrective measures are promptly instituted and carried out.
(ii) At a minimum, the Contractor's internal control system should provide for:
(A) Assignment of responsibility at a sufficiently high level and adequate resources to ensure effectiveness of the business ethics awareness and compliance program and internal control system.
(B) Reasonable efforts not to include an individual as a principal, whom due diligence would have exposed as having engaged in conduct that is in conflict with the Contractor's code of business ethics and conduct.
(C) Periodic reviews of company business practices, procedures, policies, and internal controls for compliance with the Contractor's code of business ethics and conduct and any special requirements of FAA contracting, including;
(1) Monitoring and auditing to detect criminal conduct;
(2) Periodic evaluation of the effectiveness of the business ethics awareness and compliance program and internal control system, especially if criminal conduct has been detected; and
(3) Periodic assessment of the risk of criminal conduct, with appropriate steps to design, implement, or modify the business ethics awareness and compliance program and the internal control system as necessary to reduce the risk of criminal conduct identified through this process. (D) An internal reporting mechanism, such as a telephone hotline, by which employees may report suspected instances of improper

conduct, and instructions that encourage employees to make such reports; and
(E) Disciplinary action for improper conduct or for failing to take reasonable steps to prevent or detect improper conduct.
(F) Timely disclosure, in writing, to the agency OIG, with a copy to the Contracting Officer, whenever, in connection with the award, performance, or closeout of any Government contract or OTA performed by the Contractor or a subcontract thereunder, the Contractor has credible evidence that a principal, employee, agent, or subcontractor of the Contractor has committed a violation of Federal criminal law involving fraud, conflict of interest, bribery, or gratuity violations found in Title 18 U.S.C. or a violation of the civil False Claims Act (31 U.S.C. 3729-3733).
(1) If a violation relates to more than one Government contract or OTA, the Contractor may make the disclosure to the agency OIG and Contracting Officer responsible for the largest dollar value contract/OTA impacted by the violation.
(2) If the violation relates to an order against a Government wide acquisition contract, a multi-agency contract, a multiple-award schedule contract such as the Federal Supply Schedule, or any other procurement instrument intended for use by multiple agencies, the contractor must notify the OIG of the ordering agency and the IG of the agency responsible for the basic contract, and the respective agencies' contracting officers.
(3) The disclosure requirement for an individual contract or OTA continues until at least 3 years after final payment on the contract/OTA.
(4) The Government will safeguard such disclosures in accordance with paragraph (b)(3)(ii) of this clause.
(G) Full cooperation with any Government agencies responsible for audits, investigations, or corrective actions. (d) Subcontracts.
(1) The Contractor must include the substance of this clause, including this paragraph (d), in subcontracts to large business concerns that have a value equal to or in excess of $5,000,000, and a performance period of more than 120 days.
(2) In altering this clause to identify the appropriate parties, all disclosures of violation of the civil False Claims Act or of Federal criminal law must be directed to the agency Office of the Inspector General, with a copy to the Contracting Officer.

(End of Clause)

K.8 3.3.1-35 Certification of Registration in System for Award Management (August 2012)

In accordance with Clause 3.3.1-33, System for Award Management (SAM), offeror certifies that they are registered in the SAM Database and have entered all mandatory information including the DUNS or DUNS+4 Number.

Name: _____

Title: _____

Phone Number: _____

(End of provision)

K.9 3.6.2-6 Previous Contracts and Compliance Reports (May 1997)

The offeror represents that--(a) It [ ] has, [ ] has not, participated in a previous contract or subcontract subject either to the "Equal Opportunity" clause of this solicitation, the clause originally contained in Section 310 of Executive Order No. 10925, or the clause contained in Section 201 of Executive Order No. 11114; (b) It [ ] has, [ ] has not, filed all required compliance reports; and (c) Representations indicating submission of required compliance reports, signed by proposed subcontractors, will be obtained before subcontract awards.
(End of Provision)

K.10 3.6.2-8 Affirmative Action Compliance (April 1996)

The offeror represents that (a) it [ ] has developed and has on file, [ ] has not developed and does not have on file, at each establishment, affirmative action programs required by the rules and regulations of the Secretary of Labor (41 CFR 60-1 and 60-2), or (b) it [ ] has not previously had contracts or OTAs subject to the written affirmative action programs requirement of the rules and regulations of the Secretary of Labor.

(End of provision)

K.11 3.13-4 Contractor Identification Number - Data Universal Numbering System (DUNS) Number (August 2012)

(a) Definitions. As used in this clause

"Contractor Identification Number," as used in this provision, means "Data Universal Numbering System (DUNS) number, which is a nine-digit number assigned by Dun and Bradstreet Information Services, to identify unique business entities (taken from SAM clause)

"Data Universal Numbering System +4 (DUNS+4) number" means the DUNS number assigned by D&B plus a 4-character suffix that may be assigned by a business concern. (D&B has no affiliation with this 4-character suffix.) This 4-character suffix may be assigned at the discretion of the business concern to establish additional SAM records for identifying alternative Electronic Funds Transfer.

(b) Contractor identification is essential for receiving payment and complying with statutory contract/OTA reporting requirements. Therefore, the offeror shall provide its DUNS or DUNS+4 number below. The DUNS number will be used by the Contracting Officer to verify that the offeror is registered in the SAM database.

DUNS OR DUNS+4 NUMBER: _____

(c) If the offeror does not have a DUNS number, it should contact Dun and Bradstreet directly to obtain one.

(1) An offeror may obtain a DUNS number
(i) If located within the United States, by calling Dun and Bradstreet at 1-866-705-5711 or via the Internet at http://www.dnb.com/; or
(ii) If located outside the United States, by contacting the local Dun and Bradstreet office.

(2) The offeror should be prepared to provide the following information:
(i) Company legal business.
(ii) Tradestyle, doing business, or other name by which your entity is commonly recognized.
(iii) Company Physical Street Address, City, State, and ZIP Code.
(iv) Company Mailing Address, City, State and ZIP Code (if different from physical street address).
(v) Company Telephone Number.
(vi) Date the company was started.
(vii) Number of employees at your location.
(viii) Chief executive officer/key manager.
(ix) Line of business (industry).
(x) Company Headquarters name and address (reporting relationship within your entity).

(End of provision)

PART IV - SECTION L
INSTRUCTIONS, CONDITIONS, AND NOTICES TO OFFERORS

L.1 3.1-1 Clauses and Provisions Incorporated by reference (July 2011)

This screening information request (SIR) or OTA, as applicable, incorporates by reference the provisions or clauses listed below with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make the full text available, or offerors and contractors may obtain the full text via Internet at: http://conwrite.faa.gov.

(End of clause)

3.2.2.3-1 False Statements in Offers (July 2004)
3.2.2.3-3 Affiliated Offerors (July 2004)
3.2.2.3-6 Submittals in the English Language (July 2004)
3.2.2.3-7 Submittals in U.S. Currency (July 2004)
3.2.2.3-11 Unnecessarily Elaborate Submittals (July 2004)
3.2.2.3-12 Amendments to Screening Information Requests (July 2004)
3.2.2.3-13 Submission of Information/Documentation/Offers (July 2004)
3.2.2.3-14 Late Submissions, Modifications, and Withdrawals of Submittals (July 2004)
3.2.2.3-16 Restricting, Disclosing and Using Data (July 2004)
3.2.2.3-17 Preparing Offers (July 2004)
3.2.2.3-18 Prospective Offeror's Requests for Explanations (March 2009)
3.2.2.3-72 Announcing Competing Offerors (July 2004)
3.11-6 Financial Statement (April 1999)

L.2 Type of Award

The FAA contemplates award of an OTA resulting from this Solicitation.

(End of provision)

L.3 Approval of Award

This OTA is subject to the written approval of an FAA Contracting Officer and shall not be binding until so approved. It is possible the Government may issue two OTA vehicles from this SIR.

(End of clause)

L.4 General Proposal Instructions

a. Offerors are expected to examine the entire SIR. Failure to do so will be at the offeror's own risk.

b. Replies to this SIR must follow the outline and/or instructions concerning format given below.

c. This SIR contains terms and conditions which are proposed to be included in any resultant OTA. Sections K, L, and M of this solicitation will not be issued as part of the formal OTA document, but will be retained in the OTA file and considered to be incorporated as part of the OTA.

d. Offerors assume the full responsibility of ensuring that proposals are received at the place and by the date and time specified below:

(1) Address: The Offerors shall submit all required documents as stated in Section C of this SIR in accordance with the instructions therein.

Offerors are advised of the heightened security at the FAA William J. Hughes Technical Center. Outside visitors will not have access to the facility to hand-deliver proposals unless they are in possession of a valid DOT/FAA photo ID. Therefore, proposals should be mailed to the attention of the FAA Contracting Officer identified in the solicitation. Additionally, offerors are reminded of the requirements contained in AMS Clauses 3.2.2.3-13 – "Submission of Information/Documentation/Offers" and 3.2.2.3-14 "Late Submissions, Modifications, and Withdrawals of Submittals."

(2) Date and Time: Pre Screening data submittals shall be submitted not later than 4 pm, local time on 7/1/2014. All Pre-screening data must be included in one report.

The FAA may select some of the fuels associated with the pre-screening data for Phase 1 fuel testing in accordance with Section M no later than September 1, 2014.

Updates to the Preliminary Assessment specified in Part IV, Section L.5.d.1 of this Soliciation may be submitted upon completion of the Phase 1 testing. If the offeror intends to submit an update, it must be submitted by December 31, 2015

The FAA may select some of the Phase 2 fuels for Phase 2 testing in accordance with Section M, no earlier than March 31, 2015.

The FAA reserves the right to request 10,000 gallons of unleaded avgas fuel from selected Phase 1 fuel data submittals for the purpose of developing Phase 2 test data for that fuel until January 30, 2016.

For those Phase 1 fuels selected for Phase 2 evaluation, an ASTM International avgas test specification and the accompanying research report must be submitted not later six months after notification of Phase 2 selection.

(3) Signed Originals: One copy of each submittal shall contain the signed original of all documents requiring signature by the Offeror. Use of reproductions of signed originals is authorized in all other copies of the proposal. Also, see AMS Clause 3.13-4 - Contractor Identification Number—Data Universal Numbering System (DUNS) Number, subparagraph (b).

Any proposal that does not explicitly comply with proposal instructions and SIR requirements may be considered non responsive and may not be further considered for award.

L.5 Technical Evaluation Process:

The Technical Evaluation will be conducted in two steps. The offeror will be required to submit pre-screening data for evaluation in accordance with the Step 1evaluation criteria in Section M.

Upon completion of Phase 1 testing by the FAA, the resulting data from that testing, the ASTM International avgas test specification and associated research report, and the update to the preliminary feasibility assessment (if provided), will be evaluated in accordance with the Step 2 evaluation criteria described in Section M.

Pre Screening Data Submissions:

Offerors will submit three hardcopies of the pre-screening fuel data and a CD containing the pre-screening fuel data in Microsoft Word format. The pre-screening fuel data shall meet the requirements described below. Mail the copies of the pre-screening fuel data to:

Lori McLaughlin
AAQ-620
Contracts Branch, Bldg 300, 4th floor
William J. Hughes Technical Center
Federal Aviation Administration
Atlantic City, NJ 08405

In addition (not as a substitute for the paper copy), an electronic version of the pre-screening fuel data will be e-mailed lori.mclaughlin@faa.gov.

There is no specific format for the pre-screening data. It may be preceded by a cover letter, but the cover letter will not reviewed for technical data to be considered. If there is any information in your submittal that you would like the FAA to consider "protected/proprietary", please include a specific request with your submission. At a minimum it shall contain the following items:

a. Offeror's name, phone, and mailing and email addresses.

b. A Material Safety Data Sheet (MSDS) for the proposed unleaded avgas fuel.

c. An issued ASTM International Test Specification defining the properties for the proposed unleaded avgas fuel and an issued ASTM International Research Report with the compositional and test data utilized to support approval of the specification. In lieu of an ASTM International Test Specification and Research Report, the offeror may submit alternative data in accordance with Appendix 1. NOTE - an issued ASTM Test Specification will be required for consideration into the Phase 2 testing program. For planning purposes, offerors should plan on obtaining their ASTM Test Specification within 3 years after the issuance date of this OTA.

d. A preliminary feasibility assessment of the proposed unleaded avgas that includes the following elements:

    1. Preliminary Production and Distribution Assessment: Define the production and distribution infrastructure to be used to support deployment of this fuel. Identify gaps in current avgas production and distribution system and develop preliminary plan to address gaps and to scale-up production and distribution.

2. Environmental & Toxicology Assessment: Review candidate fuel composition with consideration to use and handling from an environmental perspective relative to current aviation gasoline, including OSHA, EPA and other regulatory entities. Report with compositional data, MSDS, environment and toxicology assessment, and other relevant environmental data.
3. Preliminary Business Plan: Provide a description of your conceptual business plan to support commercialization of the proposed fuel as a potential replacement for 100LL that addresses the following:
    a. Scope of Solution: Describe the fuel, engine/aircraft hardware and operational concept proposed, as necessary for entire general aviation fleet fuel applicability
    b. Applicability: Define expectations for what engines/aircraft in the fleet will need modifications, and extent/nature of modifications, to operate on fuel (either by models, HP classes, compression ratio, etc). (see FAA UAT ARC final report at http://www.faa.gov/about/initiatives/avgas/)
    c. Cost: Describe production and distribution costs of proposed fuel solution including recurring costs of fuel and non-recurring costs associated with modification of aircraft and/or air strip infrastructure.
    d. Implementation: Describe business model concept to support production and deployment of the unleaded avgas. Include existing or planned strategic partnerships, financing strategies, infrastructure leveraging opportunities, distribution strategies and other relevant details facilitating path to market.
    e. Deployment Concept: Describe whether the proposed fuel is miscible and fungible with 100LL. Does the solution require a separate distribution and control system?
    f. Intellectual Property: Declare IP associated with the candidate fuel and include an explanation of how fuel producibility, distribution and cost will be affected by IP protections.

Pre-screening fuel data will be accepted from the time of issuance of this Solicitation until July 1, 2014. Someone who is interested in submitting a fuel for consideration but who may not be ready to provide pre-screening data until near the end of the pre-screening phase should submit a letter of intent to the address listed below as early as possible. **The FAA reserves the right to request a Phase I fuel submission from any pre-screening candidate at any time after submittal of the pre-screening data.**

Pre-Screening Data Requirements

The pre-screening data submitted by the offeror must address the following two factors, at a minimum:

Factor 1: Fuel Properties and Performance

Fuel Compositional Range.

The offeror must describe the bounds of the chemical compositions that are possible within the criteria of the fuel specification. The offeror must discuss the interactions of the various possible fuel constituents, and describe how worst case formulations were selected for testing.

The offeror should provide substantiation that test methods selected for the evaluation of the candidate fuel provide an acceptable level of precision and repeatability.

Fuel Performance

The data provided by the offeror must describe the fuel performance characteristics relative to combustion, fluidity, volatility, stability, corrosion, and other characteristics as specified in ASTM International standard practice D7826, "Standard Guidance for the Evaluation of New Aviation Gasolines and New Aviation Additives.", section 6.2.2 and 6.2.4. Offerors must describe in detail how they meet the requirements of same.

Aircraft Engine Performance.

The offeror must describe the performance of the fuel on an aircraft spark ignition piston engine relative to detonation, operability, and engine performance, based on actual engine testing.

Materials Compatibility

The offeror must provide the details describing the compatibility of the candidate fuel with metallic and non-metallic materials typically found in aircraft fuel systems as specified in ASTM International standard practice D7826, "Standard Guidance for the Evaluation of New Aviation Gasolines and New Aviation Additives.", section 6.2.5. Offerors must describe in detail how they meet the requirements of same.

Factor 2: Fuel Deployment Feasibility

The offeror must provide a preliminary feasibility assessment that includes information and data relating to the compatibility of the candidate fuel with the existing infrastructure and environment.

The offeror must address the following areas, at a minimum:

Impact on Existing Aircraft Fleet:

The offeror must describe the impact of deployment of the candidate fuel on the existing fleet of aircraft.

Environmental Impact of the Candidate Fuel:

The offeror must provide data provided describing the impact of deployment of the candidate fuel on the environment.

Fuel Definition and Control:

Offeror must describe the level of fuel definition and control provided by the fuel specification.

Producibility and Cost of Candidate Fuel:

The offeror must provide data describing the producibility and the estimated production and distribution cost of the candidate fuel. The offeror must provide justification for values submitted and a description of the scale of production on which the values are based.

Impact on Existing Avgas Distribution Infrastructure:

The offeror must provide data describing the impact of deployment of the candidate fuel on the existing avgas distribution infrastructure.

Fuel Delivery Requirements for Phase 1 Testing Upon Completion of Pre-Screening Data Review

If requested by the FAA, offerors shall deliver 100 gallons of unleaded avgas fuel for Phase 1 testing in specified batches formulated to span the compositional range of the fuel specification and meeting the fuel property and performance requirements specified in the offeror's pre-screening fuel data. This fuel shall be delivered in accordance with arrangements made with the FAA William J. Hughes Technical Center. Fuel submissions for Phase 1 testing must be made not more than sixty (60) working days after the date of the request.

Phase 1 Test Data Requirements for Admittance into Phase 2 Testing

The offeror must provide an ASTM International avgas test specification and the associated research report.

The offer may provide an update to the preliminary feasibility assessment.

The FAA will provide the data produced from the Phase 1 testing.

The data must address the following two factors:

Factor 1: Fuel Properties and Performance

Fuel Performance:

The fuel performance , weathering and long-term storage stability characteristics, compatibility with 100LL fuel, compatibility with additives and lubricating oils, and health, safety and environmental characteristics as specified in ASTM International standard practice D7826, "Standard Guidance for the Evaluation of New Aviation Gasolines and New Aviation Additives.", section 6.3.2. Offeror must demonstrate compliance with same.

Aircraft Engine Performance:

The performance of the fuel on an aircraft spark ignition piston engine relative to detonation, operability, and engine performance, based on actual engine testing.

Rig/Component Testing:

The results of testing the fuel on rigs and components as specified in ASTM International standard practice D7826, "Standard Guidance for the Evaluation of New Aviation Gasolines and New Aviation Additives.", section 6.3.4.

Materials Compatibility:

The compatibility of the candidate fuel with metallic and non-metallic materials typically found in aircraft fuel systems as specified in ASTM International standard practice D7826, "Standard Guidance for the Evaluation of New Aviation Gasolines and New Aviation Additives.", section 6.3.3.

Factor 2: Fuel Deployment Feasibility

The offeror may update the preliminary feasibility assessment based on the data produced during the Phase 1 testing to describe the compatibility of the candidate fuel with the existing infrastructure and environment.

Impact on Existing Aircraft Fleet

The number of aircraft requiring modifications and the extent of those modifications.

Environmental Impact of the Candidate Fuel

The impact of deployment of the candidate fuel on the environment.

Fuel Definition and Control:

The level of fuel definition and control provided by the ASTM International fuel test specification.

Producebility and Cost of Candidate Fuel:

The produciility and the estimated production and distribution cost of the candidate fuel.

Impact on Existing Avgas Distribution Infrastructure:

The impact of deployment of the candidate fuel on the existing avgas distribution infrastructure.

Fuel Delivery Requirements for Phase 2 Testing Upon Completion of Phase I Testing

If requested by the FAA, offers shall deliver 10,000 gallons of unleaded avgas fuel for Phase 2 testing in specified batches formulated to span the compositional range of the fuel specification and meeting the fuel property and performance requirements specified in the offeror's pre-screening fuel data. The fuel shall be delivered in accordance with arrangements made with the FAA William J. Hughes Technical Center. Fuel submissions for Phase 2 testing must be made not more than six months after the date of the request.

Any proposal that does not explicitly comply with Section L instructions and SIR requirements may be considered non responsive and may not be further considered.

In accordance with AMS Clause 3.1.7-5, Disclosure of Conflicts of Interest, you shall fully discuss the potential impact of such conflicts of interests and your ability to perform all required services under this proposed OTA. Offerors shall provide a plan for mitigating the identified conflicts. Offerors with identified organizational conflicts of interest that would preclude their ability to fully perform under this SOW in an unbiased manner may be eliminated from the competition. If an existing or potential organizational conflict of interest (either prime or subcontractor) is not applicable, then the offeror shall certify as such in accordance with AMS 3.1.7-5, and include this certification with their Phase I submittal.

Scoring Criteria and Grading Scheme are set forth in Section M. Any technical data submission that are larger than 10 MB must be submitted via separate emails or "zipped" to avoid email clogging.

In light of evolving technology and testing capabilities, the FAA reserves the right to update/amend evaluation criteria post announcement.

L.8 Submission of Questions

Questions and comments that arise from this solicitation may be submitted, in writing only, via e-mail to: lori.mclaughlin@faa.gov and will be allowed through 4 pm, local time on July 1, 2014. They will be answered in an Amendment to the SIR if deemed necessary for all interested parties to become aware of. Otherwise, an e-mail response would be initiated to the party submitting inquiry. If an amendment is issued, it will be published at http://faaco.faa.gov/ under current announcements for the William J. Hughes Technical Center. Therefore, it is the offerors responsibility to visit this website frequently for updates on this procurement.

PART IV - SECTION M
EVALUATION FACTORS FOR AWARD

M.1 Basis for Award

The Government intends to evaluate submittals using the two factors for Phase I and the two factors listed for Phase II, as stated in Section L.

The burden of providing thorough and complete information rests with the offeror. Only information supplied in full text in the proposal will be evaluated. Offerors are cautioned that failure to provide all the required information may result in elimination of the offeror from further consideration for award.

The Government reserves the right to award an OTA immediately following review of all proposals, and may or may not require communications or negotiations with the successful offeror.

Therefore, it is critical that each offer be fully responsive to this SIR and its provisions. Additionally, the Government reserves the right to conduct communications and negotiations with any competing offeror, or all competing offerors as the situation warrants.

No contractual obligation or liability on the part of the Government shall exist unless and until the OTA is awarded. Therefore, no offeror should begin work on the services and other requirements called for by this SIR until after formal notice of OTA award.

M.2 Responsibility

Prior to award, a prospective offeror must be determined responsible. To be considered responsible, an offeror must have adequate financial resources to perform the effort, or be able to obtain them, be able to comply with the delivery schedule, have a satisfactory performance record, have a satisfactory record of integrity and business ethics, have necessary skills, equipment and facilities or ability to obtain them, and be otherwise qualified and eligible to receive an award under applicable laws and regulations. The Government reserves the right to conduct a pre-award survey on a proposed contractor or any proposed subcontractors.

No contractual obligation or liability on the part of the Government shall exist unless and until the OTA is awarded. Therefore, the offeror will not begin work on the services and other requirements called for by this SIR until after formal notice by the Government that an OTA or other official document has been issued.

M.3 Technical Evaluation Process

If a conflict of interest mitigation plan is received, the CO will review and coordinate this document with legal counsel and customer organization, if necessary. The evaluation team members will independently examine each proposal in detail. The members will measure each proposal against the requirements set forth in the SIR.

The Technical Evaluation will be conducted in two steps:

Step 1

Pre-Screening Data will be evaluated for admission of the offeror's unleaded avgas into the Phase 1 testing program relative to the impact on the existing fleet of aircraft in the following areas:

1. Fuel Performance Characteristics:

    a. Fuel properties across the entire compositional range.

    b. Fuel performance characteristics relative to combustion, fluidity, volatility, stability, corrosion, and other characteristics.

    c. Detonation, performance and engine operability when operating an aircraft engine with the fuel.

    d. Compatibility with metallic and non-metallic materials typically found in aircraft fuel systems.

2. Fuel Deployment Feasibility

    a. Impact of fuel deployment on existing fleet of aircraft relative to number of aircraft requiring modifications, and the extent of those modifications

    b. Impact of fuel deployment on existing avgas distribution infrastructure relative to compatibility with existing equipment and procedures.

    c. Estimated production and distribution cost of fuel, with justification for values submitted. Can be provided at various levels of production (i.e Phase 1 quantity, Phase 2 quantity, full-scale production, etc)_

    d. Environmental impact of fuel

    e. Compatibility with the fuel definition and control requirements of the aviation fuel production, distribution and operation infrastructure

After review of the pre-screening fuel data in accordance with Step 1 above, the FAA will respond to offerors in one of three ways:

1) Requesting that the offeror provide 100 gallons of unleaded avgas fuel in specified batches formulated to span the compositional range of the fuel specification in the offeror's pre-screening fuel data for Phase I testing and request that the offeror enter into an OTA that defines the Phase I test program and the composition and volumes of the batches that comprise the 100 gallon requirement.

2) Recommending that the offeror submit a revised pre-screening fuel data package with certain changes made or conditions met.

3) Notifying the offeror that the pre-screening fuel data does not support admittance into the Phase 1 testing program.

Step 2

Test data from Phase 1, the ASTM International test specification and associated research report, and the updated preliminary feasibility assessment (if provided), will be evaluated for admission of the offeror's unleaded avgas fuel into the Phase 2 testing program relative to the impact on the existing fleet of aircraft in the following areas:

1. Fuel Performance Characteristics:
    a. Fuel performance characteristics relative to carburetor icing, fuel gauging and capacitance, conductivity and static dissipation, surface tension, thermal conductivity, dielectric constant, gum formation, microbial contamination, and other characteristics.
    b. Weathering and long-term storage stability
    c. Compatibility with 100LL fuel, additives and lubricating oils.
    d. Health, safety and environmental characteristics
    e. Detonation, performance and engine operability when operating an aircraft engine with the fuel.
    f. Compatibility with metallic and non-metallic materials typically found in aircraft fuel systems.
    g. Compatibility with fuel filtration systems and other distribution system components and materials.
2. Fuel Deployment Feasibility
    a. Impact of fuel deployment on existing fleet of aircraft relative to number of aircraft requiring modifications, and the extent of those modifications
    b. Impact of fuel deployment on existing avgas distribution infrastructure relative to compatibility with existing equipment, quality and handling procedures.
    c. Estimated production and distribution cost of fuel
    d. Environmental impact of fuel
3. ASTM International aviation fuel specification availability

After review of the Phase 1 test data, the ASTM avgas test specification and associated research report, and the updated preliminary feasibility assessment (if provided), in accordance with Step 2 above, the FAA will provide the Phase 1 test data and respond to offerors in one of two ways:

a. Requesting (1) that the offeror provide 10,000 gallons of unleaded avgas fuel in specified batches formulated to span the compositional range of the fuel specification in the offeror's pre-screening fuel data for Phase 2 testing and (2) that the offeror enter into an OTA that defines the Phase 2 test program and the composition and volumes of the batches that comprise the 10,000 gallon requirement.
b. Notifying the offeror that the Phase 1 test data does not support admittance into the Phase 2 testing program.

After receipt and testing of 10,000 gallons of unleaded avgas fuel, the FAA will provide Phase 2 test data to the offerors.

Step 1 and Step 2 evaluation criteria are described below.

Step 1 Evaluation Criteria Description

The Step 1 technical evaluation criteria is based on the following two factors. These factors are of equal importance and will be graded in accordance with the grading scheme described in paragraph entitled "Grading Scheme" in paragraph M.4 below.

Factor 1: Fuel Properties and Performance

Fuel Compositional Range:

Fuel Composition Range will be evaluated relative to the definition and control of the candidate fuel.

Fuel Performance:

Offeror's submission will be evaluated for fit for purpose for use on aircraft spark ignition piston engines.

Aircraft Engine Performance.:

Offer's submission will be evaluated for fit for purpose for use on those engines.

Materials Compatibility:

Offeror's submission will be evaluated for fit for purpose for use on aircraft spark ignition piston engines.

Factor 2: Fuel Deployment Feasibility

Impact on Existing Aircraft Fleet:

The offeror's submission will be evaluated relative to number of aircraft requiring modifications, and the extent of those modifications.

Environmental Impact of the Candidate Fuel:

Offeror's submission will be evaluated relative to current aviation gasoline and associated regulatory requirements.

Fuel Definition and Control:

Offeror's submission will be evaluated relative to the current industry requirements of the aviation fuel production, distribution and operation infrastructure.

Produceability and Cost of Candidate Fuel:

Offeror's submission will be evaluated relative to the current economics of the General Aviation industry.

Impact on Existing Avgas Distribution Infrastructure:

Offeror's submission will be evaluated relative to compatibility with existing equipment and procedures.

Step 2 Evaluation Criteria Description

The Step 2 technical evaluation criteria is based on the following two factors. These factors are of equal importance and will be graded in accordance with the grading scheme described in paragraph entitled "Grading Scheme" in this paragraph M.4 below.

Factor 1: Fuel Properties and Performance

Fuel Performance:

Offeror's data from Phase 1 testing will be evaluated for fit and purpose for use on aircraft spark ignition piston engines.

Aircraft Engine Performance:

Offer's data from Phase 1 testing will be evaluated for fit for purpose for use on those engines.

Rig/Component Testing:

Offeror's data from Phase 1 testing will be evaluated for fit for purpose for use on aircraft spark ignition piston engines.

Materials Compatibility

Offeror's data from Phase 1 testing will be evaluated for fit for purpose for use on aircraft spark ignition piston engines.

Factor 2: Fuel Deployment Feasibility

The offeror may update the preliminary feasibility assessment based on the data produced during the Phase 1 testing to describe the compatibility of the candidate fuel with the existing infrastructure and environment.

Impact on Existing Aircraft Fleet:

Offeror's data from Phase 1 testing will sbe evaluated relative to number of aircraft requiring modifications, and the extent of those modifications

Environmental Impact of the Candidate Fuel:

Offeror's data from Phase 1 testing will be evaluated relative to current aviation gasoline and associated regulatory requirements.

Fuel Definition and Control:

Offeror's data from Phase 1 testing will be evaluated relative to the current industry requirements of the aviation fuel production, distribution and operation infrastructure.

Producebility and Cost of Candidate Fuel:

Offeror's data fromPhase 1 testing will be evaluated relative to the current economics of the General Aviation industry.

Impact on Existing Avgas Distribution Infrastructure:

Offeror's data from Phase 1 testing will be evaluated relative to compatibility with existing equipment and procedures.

Any proposal that does not explicitly comply with Section L instructions and SIR requirements may be considered non responsive and may not be further considered.

> In accordance with AMS Clause 3.1.7-5, Disclosure of Conflicts of Interest, you shall fully discuss the potential impact of such conflicts of interests and your ability to perform all required services under this proposed OTA. Offerors shall provide a plan for mitigating the identified conflicts. Offerors with identified organizational conflicts of interest that would preclude their ability to fully perform under this SOW in an unbiased manner may be eliminated from the competition. If an existing or potential organizational conflict of interest (either prime or subcontractor) is not applicable, then the offeror shall certify as such in accordance with AMS 3.1.7-5, and include this certification with their Phase I submittal.

The chairperson must prepare an Offeror Technical Evaluation Report and Offeror Narrative Reports to be submitted to the CO.

The Technical Evaluation will be conducted in two steps. The offeror will be required to submit pre-screening data for evaluation in accordance with Section L. Once Pre-Screening has been accomplished, or anytime during the Pre-Screening process, the FAA may elect to request 100 gallons of unleaded avgas

in specified batches, in accordance with Phase I information in the SOW. The FAA may select some of the Phase I fuels for Phase 2 evaluation at any time during Phase I.

M.4 Scoring Definitions and Grading Scheme:

For the purpose of this evaluation plan the following definitions apply.

Strength: Any aspect of the submittal when judged against a stated evaluation criteria, which enhances the merit of the proposal or increases the probability of successful performance of the OTA. A significant strength appreciably enhances the merit of a proposal or appreciably increases the probability of successful OTA performance.

Weakness: A weakness is "a flaw that increases the risk of unsuccessful performance."

Deficiency: A deficiency is "a material failure of a proposal to meet a government requirement or a combination of significant weaknesses in a proposal that increases the risk of unsuccessful OTA performance to an unacceptable level."

Grading Scheme:

The descriptions and grading scheme listed below will be used to grade the responses to the factors outlined above.

Excellent: A proposal that meets or exceeds all of the Governments requirements, contains extensive detail, demonstrates a thorough understanding of the requirements, is highly feasible (low risk) and offers numerous significant strengths which are not offset by weaknesses.

Good: A proposal that meets or exceeds all of the Governments requirements, contains at least adequate detail, demonstrates at least an understanding of the requirements, is at least feasible (low to moderate risk) and offers some significant strengths or numerous strengths which are not offset by weaknesses.

Satisfactory: A proposal that at least meets all of the Governments requirements, contains at least minimal detail, demonstrates at least a minimal understanding of the requirements, is at least feasible (moderate to high risk. No deficiencies exist and any combination of weaknesses is not a risk to successful OTA performance.

Unacceptable: A response that does not meet the requirements of the SIR as measured by the stated evaluation criteria and is not acceptable because of some significant weakness. This weakness is a risk to successful performance. Deficiencies exist.

Any proposal that does not explicitly comply with Section L instructions and SIR requirements may be considered non responsive and may not be further considered.

> In accordance with AMS Clause 3.1.7-5, Disclosure of Conflicts of Interest, you shall fully discuss the potential impact of such conflicts of interests and your ability to perform all required services under this proposed OTA. Offerors shall provide a plan for mitigating the identified conflicts. Offerors with identified organizational conflicts of interest that would preclude their ability to fully perform under this SOW in an unbiased manner may be eliminated from the competition. If an existing or potential organizational conflict of interest (either prime or subcontractor) is not applicable, then the offeror shall certify as such in accordance with AMS 3.1.7-5, and include this certification with their Phase I submission.

APPENDIX 1

Alternative Data in Lieu of ASTM International Test Specification and Research Report

1. Introduction

The offeror shall meet the requirements defined in this Appendix if alternative data in lieu of an ASTM International Test Specification and Research Report is submitted in the pre-screening data package.

2. Fuel Specification

The fuel shall be defined and controlled by a specification that defines fuel performance and compositional properties necessary to ensure that all possible compositional formulations within that specification provide consistent full-scale engine performance. The specification property criteria should include, as a minimum, those properties listed in Table 1 of ASTM International D910, "Standard Specification for Aviation Gasolines".

3. Substantiation Report

A substantiation report providing data produced in accordance with section 6.2 of ASTM International Standard Specification D 7826-12, "Standard Guidance for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives", shall be submitted with the pre-screening data.

4. Test Batch Formulation Proposal

A proposal that defines the composition of test batches to be submitted for Phase 1 and Phase 2 testing in accordance with sections L of this solicitation shall be submitted. This proposal must be accompanied by substantiating data that analyzes the compositional range of the specification submitted in accordance with section 2 of this appendix and identifies the extreme compositional formulations necessary to support an evaluation of the fit for purpose of the proposed fuel specification for use on aircraft piston engines. The substantiating data should consider the test requirements of sections 6.2 and 6.3 of ASTM International Standard Specification D 7826-12, "Standard Guidance for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives", and any other testing necessary for FAA certification of piston engines or aircraft to operate with the proposed fuel.

Appendix II

BUSINESS DECLARATION

1. Name of Firm: _____ Tax Identification No.: _____

2. Address of Firm: _____

3. Telephone Number of Firm: _____

4. a. Name of Person Making Declaration _____

   b. Telephone Number of Person Making Declaration _____

   c. Position Held in the Company _____

5. Controlling Interest in Company *("X" all appropriate boxes)*

   ☐ a. Black American ☐ b. Hispanic American ☐ c. Native American ☐ d. Asian American

   ☐ e. Other Minority *(Specify)* _____ ☐ f. Other *(Specify)* _____

   ☐ g. Female ☐ h. Male ☐ i. 8(a) Certified *(Certification letter attached)* ☐ j. Service Disabled Veteran Small Business

6. Is the person identified in Number 4 above, responsible for day-to-day management and policy decision making, including but not limited to financial and management decisions?

   ☐ a. Yes ☐ b. No *(If "NO," provide the name and telephone number of the person who has this authority.)*

   _____

7. Nature of Business *(Specify all services/products (NAIC))* _____

8. *(a) Years the firm has been in business:* _____ *(b) No. of Employees* _____

9. *Type of Ownership:* ☐ *a. Sole Ownership* ☐ *b. Partnership*

   ☐ *c. Other* (Explain) _____

10. *Gross receipts of the firm for the last three years:*

    a.1. Year Ending: _____ *b.1. Gross Receipts* _____

    a.2. Year Ending: _____ *b.2. Gross Receipts* _____ *a.3. Year Ending:* _____ *b.3. Gross Receipts* _____

11. Is the firm a small business? ☐ a. Yes ☐ b. No

12. Is the firm a service disabled veteran owned small business? ☐ a. Yes ☐ b. No

13. Is the firm a socially and economically disadvantaged small business? ☐ a. Yes ☐ b. No

I DECLARE THAT THE FOREGOING STATEMENTS CONCERNING _____ **ARE TRUE AND CORRECT TO THE BEST OF MY KNOWLEDGE, INFORMATION, AND BELIEF. I AM AWARE THAT I AM SUBJECT TO CRIMINAL PROSECUTION UNDER THE PROVISIONS OF 18 USCS 1001.**

14. a. Signature _____ *b. Date:* _____

c. Typed Name _____ *d. Title:* _____

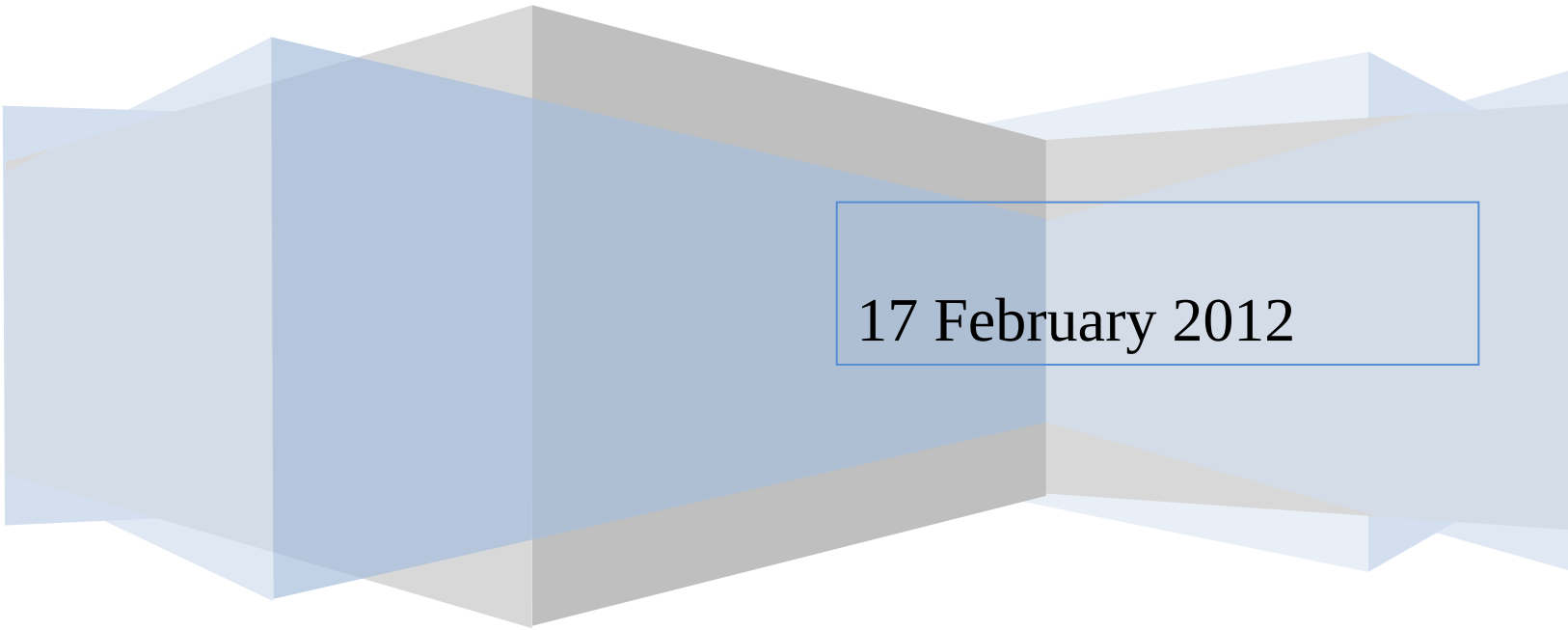
Unleaded AVGAS Transition Aviation Rulemaking Committee
FAA UAT ARC Final Report – Part I – Body: Unleaded AVGAS Findings & Recommendations, February 17, 2012

(FAA)

Unleaded AVGAS Transition Aviation Rulemaking Committee

FAA UAT ARC
Final Report
Part I Body

Unleaded AVGAS
Findings & Recommendations



17 February 2012

Table of Contents

LIST OF FIGURES

Executive Summary

Aviation gasoline (AVGAS) is a vital element of the piston engine aircraft safety system. Approximately 167,000 aircraft in the United States and 230,000 worldwide rely on 100 low lead (100LL) AVGAS for safe operation. 100LL is also the only remaining transportation fuel in the United States that contains the additive tetraethyl lead (TEL). The AVGAS used today has its origins in the development of the high power aircraft engines necessary to enable reliable and economical military and commercial flight. TEL has been used as an AVGAS additive for decades to create the very high octane levels required to prevent detonation (engine knock) in high power aircraft engines. Operation with inadequate fuel octane can result in engine failure and aircraft accidents.

Petitions and potential litigation from environmental organizations regarding lead-containing AVGAS have called for the US Environmental Protection Agency (EPA) to consider regulatory actions to eliminate or reduce lead emissions from aircraft. Similar regulatory actions are under consideration globally. These activities raise concerns about the continued availability and use of leaded AVGAS. Worldwide uncertainty and concern exists amongst piston aircraft equipment manufacturers, AVGAS producers, AVGAS distributors, fixed base operators, aircraft owners and aircraft operators regarding:

(a) Future utility and value of existing aircraft

(b) Availability and cost of aviation gasoline to maintain viable business operations

(c) Justification of new aviation product development

(d) Justification of new aircraft purchases.

With the current number of piston aircraft in the US alone more than 200 times larger than annual new aircraft production, the turnover rate of the existing fleet is very low. This low turnover rate leaves existing piston engine aircraft owners particularly vulnerable to devaluation of their aircraft should an unleaded replacement AVGAS be incompatible with the existing fleet. This vulnerability, combined with the stagnation of new aircraft sales and an overall deteriorating economic condition within the aviation industry, has created a sense of urgency regarding the development and deployment of an unleaded AVGAS that meets the performance demands of the current fleet.

In response to the rapidly increasing concerns expressed by the General Aviation community, the Unleaded AVGAS Transition Aviation Rulemaking Committee (UAT ARC) was chartered on January 31, 2011, by the Federal Aviation Administration (FAA) Administrator to investigate, prioritize, and summarize the current issues relating to the transition to an unleaded AVGAS; and to recommend the tasks necessary to investigate and resolve these issues. The committee was also tasked to provide recommendations for collaborative industry-government initiatives to facilitate the development and deployment of an unleaded AVGAS with the least impact on the existing piston-engine aircraft fleet. The committee was comprised of key stakeholders from the General Aviation community including aviation trade/membership associations, aircraft and engine manufacturers, petroleum and other fuel producers, the EPA and the FAA.

The UAT ARC has identified the following issues that must be considered in any effort to transition the aviation industry to an unleaded AVGAS:

- An unleaded replacement fuel that meets the needs of the entire fleet does not currently exist.
- No program exists that can coordinate and facilitate the fleet-wide evaluation, certification, deployment, and impact of a fleet-wide replacement AVGAS.
- No market driven reason exists to move to a replacement fuel due to the limited size of the AVGAS market, diminishing demand, specialty nature of AVGAS, safety, liability, and the investment expense involved in a comprehensive approval and deployment process.
- No FAA policy or test procedures exist to enable fleet-wide assessment and certification of a replacement unleaded fuel.
- There is no standardized method for communicating to the industry and end-users the impacts posed by a newly proposed fuel.

In response to these issues the UAT ARC has developed five Key Recommendations and fourteen additional recommendations to facilitate the transition to a fleet-wide replacement AVGAS. The UAT ARC respectfully submits these recommendations accompanied by the supporting material contained in this report and eagerly awaits FAA feedback and questions.

Key Recommendations:

1) *The UAT ARC recommends* implementation of the "Fuel Development Roadmap – AVGAS Readiness Levels (ARL)" developed by the UAT ARC that identifies the key milestones in the aviation gasoline development process and the information needed to support assessment of the viability of candidate fuels in terms of impact upon the existing fleet, production and distribution infrastructure, environment and toxicology, and economic considerations. (See Section 4.2.1)

2) *The UAT ARC recommends* centralized testing of candidate unleaded fuels at the FAA William J. Hughes Technical Center (Tech Center) funded by government and industry in-kind contributions. Centralized assessment and testing would generate standardized qualification and certification data that can be used by the fuel developer/sponsor to support both ASTM specification development and FAA fleet-wide certification eliminating the need for redundant testing. (See Section 4.3)

3) *The UAT ARC recommends* the establishment of a solicitation and selection process for candidate unleaded aviation gasolines for the centralized fuel testing program. This process should include a FAA review board with the technical expertise necessary to evaluate the feasibility of candidate fuels. (See Section 4.3.2)

4) *The UAT ARC recommends* the FAA establish a centralized certification office with sufficient resources to support unleaded aviation gasoline projects. (See Section 4.4)

5) *The UAT ARC recommends* the establishment of a collaborative industry-government initiative referred to as the Piston Aviation Fuels Initiative (PAFI) to implement the UAT ARC recommendations in this report to facilitate the development and deployment of an unleaded AVGAS with the least impact on the existing piston-engine aircraft fleet. The overall objective of this initiative is to identify candidate unleaded aviation gasolines, to provide for the generation of qualification and certification data on those fuels, and to support fleet-wide certification of the most promising fuels. (See Section 4.5)

The 14 additional UAT ARC recommendations are detailed in Section 4 and support various components of the 5 key recommendations to transition to a fleet wide replacement AVGAS.

Implementation of Recommendations – Piston Aviation Fuels Initiative

The UAT ARC believes that an integrated strategy for implementation of its recommendations provides for the greatest opportunity for a successful transition. This implementation will require an estimated $57.5M of public funds and $13.5M of industry in-kind support over 11 years. PAFI is the vehicle for implementation of this strategy. The components of PAFI will include an FAA Fuel Testing Program, FAA Centralized Certification Office and a PAFI Steering Group (PSG). The PSG will be composed of industry stakeholders and serves to marshal industry expertise and to facilitate FAA's testing and certification processes. It is important to note that the costs associated with the PAFI initiative do not include aircraft and engine recertification and incorporation of potential aircraft modifications to the existing fleet that might be necessary to accommodate any new fuel (see Section 5.5.2). It is impossible to quantify these costs without a clearer picture of the properties of the fuels that emerge from the PAFI program, but it is clear that it will represent a significant investment by industry.

The overall objective of PAFI is to utilize industry experts to support an FAA process that identifies candidate unleaded aviation gasolines, provides for the generation of qualification and certification data on those fuels, supports fleet-wide certification of the most promising fuels and facilitates deployment of those fuels throughout the industry. The UAT ARC has provided significant details on the creation, operation, costs and tasks to be performed under PAFI in section 5.0.

The projected activities, milestones, estimated resources, and estimated funding required for PAFI and the FAA to accomplish the above activities are presented in this report. The UAT ARC considers the adoption of these recommendations to be critically important to the health and welfare of the national economy due to the significant role that General Aviation and piston engine-powered aircraft play in our aviation transportation system and this nation's production of goods and services.

In the construction of these recommendations, alternate scenarios were examined that did not address the key issues identified in this executive summary and hence reduced the direct expense of the effort. These scenarios, however, carried significant risk of fleet impact, the risk of environmental regulatory action, prolonged economic uncertainty and substantive devaluation of consumer property.

1. Background

1.1. Value of General Aviation

Over the past century, General Aviation, which includes all flying except for military and scheduled airline operations, has become a significant and integral part of the U.S. economy creating millions of jobs and making a positive impact on the U.S. balance of trade. The United States continues to be one of the world leaders in the design, manufacture, and use of General Aviation airframes, engines, avionics, and supporting technologies.

General Aviation is a key catalyst for economic growth and has a profound influence on the quality of life in the United States. General Aviation today touches nearly every aspect of our daily lives, and its continued success will shape American society and the American economy over the next century.

The Societal and Economic Impacts of General Aviation and piston-engine aircraft are a key component of our nation's transportation infrastructure and economy. There are 5,261 public-use airports that can be directly accessed by General Aviation aircraft—more than ten times the number of airports served by scheduled airlines. These public use airports are the only available option for fast, reliable, flexible air transportation to small and rural communities in every corner of the country. General Aviation directly supports jobs in these communities, provides a lifeline for small to mid-sized businesses, and provides critical services to remote cities and towns, particularly in time of natural disaster or crisis. In addition, there are an estimated 11,500 additional private landing facilities in the nation giving additional rural access when necessary. As a result, General Aviation is uniquely situated to serve some of the public's most crucial transportation needs.

The economic impact of General Aviation is also significant representing more than one percent of the U.S. GDP. General Aviation contributes to the U.S. economy by creating manufacturing output, employment, and earnings that would not otherwise occur. Direct impacts, such as the purchase of a new aircraft, multiply as they trigger transactions and create jobs elsewhere in the economy (e.g., sales of materials, electronics, and a wide range of other components required to make and operate an airplane). Indirect effects accrue as General Aviation supports other facets of the economy, such as small business, rural economies, and tourism. Directly or indirectly, General Aviation accounted for over 1.25 million high-skill, high-wage jobs in professional services and manufacturing in 2005 (with collective earnings exceeding $53 billion) and contributed over $150 billion to the U.S. economy. General Aviation is one of the few remaining manufacturing industries that still provide a significant trade surplus for the United States generating nearly $5 billion in exports of domestically manufactured airplanes.
Often, General Aviation is thought of as recreational aviation, but there are many commercial and governmental operations that fall within this category of flying.

General Aviation is a particularly critical resource in rural and remote parts of the nation where surface transportation is limited or non-existent. In the State of Alaska for example, General Aviation is often the only means of transporting food, clothing, fuel, and all other forms of life

sustaining supplies throughout the state. The Alaska Department of Transportation Aviation Division estimated that in 2007 aviation contributed $3.5 billion directly and indirectly to the state economy and supported 47,000 jobs. This accounts for 8 percent of state GDP and 10 percent of average employment, making aviation the 5th largest employer in the state. General Aviation makes up by far the vast majority of aviation activity in the State of Alaska. While Alaska is the most extreme example of dependence on General Aviation, other rural and remote areas of the country in the other 49 states also depend heavily on General Aviation for their transportation and supply needs.

General Aviation also plays an important role in supporting air carrier and military flying. General Aviation piston powered aircraft are utilized in most, if not all training programs for commercial pilot training. Both single and multiengine piston aircraft serve as the primary and advanced training aircraft at the flight schools and University aviation programs that train today's and tomorrow's airline pilots. The military uses piston engine General Aviation aircraft in training programs such as the United States Air Force's Initial Flight Screening Program (IFS).

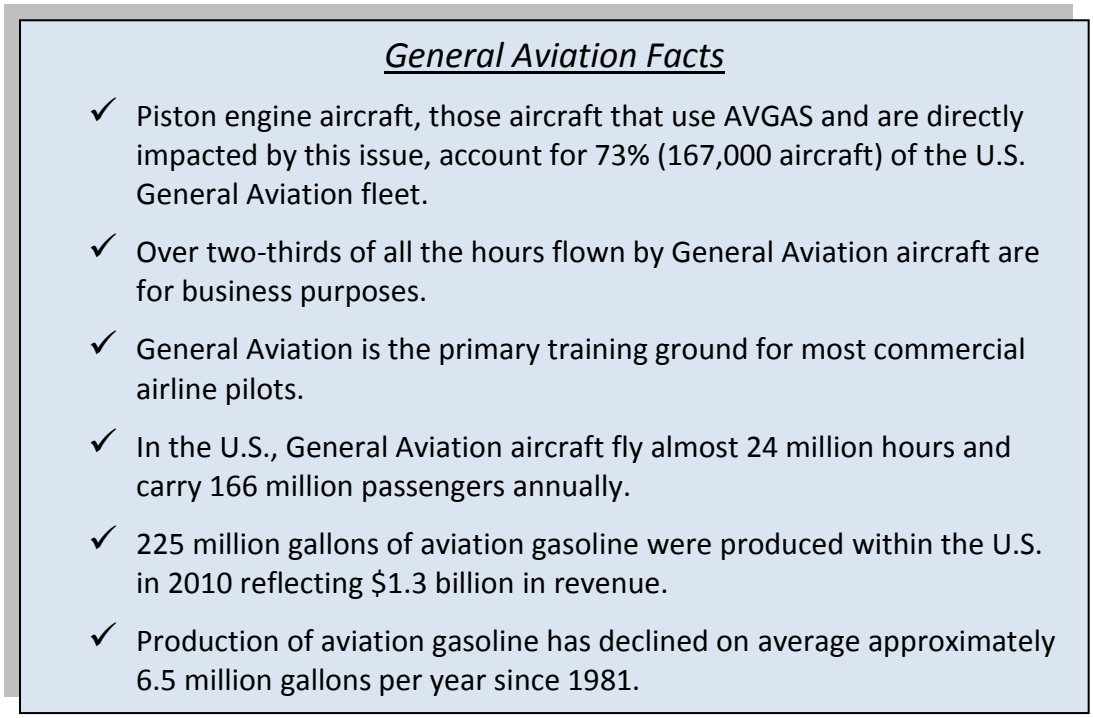


Figure 1.0 – General Aviation Facts

Refer to the following link at the General Aviation Manufacturers Association for statistics on the general aviation fleet and operation.

http://www.gama.aero/files/GAMA_DATABOOK_2011_web.pdf

Refer to the following link to the U.S. Energy Information Administration for historical data on domestic production of aviation gasoline.

http://www.eia.gov/dnav/pet/hist/LeafHandler.ashx?n=PET&s=MGAUPUS1&f=A

1.2. History of Leaded Aviation Gasoline

Aviation Gasoline evolved to its present state out of the need for maximized engine performance by producing the greatest possible power output per unit weight under all environmental conditions. The development of piston engine technology in the first decades of human powered flight was directly responsible for the evolution of ever larger, faster and more capable aircraft. This advance in engine power to weight ratio was directly attributable to advances in fuel technology.

After years of laboratory and practical testing of some 30,000 chemicals and compounds, in 1921 General Motors Corporation discovered that a lead compound called TEL could significantly improve the anti-detonation characteristics of gasoline. The anti-knock qualities of TEL was many orders of magnitude greater than any other chemical or metal researched and adding only small amounts of the lead compound to gasoline could have dramatic results. It was quickly learned that by increasing the anti-knock characteristics of the fuel or what became known as the octane rating, engines could be developed to produce significantly greater power output. By 1944 the war effort dramatically accelerated the advancement of piston powered aircraft technology to its zenith that coincided with the development of the highest octane, widely available fuel ever produced with a lean motor octane rating of 115. The fuel was referred to as 115/145 and contained a maximum of 4.6 grams per gallon of TEL.

In the 1950's, commercial aviation reached its pinnacle of aviation gasoline use and General Aviation was rapidly growing in the United States. During this decade there were six grades of aviation gasoline commonly produced ranging from a low of 73 octane up to the 115 octane fuel required for many military and commercial piston powered aircraft. However, the change in propulsion technology from piston to turbine engines was well underway in the military and finding its way into the commercial fleet. This marked the beginning of the long-standing decline in aviation gasoline production to this day.

In 1970, the original Clean Air Act was passed by Congress and this legislation targeted lead as one of the primary emissions to be controlled. Accordingly, regulations were introduced by the newly formed Environmental Protection Agency to reduce and eventually eliminate lead from motor vehicle fuels. However, while lead emissions from aviation were to be studied no specific action to remove lead from aviation gasoline was undertaken.

The public awareness and legislative/regulatory pressure to remove lead from fuels and the rapid decline in aviation gasoline consumption brought about by the transition of the commercial and military aircraft fleet to turbine engines made it economically infeasible to continue to produce multiple grades of aviation gasoline. A period of consolidation occurred in the 1970's and 1980's leading to the one grade of aviation gasoline available today; 100 octane low lead (100LL) which contains a maximum of 2.0 grams per gallon of TEL. This represented a roughly 50% reduction in lead emissions per gallon from the time when 115/145 fuel was commonly used by the airlines and the military. Lead emissions were further reduced as consumption of high octane aviation gasoline was replaced by jet fuel.

Like any good compromise, 100LL was not the best fuel for all aircraft. Those aircraft requiring the highest possible octane characteristics designed for 115/145 AVGAS were required to operate at lower power settings causing adverse impacts in payload capacity, takeoff distances, altitude and other performance characteristics. Conversely, low compression engines found in the light end of the General Aviation fleet found 100LL to contain too much lead for their best operation resulting in lead fouling of spark plugs and sticking valves among other difficulties. For the bulk of the General Aviation fleet though, 100LL proved to be an acceptable fuel and most of the aircraft and engines produced since the 1970's were designed around the octane characteristics of 100LL.

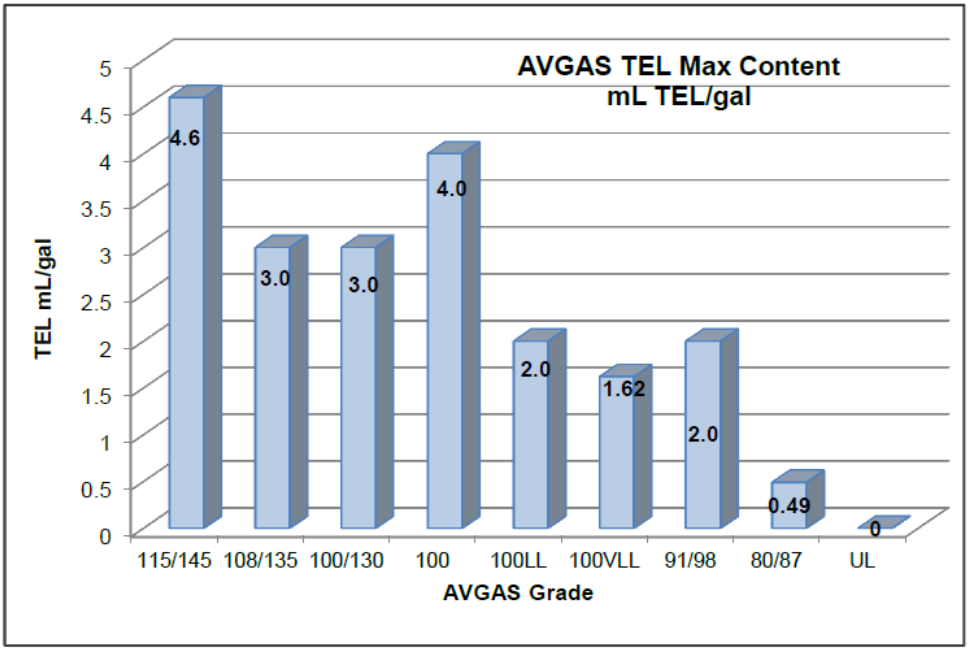


Figure 2.0 - Historical AVGAS TEL Content, Ref ASTM D910

1.3. Drivers for Development of Unleaded Aviation Gasoline

With passage of the Clean Air Act Amendments in 1990 new regulations were promulgated by the EPA to eliminate lead from the gasoline powering non-road engines and vehicles. It was feared at that time that aviation gasoline might be considered a non-road fuel and thus be subject to the lead elimination deadline in 1995. This sparked the beginning of serious exploration to remove lead from AVGAS while attempting to preserve the performance characteristics of the fuel and thus aviation safety. Over the ensuing 15 years, considerable research was undertaken by the aviation and petroleum industries to develop a direct replacement for 100LL without the use of lead. The FAA's William J. Hughes Technical Center played a key role in this effort. Test procedures were developed and numerous compounds and additives were tested including a matrix of 245 fuels examined in a blind round robin test overseen by the Coordinating Research Council. Forty-five of the most promising blends were examined more closely in full-scale engine testing. However, none of the fuels could satisfy all the performance requirements of 100LL.

With the threat of law suits by environmental groups, a potential EPA endangerment finding for lead emissions from aircraft, and mounting concern for the long-term availability of TEL, a group of organizations representing aviation consumers, manufacturers, and petroleum producers and distributors gathered together under the banner of the Aviation Gasoline Coalition to examine the state of the fuel marketplace. They examined research into unleaded fuels, the legal and regulatory landscape and fuel producibility and availability. The conclusion was that there were no technically feasible and safe options for high octane unleaded gasoline that would satisfy the existing fleet, though several research efforts were underway. Further, there was considerable uncertainty about the cost and availability of candidate fuels that came closest to approximating the performance of 100LL and recognition that these candidate fuels could not safely meet the high horsepower needs of the fleet. It was also recognized that while the high performance portion of the fleet represented a minority of aircraft (approximately 30 percent), these aircraft used a majority of the AVGAS (estimated to be 70 to 80 percent) by virtue of their higher fuel consumption per hour and concentration of these aircraft in commercial/business operations that fly far more hours relative to the broader General Aviation community. This meant that any unleaded fuel solution needed to be of the highest practicable octane level to satisfy that portion of the fleet that consumes the majority of the fuel

Economic considerations play a role including the ability to produce any new fuel in large quantities and in a cost-effective manner. Dual fuel solutions such as a high octane unleaded or partially leaded fuel for the high performance aircraft and a low octane unleaded fuel for the remainder of the fleet were considered. Upon careful examination, it was concluded that the volumes of consumption and cost for dual infrastructure would prohibit any widespread availability of two grades of aviation gasoline. In other industries where leaded fuel has been phased out, attrition of the fleet has been the primary means of implementing the change. However, the General Aviation fleet has an average age of 39 years, and growing, indicating that conversion to unleaded fuel by attrition is not viable in the near term and that recertification of the existing fleet to any new fuel would be required.

The formidable combination of technical and economic barriers to developing a satisfactory and safe replacement unleaded fuel, combined with the never before attempted challenge of recertifying the entire General Aviation piston fleet, will require the expertise and support of entities involved in aviation aircraft, engine and gasoline production, testing, distribution, sale, and use along with regulatory bodies such as the Environmental Protection Agency and the Federal Aviation Administration. Accordingly, the General Aviation AVGAS Coalition made a formal request to the FAA for the creation of a Federal/Private partnership to examine the full range of issues associated with replacing leaded aviation gasoline with an unleaded alternative that would satisfy the needs of the existing fleet. In January of 2011, the FAA responded by chartering the UAT ARC whose membership includes representatives of aviation gasoline producers and distributors, aircraft and engine manufacturers, aircraft owners and pilots, fixed base operators and environmental and aviation regulatory agencies. Friends of the Earth, an environmental organization pursuing legal action regarding lead emissions from aviation gasoline, was invited to participate but declined.

2. UAT ARC Committee

2.1. FAA Charter

The UAT ARC was established in response to a July 2010 petition from the General Aviation Coalition with the official Charter signed by the FAA Administrator on January 31, 2011. The period of performance was initially designated as being six months. The term of the Charter was subsequently extended in June 2011 by an additional six months to January 31, 2012. A copy of the Charter is included in Appendix A. The UAT ARC functioned under the provisions of FAA ARM Committee Manual ARM-001-015 latest Rev 38 which may be accessed at the following link.

http://www.faa.gov/regulations_policies/rulemaking/committees/arac

The FAA establishes an ARC to solicit the public's input on issues with potential regulatory implications and to exchange ideas with representatives of industry. The ARC serves in an advisory capacity with the work product being a final report presenting findings and recommendations. The UAT ARC goals and tasks as specified by the Charter are summarized as follows.

Goals

- Recommend a framework and implementation plan to guide the General Aviation community towards the deployment of an unleaded AVGAS as an alternative to 100LL
- The committee is NOT tasked with identifying a specific fuel

Tasks

- Investigate, prioritize, and summarize issues relating to the transition to an unleaded AVGAS
- Identify key issues
- Recommend tasks necessary to investigate and resolve key issues
- Provide recommendations for a joint industry-government framework to facilitate the development and deployment of an unleaded AVGAS
- Provide a report with recommendations by January 31, 2012

2.2. Membership

The UAT ARC membership represented many of the key constituencies of the General Aviation community. The FAA charter invited General Aviation stakeholders representing user groups, engine and aircraft manufacturers, industry associations, fuel producers, distributors, FBOs, environmental groups, FAA, and EPA (see Figure 3.0).

Discipline/Specialty		Member Organization
Leadership		**FAA Certification, Industry Consultant**
Certification		**FAA Certification**
Manufacturing		**GAMA, Cessna, Cirrus, Continental, Lycoming**
Environment		**EPA, FAA Office Environment & Energy**
Distribution		**NATA**
Research & Development		**FAA Tech Center**
Petroleum Industry		**API**
Owners/Operators		**AOPA, EAA, Clean 100**
Fuels		**ExxonMobil, Shell Aviation, Swift, GAMI**

Figure 3.0 – UAT ARC Membership

2.3. Meetings, Telecons, & Deliberations

The UAT ARC performed most of its work from March 2011 to January 2012. During this time there were 7 full committee meetings of 3 days duration each held in Washington DC. This represented in excess of 3300 hours of commitment on the part of the combined membership. These meetings were complemented by 11 full committee telecons with an additional 35 focus area telecons which encompassed an estimated additional 800 man hours of participation. All meetings and deliberations were conducted in accordance with FAA ARM Committee Manual ARM-001-015 antitrust guidelines, which are included in Appendix B.

3. UAT ARC Assessment of Key Issues

3.1. Summary of Key Issues Affecting Development and Transition to an Unleaded AVGAS

The following is a list of key issues identified by the UAT ARC as affecting the development and transition to an unleaded AVGAS. Further discussion follows in Section 3 providing additional insight into the group's discussion of the issues.

3.1.1. General Issues

- Replacement fuel will not be a drop-in or transparent fuel for the entire fleet.
- The existing fleet of approximately 167,000 aircraft and engines were designed and certified to operate on a known leaded AVGAS fuel meeting the ASTM D910 Specification. This fleet will require re-certification to operate with a different fuel.
- No program exists that can coordinate and facilitate the fleet-wide evaluation, certification and deployment of a non-drop in replacement AVGAS.

3.1.2. Market & Economic Issues

- With neither a drop-in replacement fuel nor a regulatory mandate to use an unleaded fuel, no market driven reason exists to move to a replacement fuel.
- Market forces have not supported the development and transition to a replacement unleaded AVGAS. The size of the AVGAS market, diminishing demand, specialty nature of AVGAS, safety ramifications and liability concerns limit the business case for the development of replacement fuels and aircraft modifications.
- Aircraft owners, present and prospective, are uncertain about the future of AVGAS, the cost of transition to an unleaded AVGAS, and the potential impact on the utility and value of their aircraft. They have no horizon or understanding of information needed to make decisions, stifling the purchase of new aircraft and modification/sale of existing aircraft.
- It will be very challenging to provide an unleaded replacement fuel that meets the demands of the two major sub-groups of the piston powered aircraft fleet; the low-utilization recreational aircraft, and the high-utilization business aircraft.
- The participation of aircraft and engine Design Approval Holders (DAHs) in the effort to develop and deploy a replacement unleaded aviation gasoline may be constrained by liability concerns.

3.1.3. Certification & Qualification Issues

- FAA regulations and policy are structured to approve specific engine and aircraft type designs for operation on a known AVGAS fuel specification. There are no FAA policy or test procedures for fleet-wide assessment and certification of a non-drop-in replacement fuel.

- Fuel testing and data requirements necessary to develop an ASTM specification and to obtain FAA certification for engine and aircraft are redundant, extremely costly, and time consuming.
- Applicants seeking both a design and fuel approval must deal with multiple FAA offices, such as ACOs and Directorates that may have limited experience with AVGAS related certification projects. This may lead to standardization issues and make efficient and timely certification difficult.
- Diversity of the fleet provides for daunting certification programs.
  - Small numbers and uniqueness of some models provides technical and economic challenges.
  - It is expected that engineering and recertification efforts for approval of a new unleaded AVGAS for many aircraft will not be supported by type certificate holders.
  - The existing fleet is comprised of different classes of aircraft, such as type certificated, light sport aircraft, and experimental, that will require different approval procedures.

3.1.4. Aircraft & Engine Technical Issues

- Research and testing to date has not identified an AVGAS formulation that meets all of the performance requirements of the current AVGAS specification on which the general aviation fleet was certified.
- The anti-knock capability or octane number of unleaded aviation gasolines is difficult to correlate to full-scale engine performance.
- Achieving the necessary octane number with unleaded AVGAS formulations results in undesirable trade-offs with other important fuel properties.

3.1.5. Production & Distribution Issues

- There is no existing method of determining the production and distribution impact posed by a new fuel.
- There is no standardized method for communicating to the industry the impacts posed by a newly proposed fuel.
- There are multiple third party regulations, standards and codes that may impact the deployment of any newly proposed fuel.

3.1.6. Environmental & Toxicology Issues

- There is no process to assess potential environmental and toxicology issues related to a candidate unleaded AVGAS formulations.

3.2. General Issues – Will not be a drop-in

After 20 years of research, no unleaded formulation has been found that can meet the octane needs of the existing fleet while also maintaining the other necessary safety qualities of an aviation gasoline such as vapor pressure, hot and cold starting capabilities, material compatibility, water separation, corrosiveness, storage stability, freeze point, toxicity and a host of other necessary traits necessary to be a true drop-in.

Consumers consistently demanded that a replacement fuel be drop-in and envision a seamless transition with little or no negative impacts. Because of this demand from the consumer, research into fuels that were near or only partially drop-in and did not meet all of the safety and performance parameters of the existing fuel were quickly discarded. Fuels that were advanced (i.e. UL82) and that fell short in some areas were not manufactured and distributed due to lack of consumer demand. It is now apparent that a replacement unleaded AVGAS will not be a drop-in fuel.

3.2.1. Drop-In vs. Transparent

The terms “drop-in” and “transparent” are often used in the discussions surrounding AVGAS. It is apparent that these terms have different meanings to many in the aviation world and have still different meanings when considering the broader scope of the production, distribution and consumption of AVGAS. For the purposes of the UAT ARC discussion and to have all players working from common understanding, it was discussed and ultimately agreed that it is unlikely that any replacement fuel will be completely drop-in for the entire fleet. Depending on the fuel composition, it is possible however that a new fuel could be transparent to large portions of the fleet thus reducing the challenges of transitioning to an unleaded fuel. To avoid any possible ambiguity or confusion over the use of these terms in this report, definitions and examples are provided in the following three paragraphs.

***Drop-In Fuel*:** A “Drop-In” fuel does not affect the airworthiness and performance of the existing fleet of aircraft and engines and typically does not require new aviation fuel operating limitations. An extensive qualification test program that encompasses both fuel property evaluation and engine and aircraft testing would be required to determine if a new fuel is a drop-in. However, FAA certification approval is typically not required for existing aircraft and engines to operate with the new fuel. An example of a lead-containing Drop-In fuel is the 100 Very Low Lead (100VLL) fuel, which has been added to the current AVGAS fuel specification, ASTM D910. This fuel was introduced to the existing fleet without the need for FAA approval because it met all the compositional and performance criteria of existing 100LL AVGAS. If a fuel is not a drop-in fuel for the entire fleet, then the following definitions apply:

Transparent Fleet: The segment of the existing fleet of engines and aircraft for which a new fuel is a drop-in is called the “transparent fleet”. Changes such as new or modified hardware, adjustments, or new operating procedures/limitations are not required for the aircraft and engines in the “transparent fleet”, but FAA approval may be required to enable operation under the existing operating limitations.

Non-Transparent Fleet: The segment of the existing fleet of engines and aircraft for which a new fuel is not a drop-in is called the "non-transparent fleet". FAA approval of new operating limitations and changes such as new or modified hardware, adjustments, or new operating procedures/limitations will be required for aircraft and engines in the non-transparent fleet.

It is likely that replacement fuels will not match or mirror all of the performance characteristics of current AVGAS, thus the transition will have some impact on segments of the fleet. Assuming the new fuel meets many, but not all of the characteristics of current AVGAS, its impact would be felt differently by various segments of the industry. For the transparent segment of the fleet, the only likely impact would from FAA approval requirements, but this could be mitigated through FAA fleet-wide actions that address a large number of aircraft/engines. For the non-transparent segment of the fleet, new materials, operating procedures/limitations or hardware will be required in addition to FAA approval. These costs could be mitigated by FAA support of testing and approval of the required modifications.

3.2.2. Historic Efforts Focused on Drop-In

There has been extensive testing to find a fuel that meets all of the current ASTM D910 leaded aviation gasoline specification properties for 100LL, satisfies the safety and performance requirements of engines and aircraft, is compatible with the existing infrastructure, and poses no additional compositional issues. Thus, the fuel would have been considered a drop-in fuel, and if such a fuel had been available, it is likely the industry would have transitioned to this fuel once it became available to the General Aviation market.

Unleaded fuels typically require the addition of significant amounts of specialty chemicals to meet the same anti-knock performance that can be attained from the addition of a relatively small amount of TEL. These proposed high octane chemical additions often include heavier molecules with higher boiling points that when added in the quantity necessary to meet the same anti-knock performance of leaded fuels, often produces fuel blends that exceed many other current aviation gasoline specification limits. The legacy fleet was designed to operate safely on fuels that met the ASTM D910 specification property limits, with each fuel property addressing a different safety, performance or operability characteristic. The impact changes to these specification properties will have on the safety, operability and performance of engines and aircraft is understood in general terms but has never been studied or quantified.

In addition to the properties listed above, there are additional critical fuel properties that determine whether the fuel is fit for the purpose it was intended, such as the need for fuel to be compatible with the fleet infrastructure and co-mingle with the existing fuel to ease the transition.

3.2.3. No Program to Support Development of AVGAS

With a drop-in replacement for leaded aviation gasoline unavailable, it is clear that a replacement fuel will need to be developed. As detailed in Section 1.2, the development of the current leaded aviation gasoline was an evolutionary process that occurred over decades in response to the performance needs of piston aircraft engines and aircraft safety. Each successive evolution of AVGAS further improved the performance, capability and safety of the

aircraft engines in which it was used. This effort intended to transition the General Aviation industry to a fleet wide replacement AVGAS proposes, for the first time, to develop an entirely new fuel and apply it to a large existing fleet while attempting to minimize the impacts or possible changes to the existing fleet. Such a new fuel would need to be developed in a manner that ensured that the existing performance and safety characteristics of AVGAS were replicated or differences clearly identified and understood in areas where they could not be matched.

While some have already begun independent processes of developing replacement fuels, there currently exists no widely accepted development process. Without such a process, the industry and regulators have no standard or criteria by which to review the sufficiency of the varied development processes undertaken by prospective fuel developers.

In addition, there exists no organizational entity around which the aviation gasoline stakeholders can organize and work the development process for candidate fuels. Such a process is necessary to coordinate the many faceted dimensions of this type of program.

3.3. Market & Economic Issues

3.3.1. Market Forces

Market forces have not supported the development of and transition to a replacement unleaded AVGAS. The size of the AVGAS market, diminishing demand, specialty nature of AVGAS, safety considerations and liability concerns limit the business case for the development of replacement fuels and aircraft modifications. Since the 1970's, 100LL has been the primary fuel used in General Aviation piston aircraft. The industry and market have developed in a way that not only relies on this fuel, but has evolved in a way that has maximized the value and efficiencies of the production, distribution, and performance of aviation fuel and engines that operate on this fuel. This is because market forces strongly support 100LL as the best aviation gasoline in terms of performance and cost. This is not surprising since the industry has relied on and maximized aircraft engines based on the capabilities of the fuel.

It is also important to understand that the pressures to replace 100LL are not market driven but are extraneous to the markets. Current pressures include the threats of legal action at the state level, and EPA consideration of potential regulatory actions at the federal level driven by the Clean Air Act. Prior to these actions, the market continued to maximize itself to the existing fuel.

Market forces alone to date have not and are not likely to support, by themselves, the development and deployment of an unleaded AVGAS in the future. This is not unexpected considering that no unleaded fuel to date has been able to match the characteristics of 100LL in and thus compete naturally in the market. Couple this with the many challenges and business risks, including the relatively small size of the market, diminishing demand, certification challenges, specialized nature of AVGAS and liability issues and it becomes apparent that the market alone cannot drive this change. There is also concern about the return on investment and potential demand for an unleaded AVGAS once it is developed and certified. Recognizing

that an unleaded AVGAS will not be a drop-in replacement for 100LL, there is going to be some adverse impact upon the existing fleet.

Within the constraints of any regulatory drivers, the market must decide which of the fuels will emerge and be manufactured, supplied, distributed and sold at airports. The market consists of those companies that will use private funding to manufacture and deploy the new product in response to consumer demand. It is the candidate fuel developers' responsibility to solicit and acquire business agreements from these different companies that shows the government review panel that their product is viable in the open market and is capable of replacing 100LL.

3.3.2. Aircraft Owner Market Perspective

The current situation surrounding AVGAS has generated uncertainty and concern among piston aircraft owners and operators regarding (a) the future utility and value of their current assets, (b) the availability and price of aviation gasoline to maintain viable operations and (c) the uncertainty of justifying new aircraft purchases. Worldwide shipments of General Aviation airplanes fell for the third year in row. In 2010, 2,015 units were delivered around the globe, as compared to 2,274 units in 2009, an 11.4 percent decline. The piston airplane segment shipped a total of 889 units in 2010, compared to 963 units in 2009, a 7.7 percent decline. With the current fleet more than 200 times larger than annual new production, sales of new aircraft stagnating and the resulting overall economic condition of the industry deteriorating, a sense of urgency has evolved regarding the development and deployment of an unleaded AVGAS.

Consumers have multiple concerns ranging from the grounding of their aircraft due to lack of a suitable fuel if action to ban the sale of the current fuel is taken too quickly to the premature devaluation of their existing aircraft if a process is not established to qualify and implement a suitable alternative. The concerns and the impact on consumers include but are not limited to the fuel price and availability, cost and impacts of modifications, lifespan and cycle of aircraft including typical overhaul cycles and the various uses of aircraft and how users would be impacted differently. These and other consumer concerns will need to be considered in the ongoing effort to establish an implementation plan, milestones and timeline after an alternative to existing fuel has been established. Each of these concerns and issues varies greatly depending on the attributes, performance characteristics and composition of actual fuel alternatives and any associated modifications to the fleet. Of paramount consideration in the UAT ARC discussions was the need to develop mitigation strategies for these issues prior to and during the implementation process.

An additional significant point of discussion during the UAT ARC deliberations was the need to consider the value of the existing fleet and the affects transitioning to a new fuel could have on the current and future value of aircraft. PAFI and fuel developers will need to be cognizant of the impact of potential alternatives on the market value of aircraft. If, for instance, a solution comes to market that has an adverse impact on aircraft capabilities because they are either grounded (zero value) or have a reduction in their operating envelopes, there will be substantive impact on their value. The number of aircraft impacted by this devaluation is

largely dependent on the proposed fuel so it is nearly impossible to define in detail at this stage, but it remains a key consideration when evaluating each potential alternative fuel.
Another important consideration is the timeline by which alternatives are implemented and ultimately brought to market. An alternative that has a substantial impact, including the devaluation of a portion of the fleet, would require a significantly longer implementation timeline, perhaps decades, to allow for the use of the remaining life of the airframes and engines and allow natural retirement and attrition of the this portion of the fleet. The challenge with this approach is that the industry keeps heavy utilization aircraft active for decades. These aircraft are flying critical missions and are difficult, expensive, or in many cases, impossible to replace due to a lack of new aircraft produced that can fit the mission profile. The average age of the General Aviation piston fleet is 39 plus years highlighting the need for an extended transition for any alternative fuel that could significantly devalue the existing fleet.

3.3.3. Fleet Utilization

The current fleet of aircraft ranges from low octane light utilization with small volumes of fuel consumption to high octane high utilization with large volumes of fuel consumption and combinations in between. Each type of General Aviation aircraft owner/operator is important to the future health of General Aviation for a host of varying reasons. The impact of alternatives on each segment must be considered and mitigated in the evaluation and implementation phases.

The light utilization group of owners and operators represents one extreme in the composition of the fleet. These aircraft likely fly less than 100 hours per year, do not require high octane fuel, and purchase a relatively small volume of the total fuel consumed. However, they represent the largest number of actual aircraft in the fleet. The typical profile of this group would be an aircraft in private ownership utilized for primarily recreational flying. Because of their recreational/personal use and private ownership, these aircraft represent the group most sensitive to price fluctuations. Their reaction to a significant increase in the price of fuel would be to reduce their amount of flying or to stop flying altogether. The negative effect of either of these outcomes would be felt throughout the industry in the form of reduced operations at airports, fewer aircraft transactions, and a general degradation of the General Aviation industry through reduced participation.

The other extreme in fleet composition is represented by owners and operators of heavy utilization aircraft. These aircraft likely fly more than 300 hours per year in commercial service or in support of business activities and typically demands the highest performing fuel. This group represents perhaps the smallest number of aircraft, but because it has such a high utilization rate and includes large and multiengine aircraft it represents the majority of actual fuel consumed by the industry. A primary consideration for this group is that of aircraft performance and utility. Two examples are aircraft payload and takeoff performance. A reduction in either of these imposed by a limitation of the fuel significantly reduces the viability of these aircraft. In many cases, the reduction would exceed the point at which the aircraft is no longer viable for this type of operation. This is compounded by the fact that suitable replacements for these aircraft are not available in a commercially and economically viable manner. The inability of these aircraft to continue to perform their missions would have a

significant impact on the industry through not only the loss of utility and size of the General Aviation fleet but also a major reduction in the amount of fuel burned. This loss of fuel consumption could reach the point at which fuel volume is reduced sufficiently to no longer warrant production at an economically suitable price to sustain the industry. The loss would also have an extreme effect on other industries and the communities supported by these aircraft.

While these two scenarios attempt to represent the extremes of the current market, they are not provided to attempt to illustrate a greater importance or significance of one over the other. The purpose of these discussions by the UAT ARC was to understand how alternatives and their impacts could impact various segments of the industry.

3.3.4. Design Approval Holder (DAH) Perspective

The current state of the General aviation industry has DAHs bearing disproportionately large costs for products liability insurance and litigation. As a result, the DAHs will likely not want to increase their liability by participating directly in the determination of an unleaded fuel, unleaded fuel approval and distribution process.

The passage of the General Aviation Revitalization Act (GARA) in 1997 established an 18-year time limitation (statute of repose) on civil actions that could be brought against aircraft manufacturers, with certain exceptions. If the transition to a non-drop-in unleaded aviation gasoline opens the door to additional OEM liability a "chilling effect" on DAH participation in recertification activities would result. Also considering the large number of aircraft in the General Aviation fleet no longer in production, it is highly unlikely that DAHs will be willing to recertify equipment, develop new performance data, and re-issue manuals to accommodate the anticipated fuel because of the expense and lack of accessibility to assets for confirming flight tests.

Of further concern is the potential for class action suits based on a potential devaluation of consumer asset value. In the event that the unleaded AVGAS solution results in performance degradation or aircraft grounding, the parties involved in the determination process would likely be targeted for litigation.

Based on the aforementioned considerations, it is anticipated that DAHs will not actively participate in the determination and recertification process without mechanisms for liability protection. Without such protections, DAHs would support the overall PAFI effort, however, determination, approval and transition will require the FAA to lead and mandate the action. While this would not redress the situation for DAH products and aircraft no longer in new unit production, it would likely provide an acceptable basis for support of active production. The alternative to DAH participation on either inactive or active production would be for third parties to create, test, and approve data to support the issuance of a Supplemental Type Certificate (STC) or STCs to certify the new fuel. Examples are the STCs currently in place for automotive gasoline. This scenario also presents challenges in that third parties typically do not have access to the entire scope of data in the same manner as a DAH, thus the expense of a

comprehensive validation program via STC or other means may be larger than that which could be conducted with DAH participation.

3.4. Certification & Qualification Issues

3.4.1. FAA Regulatory Structure

Historically, the commercial Aviation industry has relied on a very limited number of well proven, conventional fuels for certification and operation of aircraft and engines. The vast majority of today's engines and aircraft were designed and certified to operate on one of two basic fuels; kerosene-based fuel for turbine powered aircraft and leaded AVGAS for spark ignition reciprocating engine powered aircraft. These fuels are produced and handled as bulk commodities with multiple producers sending fuel through the distribution system to airports and aircraft. These fuels are defined and controlled by industry consensus-based fuel specifications; ASTM International D1655 for jet fuel and ASTM D910 for aviation gasoline. These specifications, along with the oversight of the ASTM International aviation fuel industry committee, accommodate the need to move the fuel as a commodity.

The ASTM consensus standard process is well suited to support the development of a new fuel specification for use in future aviation products designed to operate on an unleaded fuel. However, the evaluation and qualification process is far more complex if the new fuel specification is intended for existing aircraft and engines that are designed to operate on 100LL. The procedure to evaluate new aviation gasoline is progressive and iterative in nature, with the extent of continued testing determined by the fuel properties, characteristics and test results revealed at each successive stage. The extent of testing that may be necessary grows with increasing degree of divergence from the composition, properties, performance, and experience with existing 100LL. ASTM committee members evaluate this degree of divergence and its consequences during the analysis of research report data provided by the fuel developer during the creation and maturation of new specifications.

The FAA regulations pertaining to aircraft, engines, and aviation fuel were structured to compliment this industry development and oversight concept. They require that type certificate applicants identify the fuel specifications that are used in their products during certification. Once compliance with the airworthiness certification regulations has been demonstrated, the grade designation or specification becomes part of the airplane, rotorcraft, and engine operating limitations. These operating limitations are specified in the type certificate data sheet (TCDS) and in the airplane flight manual (AFM) or rotorcraft flight manual (RFM). Aircraft operators are required by 14 CFR § 91.9 to only use fuels and oils listed in the AFM or RFM (see Figure 4.0). These fuels must, therefore, be identified with sufficient specificity to ensure that the engine and aircraft continue to meet their airworthiness certification basis during service.

The fuel must be shown to have no adverse effects on durability or safety and must perform satisfactorily on the products for which it is specified. This is demonstrated during the type certification program, amended type certification program, or supplemental type certification program. Specifically, applicants must demonstrate that the type-certificated product meets

certification standards when operated with the new fuel over the complete range of operating conditions that the product originally satisfied. FAA Advisory Circular (AC) 20-24C describes the applicable regulations for fuel related certification projects.

FAA regulations are structured to approve specific engine and aircraft type designs for operation with a fuel specified by the type design holder. Therefore, it is difficult to "certify" a fuel for the entire fleet of certificated aircraft, or for a large portion of that fleet. The FAA needs to develop policy to accommodate this.

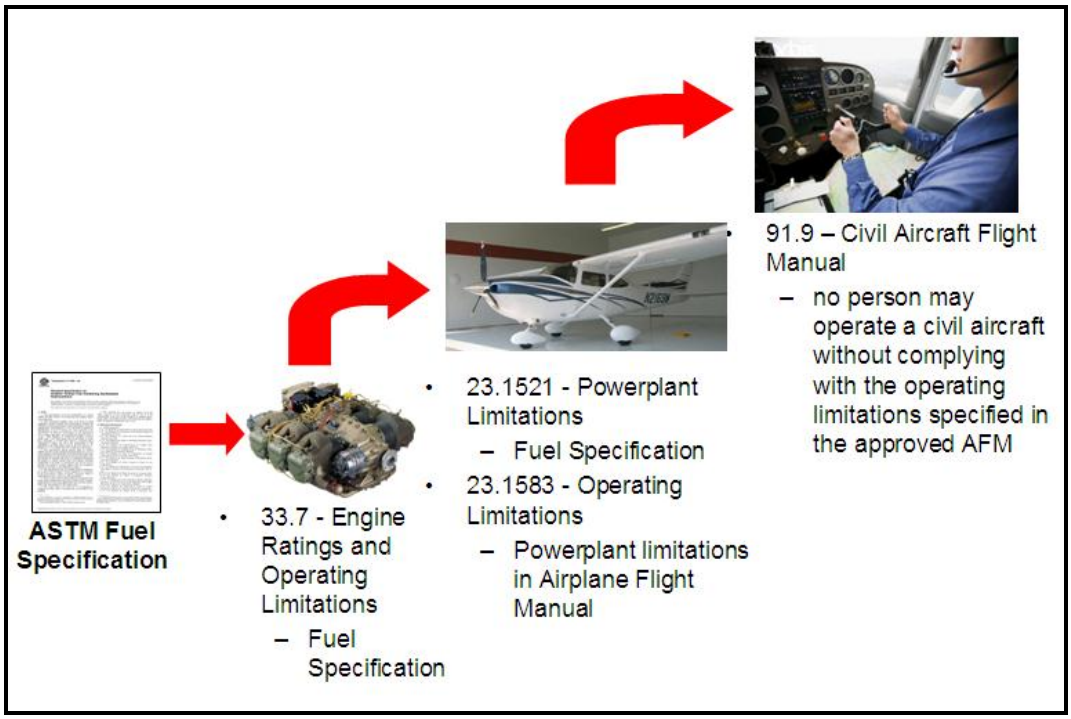


Figure 4.0 - FAA Regulatory Structure for Aviation Fuels

3.4.2. ASTM and FAA Data Requirements

As described above, the current ASTM and FAA processes are based on the historical practice and experience of being conducted in series and completely independent of each other. This is because engine/aircraft are designed and certified to an existing fuel specification and certification is conducted completely independently from the development of new fuels. ASTM report data on fuel specification and fit-for-purpose properties are recognized and accepted by FAA in certification programs as acceptable definition of the fuel, but are not acceptable as certification data to support the issuance of design approvals for engine or aircraft Type Certificates (TC)/STC.

Certification data must be developed in accordance with 14 CFR Part 21 certification procedures that require FAA approval of applicable requirements and test plans, as well as conformity inspection of test materials and equipment. This traditional process of defining an aviation fuel through the development of an ASTM specification independently and prior to the certification of engines/aircraft specifying that fuel as an operating limitation is not conducive

to developing a non-drop-in unleaded AVGAS. Since fuel development and qualification is an iterative process, a prospective new fuel proponent must determine during the specification development that the new fuel also meets FAA safety requirements for operational approval. This is because the overall potential market for the new fuel depends on the ability to certify engines and airplanes to operate on that fuel. It is extremely redundant, costly and time consuming for ASTM and FAA fuel qualification processes and test data to be conducted independently resulting in significant uncertainty and risk. Background information on ASTM is included in Appendix K.

3.4.3. FAA Certification Offices

Applicants typically interface with multiple FAA offices, such as ACOs and Directorates based on the nature of the project and the geographic location of the applicant. This situation poses significant risk to the success of the unleaded fuel initiative due to varying degrees of experience and knowledge of fuel related certification policy from office to office and the need for national coordination for what has to be a national solution. Other risks include the potential for non-standardized application of FAA regulations and policy, difficulty in sharing and comparing data between fuel programs and certification programs, prioritization of aviation fuel related certification projects, and FAA management support of these projects.

3.4.4. Existing Fleet

Of paramount importance and complexity is the impact of transitioning to a new fuel including upfront costs to develop and qualify an unleaded fuel as well as the long-term cost impact of deploying a new fuel. Converting in-use aircraft/engines to operate on a non-drop-in unleaded aviation gasoline is a significant logistical challenge, and in some cases, a technical challenge as well. A change of approved fuels with different performance characteristics and modifications to engines and aircraft require FAA certification to ensure compliance with applicable airworthiness standards necessary for safety. The FAA certification process is comprehensive and requires significant investment of resources, expertise and time to complete. The cost and resource impact upon both industry and government could be extremely significant depending upon the level of effort and number of modifications that may be necessary to support a transition of the in-use fleet to an unleaded AVGAS. However, the closer the physical and performance properties of an unleaded AVGAS to 100LL, the less upfront economic impact there would be to the existing fleet, not including the cost of the new fuel. In particular, octane rating is a critical fuel property for aircraft engines to maintain rated horsepower which in turn is necessary for aircraft to continue to meet performance limitations.

Fleet Makeup & Typical Mission Scenarios

As the future Unleaded AVGAS is not expected to be 100% drop-in with full comparability to the current 100LL fuel, some percentage of the certificated piston powered fleet may not be able to operate safely (properly) without procedural and/or hardware modifications. In all cases, some form of approval process will be necessary for every aircraft in the existing fleet to be able to legally use the future unleaded AVGAS. In addition, there are other portions of the diverse piston powered fleet that are non-FAA certified aircraft. The following describes the piston

powered General Aviation fleet with an emphasis on impact and special considerations for implementation of approval of use for a new unleaded fuel. Figure 5.0 indicates the piston fleet basic categories of certificated and non-certificated aircraft.

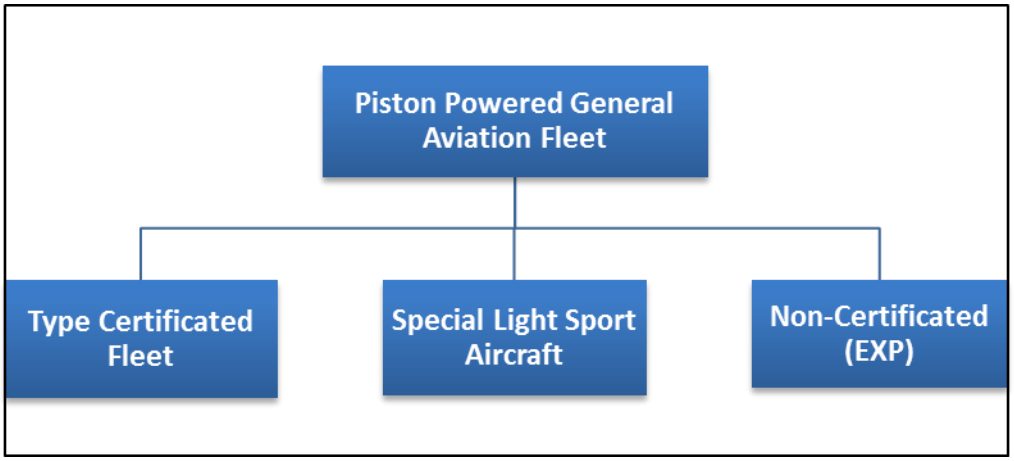


Figure 5.0 –Piston Powered General Aviation Fleet Categories

Type Certificated Fleet

Certification issues relative to the type-certificated fleet are described above in the certification discussion (Section 3.4). Approval mechanisms for use of a new unleaded AVGAS may involve one or more of the following.

- Change to type certificate for in-production aircraft/engines
- Manufacturer approval via Information Service Bulletins for legacy fleet
- Other FAA approval method providing blanket approval of engines and airframes
- FAA STC approval by industry sponsors if equivalency to 100LL cannot be demonstrated or manufacturer approval via TC change is not available

Orphaned Type-Certificated Fleet

The General Aviation piston fleet includes a significant group of FAA certified engine and aircraft where, although the TC holder may remain active, the product is no longer supported by the TC holder. The orphaned category may also include engine and aircraft products where the TC has been abandoned or the DAH TC/Production Certificate (PC) holder is no longer active. Orphaned type-certificated aircraft are limited to using the fuel specified on their type certificate or a fuel deemed by the FAA to be acceptable. A broad based FAA approval process, individual STCs, or some combination of the two would likely be required to transition these legacy orphaned type-certificated aircraft to a new unleaded fuel.

Type-Certificated Fleet Modified by Supplemental Type Certificate

Many aircraft in the General Aviation piston fleet have been modified by STC over the years. Of particular concern relating to the transition to an unleaded AVGAS are aircraft that have received STC modifications to the engine installation. These modifications can range from "bolt-on" changes to the induction, ignition, or exhaust systems, to complete firewall forward replacements of the original engine installation. Cessna estimates that in the past 20 years, as many as 3,000 to 4,000 Cessna piston engine aircraft in the U.S. registered fleet (approximately 5% of the U.S Cessna fleet) have received STCs that have either completely replaced the originally certified engine installation, or modified the original engine to a significantly different build standard. It is unknown how many additional Cessna piston engine aircraft have received STCs that modify the factory engine installation without changing the build standard of the factory-installed engine. A similar situation is present across the entire General Aviation fleet from the major manufactures past and present.

This creates the following challenges for an unleaded AVGAS transition:

- The variety of aircraft and engine combinations is much greater than an examination of the FAA registration and type certificate databases would indicate.
- Many engine STCs are done to increase performance of the aircraft, and in many cases replace engines that are more tolerant of a variety of fuels, including lower octane fuels, with engines that are more dependent on high octane fuels.
- The technical data to support a transition of aircraft equipped with engine STCs resides with a diverse base of General Aviation aftermarket modification companies with varying levels of technical expertise and financial resources to support their STCs through a transition. Many STC holders are no longer in existence.
- Owners who install engine STCs generally use their aircraft more and invest in them at a higher level than owners of unmodified aircraft. A transition to a non-drop-in unleaded fuel could potentially have a higher economic impact on this group of owners.

Special Light Sport Aircraft (S-LSA)

In recent years a new category of manufactured recreational aircraft, Special Light Sport Aircraft (S-LSA), have evolved that do not hold type certificates in the traditional sense but rather are shown by the manufacturer to conform to industry consensus standards. These aircraft are unique in the sense that they cannot be legally modified without the express approval of the manufacturer and therefore it falls solely on the manufacturer to approve the use of a new fuel in their aircraft. Changes cannot be legally accommodated by STC or other means. In instances where there is no longer a manufacturer supporting in-service S-LSA aircraft, the aircraft loses its S-LSA airworthiness certification status and is issued an experimental airworthiness certificate in the E-LSA category with all of the attendant operational limitations that accompany E-LSA experimental certification. At this point the aircraft is treated like any other aircraft certificated in the experimental category (such as amateur-built) and modifications including fuel use is at the discretion of the owner/operator.

Most S-LSA aircraft are certificated to operate on low octane unleaded fuels as well as 100LL so are not critical applications for a high octane future fuel. The primary considerations for this fleet will likely not be performance but rather materials compatibility assurance and actual final approval for use.

Non-Type-Certificated Experimental Fleet

There are a large number of non-type certificated aircraft in the fleet that are not supported by a DAH manufacturer. These aircraft are certificated in the Experimental category. This fleet is wide ranging in terms of performance, octane requirement, size, age and materials. This fleet includes amateur built aircraft, former military aircraft that were not certificated under civilian standards, imported aircraft, and aircraft used for other experimental purposes. Amateur built aircraft alone comprise more than 33,000 registered aircraft making them a significant portion of the General Aviation fleet. Experimental aircraft have no regulatory requirement to operate on a particular fuel provided the owner determines the fuel to be suitable.

The following are principle assessments that should be performed relative to evaluation of use of a new fuel in the Experimental fleet.

1) Composition and size of the fleet
2) Technical challenges in operating these airplanes using a new unleaded fuel
3) FAA fleet data (group of engines) should be made available to the end consumer (experimental category) and type clubs to enable the owner/operator to determine the impact of any new fuel
4) Economic impact of any new fuel on the Experimental fleet should be included in any total aviation industry economic impact assessment

3.5. Aircraft & Engine Technical Issues

3.5.1. Aviation Gasoline Performance Requirements

There has been extensive testing to find a fuel that meets all of the current ASTM D910 leaded aviation gasoline specification properties for 100LL, satisfies the safety and performance requirements of engines and aircraft, is compatible with the existing infrastructure, and poses no additional compositional issues. The fuel specification, which is listed in the Type Certificate Operating Limitations, is a key component of engine and aircraft certification.

Typically, aviation fuel specifications set forth performance criteria in the following seven categories.

1. Combustion
2. Fluidity
3. Volatility
4. Corrosion
5. Contaminants
6. Additives
7. Stability

For example, anti-knock performance is a combustion category performance requirement. Unleaded fuels typically require the addition of significant amounts of specialty chemicals to meet the same anti-knock performance that can be attained from addition of a relatively small amount of TEL. These proposed high octane chemical additions often include heavier molecules with higher boiling points. They often produce fuel blends that exceed many other current aviation gasoline specification limits when they are added in the quantity necessary to meet the same anti-knock performance of leaded fuels. The legacy fleet was designed to operate safely on fuels that met these specification property limits, with each fuel property addressing a different safety, performance or operability characteristic. It is unknown what impact changes to these specification properties will have on the safety, operability and performance of engines and aircraft.

In addition to the properties listed above, there are additional critical fuel properties that determine whether the fuel is fit for the purpose it was intended, such as:

- Co-mingling/compatibility of the fuel with the fleet infrastructure and existing fuel
- Other combustion issues, such as flame speed
- Other fluidity issues, such as latent heat of vaporization

The safety, performance, and operability impacts of the above discussed specification and fit for purpose properties on engine and aircraft performance are shown with more detail in Appendix H.

The areas of greater concern for any new proposed unleaded fuel requiring additional extensive testing are directly related to the composition of the proposed new fuel. Complex or novel fuels may produce additional areas of concern due simply to their significantly different nature.

3.5.2. Unleaded Aviation Gasoline Anti-Knock Performance

Octane is one of the most important parameters for a replacement unleaded aviation fuel. Extensive historical testing has indicated a difference in full-scale engine detonation performance between unleaded and leaded aviation fuel of equivalent motor octane number. Fuel motor octane number is determined from an ASTM single cylinder test that was originally designed for leaded fuels and it provided a high degree of predictability of fuel anti-knock performance in a full-scale engine. Further, the addition of a relatively small amount of the lead additive TEL to aviation alkylate provides significant octane increase to the base fuel, which can only be equaled in the absence of TEL by the addition of significant amounts of specialty unleaded chemicals to the base fuel.

Appendix H contains a presentation that illustrates these complex detonation chemical reactions. The presentation provides detailed explanation of why the TEL based additive provides superior anti-knock effectiveness.

3.5.3. Aviation Gasoline Property Trade-offs with Octane Number

Some of the aircraft safety, performance, and operability issues that may be impacted by replacing the current 100LL with an unleaded fuel are as follows.

- Detonation
- Cooling Airflow
- Fuel Consumption
- Performance
- Restarts
- Cold/Hot Fuel
- Icing
- Min Climb Gradient
- Engine Out Performance (Twins)
- Ceiling
- Go Around
- Payload
- Noise
- Takeoff

Removal or reduction of the TEL additive in current aviation gasoline results in significant reduction in fuel octane values. Attempts to increase the unleaded fuel octane or pursue novel unleaded fuel compositions have typically included the use of significant amounts of novelty or specialty chemicals. The higher the unleaded fuel octane requirement for any future fuel, the greater the complexity of the unleaded fuel blend. A trade-off ensues between engine and aircraft performance and the compatibility of the fuel with the current distribution infrastructure, existing fuel, and current fleet infrastructure. Attempts to reduce the fuel octane and move the fuel closer to the octane of the existing base alkylate increases the issues related to the engine and aircraft safety and performance. In short, the greater the compositional deviation of the proposed unleaded fuel from the current aviation gasoline composition, in attempting to meet the performance, operability and safety of the existing engines and airframes, the greater the impact on distribution infrastructure, comingling with the existing fuel, and current fleet infrastructure compatibility issues. The closer the unleaded fuel composition is to the existing aviation gasoline composition, in attempting to meet the distribution infrastructure, existing fuel, and current fleet infrastructure compatibility requirements of a new unleaded fuel, the lower the motor octane number of the fuel and the greater the impact on engine and aircraft safety and performance issues.

Appendix H contains a presentation that illustrates the trade-off of fuel complexity with fuel octane requirement.

3.5.4. Aviation Gasoline Conclusions

As previously stated, the motor octane of a fuel is significantly impacted by removal of the TEL additive. Fuel motor octane is determined by a single cylinder ASTM standard test and for leaded fuels the value obtained provides a high degree of correlation with the full-scale engine anti-knock performance. However, for unleaded fuels using chemical components such as aromatics or aromatic amines to boost anti-knock capability, the motor octane number (MON) of the fuel may not translate to a predictable engine anti-knock performance. There are a

number of detonation issues that will need testing and evaluation to address. These issues are listed below. A more detailed breakdown of the following issues can be found in Appendix H.

- Unleaded fuels possessing the same MON as leaded fuels (that defines a given engine minimum octane requirement) may not provide a full-scale engine the octane performance it requires.
- Use of mixtures of high octane chemical components may result in significant antagonistic and synergistic effects of octane response.
- An unleaded fuel possessing a supercharged rich (SR) octane value that is equivalent to or greater than a leaded fuel that is known to satisfy a given full-scale engine, may not provide the same engine the octane performance that the engine requires.
- FAA AC 33.47-1, providing guidance for detonation testing, includes outdated test equipment and analyses methods.
- Detonation instrumentation and combustion instability measurement methods have not been standardized or correlated among the FAA Tech Center, engine DAHs, and others.
- There is no agreement on what constitutes limiting detonation among FAA Tech Center researchers, engine DAHs, and others.
- Detonation onset response for unleaded fuels is different from leaded fuels and can affect detonation margin.
- A significant percentage of engines and airframes may require modifications to compensate for the reduced octane performance of unleaded fuels.

3.6. Production & Distribution Issues

Any effort to transition the aviation industry toward an unleaded fuel raises concerns relating to the production and distribution of a new fuel. In recognition of this fact, the charter establishing the UAT ARC specifically required the committee to address factors relating to production and distribution infrastructure when performing its analysis of issues involved in transitioning to an unleaded AVGAS.

AVGAS is a blended petroleum product that is produced using typical and traditional refining processes. Currently, nine refiners across the U.S. produce AVGAS, although often only in limited runs at specific times of the year. As an aviation fuel, AVGAS is subject to certain quality control procedures, such as dedicated tankage and piping, which require refineries to ensure that aviation fuels are completely segregated from other products.

After production, AVGAS enters the distribution system, which, as opposed to being a fixed system that moves a product to market by well-defined routes and transportation systems, is a

flexible system utilizing barges, rail cars, and over the road transport trucks. Typically, AVGAS will leave the refinery via rail car for eventual delivery to a terminal. At the terminal, the AVGAS is stored until loaded onto an over-the-road truck for final delivery. However, the AVGAS may be transported from the refinery via barge to a terminal or to railcars. Also, the terminal storage and delivery may be completely skipped and over-the-road trucks loaded directly from railcars by a process known as trans-loading. The final step in the distribution chain is on-airport storage from which the fuel is either directly delivered to aircraft or loaded into mobile refuelers that then refuel aircraft. In Alaska and other remote regions, AVGAS may be flown in barrels to outlying airports and landing facilities.

The signature quality of the AVGAS distribution system is its flexibility, allowing AVGAS to be transported from the limited number of production facilities to the over 5000 airports across the country that sell aviation gasoline.

Early discussions focused on identifying any systematic obstacles inherent in the existing production and distribution system that would prevent the adoption of a lead free AVGAS. The UAT ARC found that there were not any generalized systematic issues that prevent the production and distribution of a lead free AVGAS. Existing refinery technology and infrastructure combined with the existing distribution system is currently capable of providing a lead-free AVGAS; however, that fuel would only satisfy a limited percentage of the fleet. The UAT ARC recognized that production and distribution issues would occur as fuel developers attempted to craft a new fuel that would address a greater percentage of the existing fleet. These impacts would be specific to any newly proposed fuel and have the potential to be highly variable between fuels. New fuels that closely followed existing production methods and composition of AVGAS would pose little to no production and distribution impact while novel fuels that utilized new production methods and a significantly different composition could pose a very large impact. Since the impacts would be based on the specifics of any newly proposed fuel, the UAT ARC steered away from attempting to develop mitigation strategies for hypothetical impacts and focused on developing a structure for ensuring that the impact arising from newly proposed fuels could be identified in a manner that allowed the industry to assess adequately the impact arising from changes to the existing production and distribution systems required to utilize those fuels.

Three basic issues related to production and distribution impact were defined as follows.

1. There is no existing method of determining the production and distribution impact posed by a new fuel.
2. There is no standardized method for communicating to the industry the impacts posed by a newly proposed fuel.
3. There are multiple third party regulations, standards and codes that may impact the deployment of any newly proposed fuel.

3.6.1. Impact Assessment

Since production and distribution issues are not tied to the existing system but rather to the particularities of any new proposed fuel, the UAT ARC did not attempt to quantify any impact but rather develop a system that would ensure that those impacts were properly identified.

From a production standpoint, four areas were identified that should be addressed to ensure the impact is accurately addressed.

1. Feedstock Issues
2. Production Pathway Issues
3. Production Facility Issues
4. Quality control during production scale-up

Impacts that need to be determined from a distribution standpoint include the following.

1. *Materials compatibility* - If an unleaded replacement fuel to be found incompatible with some portion of the existing distribution system, including base metals, seals or transfer components, alternative components would need to be developed and installed prior to distribution of the new fuel.
2. *Geographic Impact* - If a new fuel could only be produced in one geographic location, there would be an impact upon the distribution system that would need to be determined.
3. *Fuel Compatibility* - If a new fuel is not compatible with existing AVGAS, individual aircraft, tanks, and distribution systems would need to be segregated to ensure the two fuels did not come into contact, this would create an impact that would need to be addressed.
4. *Storage Stability* – Due to the low volume of AVGAS consumption relative to other petroleum products, AVGAS is produced in short runs and stored for long periods. AVAS is a very stable product. The ability of an unleaded replacement fuel to be stored for prolonged periods while retaining all of its specification requirements will need to be assessed.

3.6.2. Communication of Distribution System Changes

Currently, no standardized method to communicate potential impacts of a new fuel(s) on the distribution network to the industry exists. The UAT ARC believes that it will be necessary to develop standardized methods for communicating any change to the industry. This would facilitate decision making by industry stakeholders on methods to eliminate miscommunication and potential adverse flight safety conditions related to miss-fueling, improper handling and storage or materials compatibility.

3.6.3. Third-Party Regulations, Standards and Codes

The distribution, sale and use of aviation gasoline are currently controlled by a number of third-party regulations, standards and codes. These standards are created and maintained by

organizations and local, state and federal agencies covering everything from fire safety, occupational health, and the markings that are applied to storage tanks and piping. Any new fuel will present the possibility that these regulations, standards or codes will need to be modified or adapted based upon the specific properties and composition of the proposed fuel.

3.7 Environment & Toxicology Issues

General Aviation has come under scrutiny due to the use of the TEL additive in the current 100LL aviation gasoline. New fuels should be assessed for their environmental, toxicological and emissions properties relative to current fuels. Testing will need to address additional areas of concern, that are not covered by the current specification, important to ensuring that any new proposed fuel does not worsen environmental impact. For this reason bulk gas, air toxic gas engine emissions testing, and fuel toxicity testing may be needed. The extent of the testing is directly related to the complexity of the proposed unleaded fuel.

For instance, fuel developers and the General Aviation community should be made fully aware early in the process if a new fuel is proposed that may contain metallic additives to boost octane or substances like methyl-tertiary butyl ether (MTBE) which has been banned as an automotive fuel additive in numerous states. This ensures a more informed decision regarding possible adoption, handling and use, and consideration of approaches to mitigate the potential impact upon environment and/or health. Likewise, if a new fuel is proposed that is very similar to current, petroleum based fuels, it may be considered to present less risk in terms of its long-term future availability with respect to environmental and handling considerations. Preference might also be considered for renewable and sustainable alternative fuels that do not come from traditional fossil sources, in order that they may help meet national goals for the purposes of energy security, price stability, and environmental benefit.

Several environmental actions have recently led to increased pressure to remove lead from AVGAS. In 2006, Friends of the Earth (FOE) petitioned the EPA to: 1) make a finding under the Clean Air Act (CAA) that lead emissions from General Aviation aircraft engines cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare and issue proposed emission standards for such lead emissions or, alternatively, 2) if the Administrator of EPA believes that insufficient information exists to make such a finding, commence a study and investigation under the CAA of the health and environmental impacts of lead emissions from General Aviation aircraft engines, including impacts to humans, animals and ecosystems, and issue a public report on the findings of the study and investigation. In response to the FOE petition, the EPA has undertaken studies to inform issues of lead emissions and exposure resulting from the use of leaded AVGAS in General Aviation, and has published two notices in the Federal Register describing the agency's progress to date. The EPA continues to evaluate the data and issues, and has not yet issued a final response to FOE's petition.

In a separate action, in 2008, the EPA revised its National Ambient Air Quality Standards (NAAQS) for lead, tightening the NAAQS by a factor of ten. Related to the NAAQS revision, the EPA also promulgated regulations that require lead monitoring by local air monitoring agencies at airports with lead emissions greater than one ton and at 15 additional airports where there is

a high volume of piston engine aircraft operations and annual lead emissions of 0.5 to 1.0 tons per year. The data from these monitors will be used to evaluate compliance with the NAAQS for lead and will also be used by EPA to assess the need for additional lead monitoring at airports. If ambient air near an airport was found to be exceeding the NAAQS, there would be limits under federal law as to the measures a state could propose to adopt to limit lead emissions from General Aviation aircraft operations. See Appendix I for additional background information on the CAA, the NAAQS, and EPA and FAA authorities related to the regulation of aircraft fuel and emissions standards. Appendix J contains the General Aviation Coalition's response to the EPA Advance Notice of Proposed Rulemaking (ANPR).

Separate from activities focused on the possible public health and environmental effects of lead emissions from General Aviation aircraft engines, it is also noted that General Aviation is the only remaining user of lead additives in the U.S. transportation sector.

Although lead emissions from piston engine aircraft are not currently subject to CAA standards, a description of the statutory responsibilities between the EPA and FAA that are pertinent to AVGAS and lead emissions under the CAA and U.S. Code has been provided in Appendix I. In summary, the EPA is authorized under section 231(a)(2)(A) of the CAA (42 U.S.C. § 7571(a)(2)(A)) to determine if aircraft engine lead emissions cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare (referred to here as the "endangerment finding"). If EPA makes a positive endangerment finding, then EPA would be required under CAA section 231(a)(2)-(3) to prescribe standards applicable to the emissions of lead from General Aviation engines, and the Secretary of Transportation would be required under CAA section 232 to prescribe regulations to ensure compliance with such standards (42 U.S.C. § 7572). In addition, the FAA would be required under section 44714 of the U.S. Transportation Code to prescribe standards for the composition or chemical or physical properties of AVGAS to control or eliminate aircraft lead emissions (49 U.S.C. § 44714). In the evaluation and setting of any new standards, the EPA and FAA must work in consultation so that necessary and appropriate considerations are given to safety, noise, and the ability and time needed to implement new technology.

The level and types of screening or testing required for candidate fuels will depend upon the exact nature of the fuel being proposed. Fuels that have novel additives or components and that are less like current, petroleum-based fuels should be given close attention. Compositional data and Material Safety Data Sheets about the candidate fuels should be made available early in the fuel development and approval process so that they may be assessed from an environmental and toxicological perspective with respect to current fuels. In addition, changes in emissions should be assessed and characterized through engine testing as early as possible in the research and development phase. Fundamental emissions test data can be obtained through the FAA Tech Center in conjunction with other engine testing during the research and development phases. If the capability for more advanced testing is needed, this may be performed through coordination with the EPA or a contractor.

4. UAT ARC Recommendations

4.1. Summary of UAT ARC Recommendations

The following is a summary of the recommendations made by the UAT ARC to support the development and transition to an unleaded aviation gasoline. The recommendations were developed with the strategic recognition that the fuels industry, engine/aircraft DAHs, regulatory authorities, and owner/operators must work together in a coordinated way if we are to develop a new unleaded aviation gasoline that will have the least impact to the existing fleet and the production and distribution infrastructure. The broad-based approval of a novel composition fuel is unprecedented in the fleet; this led the UAT ARC to develop an integrated and structured process for bringing a fuel from concept to full transition. As outlined in Section 3, there are many barriers to market entry for a new fuel. This structured process is designed to lower the barriers to the fuel entering the marketplace. Further discussion follows in Section 4 providing additional insight into the structured process and the recommendations.

4.1.1. Key UAT ARC Recommendations

1) *The UAT ARC recommends* implementation of the "Fuel Development Roadmap – AVGAS Readiness Levels (ARL)" developed by the UAT ARC that identifies the key milestones in the aviation gasoline development process and the information needed to support assessment of the viability of candidate fuels in terms of impact upon the existing fleet, production and distribution infrastructure, environment and toxicology, and economic considerations. (See Section 4.2.1)

2) *The UAT ARC recommends* centralized testing of candidate unleaded fuels at the FAA William J. Hughes Technical Center (Tech Center) funded by government and industry in-kind contributions. Centralized assessment and testing would generate standardized qualification and certification data that can be used by the fuel developer/sponsor to support both ASTM specification development and FAA fleet-wide certification eliminating the need for redundant testing. (See Section 4.3)

3) *The UAT ARC recommends* the establishment of a solicitation and selection process for candidate unleaded aviation gasolines for the centralized fuel testing program. This process should include a FAA review board with the technical expertise necessary to evaluate the feasibility of the candidate fuel. (See Section 4.3.2)

4) *The UAT ARC recommends* the FAA establish a centralized certification office with sufficient resources to support unleaded aviation gasoline projects. (See Section 4.4)

5) *The UAT ARC recommends* the establishment of a collaborative industry-government initiative referred to as the Piston Aviation Fuels Initiative (PAFI) to implement the UAT ARC recommendations in this report designed to facilitate the development and deployment of an unleaded AVGAS with the least impact on the existing piston-engine aircraft fleet. The overall objective of this initiative is to identify candidate unleaded

aviation gasolines, to provide for the generation of qualification and certification data on those fuels, and to support fleet-wide certification of the most promising fuels. (See Section 4.5)

4.1.2. Additional UAT ARC Recommendations

6) *The UAT ARC recommends* the use of a consensus standard peer review process as an integral and required element of the UAT ARC's recommendations. ASTM is the historically accepted consensus body for aviation fuels and is the practicable and accepted means to universally produce and distribute aviation gasoline as a commodity. (See Section 4.6.1)

   NOTE: Appendix L, "UAT ARC Member Dissenting Opinion & ARC Response", includes a dissenting opinion submitted by a UAT ARC member that is directed at the above recommendation. A response to that submittal prepared by the UAT ARC is also provided in this appendix.

7) *The UAT ARC recommends* the completion of the new ASTM "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives". This standard will significantly reduce the uncertainty, risk, timeline and cost to developers or sponsors of new unleaded aviation gasolines by describing the test and analysis requirements necessary to generate data to support the development of a new ASTM specification. (See Section 4.6.1.1)

   NOTE: Appendix L, "UAT ARC Member Dissenting Opinion & ARC Response", includes a dissenting opinion submitted by a UAT ARC member that is directed at the above recommendation. A response to that submittal prepared by the UAT ARC is also provided in this appendix.

8) *The UAT ARC recommends* development of specialized test procedures to support centralized testing of candidate unleaded aviation gasolines. The specialized test procedures will be used by the FAA Tech Center to generate fuel property data and engine/aircraft performance data necessary to support ASTM specification development and certification approval of existing engines and aircraft that can operate transparently using a new unleaded aviation gasoline. (See Section 4.6.2)

9) *The UAT ARC recommends* the development of specialized certification guidance to support the centralized certification of unleaded aviation gasoline. The certification guidance should define the applicable certification basis and compliance requirements for Part 33 reciprocating aircraft engines, Part 23 airplanes, and Part 27/29 rotorcraft and should provide acceptable methods of compliance to assess and qualify expected differences in fuel properties, performance and composition from 100LL. (See Section 4.6.2)

10) *The UAT ARC recommends* that the FAA Centralized Certification Office coordinate with the FAA Tech Center to develop certification test plans, conformity requirements, and test witnessing protocols that are acceptable for certification of unleaded aviation gasoline/s participating in the centralized testing. (See Section 4.6.2)

11) *The UAT ARC recommends* that methods and/or guidelines be developed to assess the impact of a candidate unleaded aviation gasoline on the existing fleet, including the need for proposed aircraft/engine modifications that could mitigate those impacts. (See Section 4.7.1)

12) *The UAT ARC recommends* that methods and/or guidelines be developed to assess the impact of a candidate unleaded aviation gasoline on the existing production and distribution infrastructure. (See Section 4.7.2)

13) *The UAT ARC recommends* the identification of appropriate environment and toxicological issues that a candidate unleaded aviation gasoline should be assessed against. (See Section 4.7.3)

14) *The UAT ARC recommends* the FAA develop specialized policy and procedures to facilitate the most efficient approach possible for fleet-wide approval of aircraft and engines to use a new aviation gasoline. Fuel qualification and certification data from the centralized FAA fuel test program would support fleet-wide approval of the "in-scope" fleet of aircraft that can operate transparently on an unleaded aviation gasoline. (See Section 4.8)

15) *The UAT ARC recommends* that a mechanism be developed to mitigate the liability exposure of design approval holders (DAH) due to modification of the type design of their products in approving a new aviation gasoline. (See Section 4.8.1)

16) *The UAT ARC recommends* that the centralized FAA test program and the centralized FAA Certification Office support the approval of key aircraft and/or engine modifications that will allow the largest portions of "out-of-scope" aircraft and engines to operate with a new unleaded aviation gasoline. The FAA would have to develop procedures/guidance to facilitate certification of the out-of-scope aircraft/engines requiring modifications. (See Section 4.8.4)

17) *The UAT ARC recommends* that the FAA, working with industry, develop a deployment and transition plan and timeline only after unleaded aviation gasoline(s) with least impact upon the piston-engine aircraft fleet has been identified and a process for fleet-wide approval to use the new fuel in aircraft has been clearly established. Any FAA action should support the efforts of the industry to transition to unleaded aviation gasoline(s) in a safe and orderly manner. (See Section 4.9.1)

18) *The UAT ARC recommends* that the FAA and EPA continue to coordinate closely with stakeholders and take into consideration implementation of the UAT ARC's recommendations in any potential rulemaking efforts. Consideration must be given to safety, costs, and the ability and time needed to implement new technology. (See Section 4.9.2)

19) *The UAT ARC recommends* the FAA establish a line item in its annual 2013-2020 budget requests to fully support the UAT ARC recommendations for PAFI which includes centralized FAA fuel testing to support the development of an ASTM unleaded aviation gasoline specification and fleet-wide certification approval. (See Section 4.9.3)

4.2. Fuel Development Roadmap

The UAT ARC was tasked with identifying the key issues and obstacles to the development, certification and deployment of an unleaded aviation gasoline with the least impact upon the existing piston engine fleet of aircraft, and to develop recommendations to overcome those obstacles. Several recommendations discussed in this report address some of the technical and process issues designed to reduce the overall uncertainty, risk and cost of developing an unleaded AVGAS. But, in order to facilitate a successful initiative, the UAT ARC recommendations must also address the overarching economic and market issues affecting the business case for fuel producers and aviation equipment manufacturers to invest in the development and deployment of an unleaded replacement for high octane aviation gasoline.

The UAT ARC believes it is essential to establish a "Fuel Development Roadmap" which identifies the key milestones in the aviation fuel development process and information necessary to address the technical issues related to ensuring aviation safety as well as market and economic issues related to deployment. Development of this "roadmap" serves several roles, all with the fundamental purpose of ensuring that a new unleaded fuel is developed in a manner that replicates the existing performance and safety characteristics of leaded AVGAS or clearly identifies the areas where those characteristics are not matched and how they are to be addressed.

1. *Facilitation of Development* – The recommended roadmap will serve to inform prospective replacement fuel producers of the numerous factors that need to be considered and accounted for in an aviation fuel development endeavor.
2. *Communication Standard* – By creating a standardized process for development of a fleet-wide replacement AVGAS, a "roadmap" would allow for standardized communication about development progress within the industry and General Aviation community. Specifically such a roadmap would provide guidance to fuel developers on the criteria that would need to be evaluated in order to perform various assessments on the impact to the industry of the new fuel. This data could then be utilized by others to determine the "viability" of the fuel under development.
3. *Process Standard* – A "roadmap" would also serve as a standard by which parties could evaluate multiple unleaded aviation gasolines on a level playing field. The nature of the

"roadmap" would work to standardize data and information presentation so that fair and accurate comparisons could occur.

4.2.1. AVGAS Readiness Levels (ARL)

The UAT ARC has begun the process of defining a framework for a fuel development roadmap. The Commercial Aviation Alternative Fuels Initiative (CAAFI) concept of jet "fuel readiness levels (FRLs)" has been evaluated and applied by the UAT ARC to the unique needs of aviation gasoline development and definitive AVGAS Readiness Levels (ARLs). The resulting AVGAS ARLs are specifically designed to facilitate the development of a **non-drop-in fleet-wide replacement unleaded aviation gasoline**, and as such do not represent every possible approach for developing and bringing to market an aviation gasoline. All of the recommendations in this report to facilitate the development and deployment of unleaded AVGAS support the following roadmap ARLs.

Unleaded AVGAS Transition Fuel Development Roadmap
AVGAS Readiness Levels (ARL)

ARL	Title	Description	Deliverable
1	**Fuel Definition**	Utilize data developed during experimentation phase to establish process elements and parameters (such as reactor hardware and catalyst materials) and fuel compositional definition by GC analysis.	Fuel sample and report including process flow diagram and fuel compositional analysis
2	**Material Safety Review**	Initial review of candidate fuel composition relative to published guidance on material safety with respect to environmental and safe handling considerations. Develop Material Safety Data Sheet (MSDS).	MSDS and other data as needed
3	**Basic Fuel Properties and Composition**	Intended to support initial engagement with ASTM to form Task Force. Lab analysis of fuel sample to identify composition and measure key Fit-For-Purpose properties per test methods defined in ASTM International Standard Practice, "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives" : ▪ Motor Octane Number (detonation) ▪ Vapor Pressure (starting, vapor lock) ▪ Freezing Point (high-altitude operation) ▪ Corrosion, copper strip (metal fuel system components) ▪ Oxidation stability (gumming) ▪ Water reaction (hygroscopic effect) ▪ Electrical conductivity (fuel handling) ▪ Distillation curve ▪ Initial material compatibility testing	Independent lab analysis report(s), report how the fuel was produced (blending purchased components, lab scale production, etc.)

Unleaded AVGAS Transition Fuel Development Roadmap AVGAS Readiness Levels (ARL)			
ARL	**Title**	**Description**	**Deliverable**
4	**Preliminary ASTM Research Report**	Compile data derived from laboratory analysis of candidate fuel in accordance with Section 6.2 of ASTM International Standard Practice, "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives". This data will include: ▪ Basic Specification properties ▪ Compositional analysis ▪ Preliminary Fit-For-Purpose (FFP) Properties ▪ Preliminary Materials Compatibility Assessment ▪ Information from preceding ARLs	Preliminary ASTM Research Report
5	**ASTM Test Specification**	ASTM Test Specification defines the properties of the fuel for subsequent testing and analysis.	Issued ASTM Test Specification
6	**Preliminary Feasibility Assessment**		
6.1	**Preliminary Production and Distribution Assessment**	Analyze current AVGAS production and distribution infrastructure to identify gaps in current system and develop preliminary plan to address gaps and to scale-up production and distribution to commercially viable volumes.	Report
6.2	**Environmental & Toxicology Assessment**	Review candidate fuel composition with consideration to use and handling from an environmental perspective, including OSHA, EPA and other regulatory entities.	Report with compositional data, MSDS, environment and toxicology assessment, and other relevant environmental data.

Unleaded AVGAS Transition Fuel Development Roadmap AVGAS Readiness Levels (ARL)			
ARL	**Title**	**Description**	**Deliverable**
6.3	**Preliminary Business Plan**	Provide a business plan that addresses the following: a) Scope of Solution: Describe the fuel, engine/aircraft hardware and operational concept proposed. If hardware or operational changes are proposed summarize and characterize in accordance to CFRs as minor, major or model changes. b) Production Concept: Describe how the candidate fuel composition can be scaled up and commercialized. Include summary of fuel production process flow and related hardware c) Applicability: Define fleet satisfaction concept relative to either actual aircraft cross section as defined in the FAA Aviation Fuels Reciprocating Engine Aircraft Fleet Fuel Distribution Report or BMEP/detonation propensity as defined by TBD document. d) Cost: Describe market cost of proposed solution inclusive of recurring cost/volume and non-recurring associated with hardware or operational limitation changes. e) Implementation: Describe defined or to-be-defined strategic partnerships, financing strategies, infrastructure leveraging opportunities, distribution strategies and other relevant details facilitating path to market. f) Deployment Concept: Describe whether the proposed fuel is miscible and fungible with 100LL. Does the solution require a separate distribution and control system? g) Intellectual Property: Declare IP associated with the Scope of Solution and how stated IP is protected or public domain considerations.	Report
7	**Initial Pilot Production Capability**	Scale-up lab production capability, and define production process flow and hardware for novel production capability requirements.	Fuel sample produced by the defined process
8	**Final ASTM Research Report**		
8.1	**Final ASTM Research Report – Part 1**	Compile data derived from laboratory analysis and of candidate fuel in accordance with Section 6.3 of ASTM International Standard Practice, “Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives”. This data will include: ▪ Final Fit-For-Purpose (FFP) Properties ▪ Final Materials Compatibility Assessment	Report

Unleaded AVGAS Transition Fuel Development Roadmap AVGAS Readiness Levels (ARL)			
ARL	**Title**	**Description**	**Deliverable**
8.2	**Final ASTM Research Report – Part 2**	Compile data derived from equipment testing of candidate fuel in accordance with Section 6.3 of ASTM International Standard Practice, "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives". This data will include: ▪ Engine Testing ▪ Aircraft Testing	Final ASTM Research Report
9	**ASTM Production Specification**	ASTM Production Specification defines the properties of the fuel and other criteria necessary for high-volume production and distribution.	Issued ASTM Production Specification
10	**Pilot Production Capability**	Scale-up initial pilot production capability, using the production process flow from the initial pilot production capability requirements (ref: ARL 7). Demonstrate the ability to produce at least 10,000 gals/yr (40,000 liters/yr).	Production Process Demonstration
11	**Airworthiness Certification**		
11.1	**Engine Certification Testing**	Completion of all rig, component and engine certification tests in accordance with compliance program established by the cognizant airworthiness regulatory authority.	Certification Test Reports
11.2	**Engine Certification**	Obtain certification approval from cognizant airworthiness regulatory authority.	Issued Amended or Supplemental Type Certificate(s)
11.3	**Aircraft Certification Testing**	Completion of all ground and flight testing in accordance with compliance program established by the cognizant airworthiness regulatory authority.	Certification Test Reports
11.4	**Aircraft Certification**	Obtain certification approval from cognizant airworthiness regulatory authority.	Issued Amended or Supplemental Type Certificate(s)
12	**Final Feasibility Assessment**		
12.1	**Final Production and Distribution Assessment**	Update preliminary report based on data and information developed during the fuel development.	Report
12.2	**Final Environmental & Toxicology Assessment**	Update preliminary report based on data and information developed during the fuel development. This may include testing for baseline emission data.	Report and MSDS
12.3	**Final Business Plan**	Update preliminary report based on data and information developed during the fuel development.	Report
13	**Initial Production Capability**	Scale-up pilot production capability, using the production process flow from the pilot production capability requirements for the large-scale (ref: ARL 10). . Establish production capability to produce at least 100,000 gals/yr (400,000 liters/yr).	Fuel inventory

Unleaded AVGAS Transition Fuel Development Roadmap AVGAS Readiness Levels (ARL)			
ARL	**Title**	**Description**	**Deliverable**
14	**Initial Limited-Scale Fleet Operations**	Introduce fuel on a regional basis to gain experience with commercial operations.	Coordinated plan with fuel distributors and fleet operators to demonstrate operational use of fuel
15	**Production Scale-up**	Construct facilities to produce at least 10,000,000 gals/yr (40,000,000 liters/yr).	Fuel inventory
16	**Wide-Scale Fleet Operations**	Fuel availability and usage over several geographic regions.	Coordinated plan to transition production, distribution, and use on a regional basis

These ARLs are specifically designed to identify the steps and information necessary to address all of the issues and challenges discussed in Section 3 of this report including market and economic issues as well as the assessment of the viability of candidate fuels in terms of impact upon the existing fleet, production and distribution infrastructure, and environment and toxicology. The ARL's are laid out in chronological order for a typical development project, however, it is in envisioned that fuel developers may approach various elements in a slightly different order to align with their own business needs.

1) *The UAT ARC recommends* implementation of the "Fuel Development Roadmap – AVGAS Readiness Levels (ARL)" developed by the UAT ARC that identifies the key milestones in the aviation gasoline development process and the information needed to support assessment of the viability of candidate fuels in terms of impact upon the existing fleet, production and distribution infrastructure, environment and toxicology, and economic considerations.

4.3. Centralized Testing at FAA William J. Hughes Technical Center

Aviation fuels are defined and controlled by industry consensus-based ASTM fuel specifications that specify the properties, performance, and composition necessary to provide a level of control to support large-scale production, distribution, and the conduct of commerce for use in aircraft. In addition, FAA regulations pertaining to aircraft, engines, and fuel recognizes and accepts the well-proven ASTM specifications to define and control the properties, performance and composition of aviation fuels. The FAA has not established specific airworthiness requirements for fuel or required design or production approval for fuel due to the dependability of ASTM specifications. FAA regulations require that a fuel grade or specification be identified as an operating limitation for each make/model type certificated aircraft and engine in order for them to be able to operate using the fuel.

The UAT ARC recommendations to facilitate the development and deployment of an unleaded AVGAS address both the development of a new ASTM specification and the use of that specification to accomplish FAA fleet-wide certification approval of the fuel. As discussed in Section 3 of this report, both the ASTM specification development and FAA certification processes are progressive and iterative in nature. The scope of applicable data requirements for these processes and extent of testing that may be necessary grows with increasing degree of divergence from the properties, performance, and experience with existing 100LL. However, there are a significant number of identical or similar requirements and data needed to support the evaluation and qualification of candidate unleaded fuels through both the ASTM and FAA processes.

Ideally, fuel tests and generation of assessment data would be performed in such a way that it would be acceptable to support both ASTM specification development and FAA certification approval processes to the greatest extent possible. However, the UAT ARC recognizes that this poses significant challenges as the two processes and associated requirements are completely independent from one another. The FAA presently is not directly involved with fuel development programs and the data to support development of a fuel specification is not generated in accordance with 14 CFR Part 21 requirements for certification.

In addition, the UAT ARC discussed various concepts that would not only reduce the uncertainty and cost of fuel qualification and approval through the ASTM and FAA processes, but also address economic and market issues in order to incentivize businesses to pursue the development of an unleaded AVGAS. Considering the small size of the AVGAS market, significant diversity in the types of aviation products and operations, and importance of ensuring safety is not compromised; the UAT ARC concluded that centralized fuel testing through a collaborative industry-government process is the best approach to address the overarching issues.

> 2) *The UAT ARC recommends* centralized testing of candidate unleaded fuels at the FAA William J. Hughes Tech Center funded by government and industry in-kind contributions. Centralized assessment and testing would generate standardized qualification and certification data that can be used by the fuel developer/sponsor to support both ASTM specification development and FAA fleet-wide certification eliminating the need for redundant testing.

4.3.1. Benefits of Centralized AVGAS Test Program

The FAA Tech Center has established itself as the leading expert resource and world class capability for testing of aviation gasolines. A centralized FAA fuel testing program would utilize the FAA Tech Center to perform fuel property testing during fuel development stages and engine and aircraft equipment testing during fit-for-purpose fuel assessment and certification stages. A centralized AVGAS test program managed by the FAA would be able to generate standardized data in such a way that it can be used to support both the ASTM specification

development process and FAA certification approval process. This will provide for a more efficient and expeditious approach to the overall process for fuel development and support the qualification and certification of the most promising fuels.

In addition, a centralized AVGAS test program will offer the significant incentive to fuel developers/sponsors of government funded and industry in-kind contribution to test candidate unleaded AVGAS fuels. This approach also offers a significant benefit of testing candidate fuels in the same manner using the same equipment, instrumentation and test facilities. This will allow for more accurate comparisons of the results and fleet impact assessment.

4.3.2. FAA Solicitation & Selection Process

A centralized fuel testing program will require the establishment of an FAA solicitation process for prospective unleaded AVGAS producers to submit candidate fuels for testing. In the event that there are more candidates than program funding can accommodate, a selection process will need to be established in order for FAA to select a limited number of the most promising fuels for testing.

> 3) *The UAT ARC recommends* the establishment of a solicitation and selection process for candidate unleaded aviation gasolines for the centralized fuel testing program. This process should include a FAA review board with the technical expertise necessary to evaluate the feasibility of the candidate fuel.

4.4. FAA Centralized Certification Office for AVGAS Approvals

Applicants for a design and fuel approval have historically dealt with multiple FAA offices, such as ACOs and Directorates that may have had limited experience with AVGAS related certification projects. Continuing this pattern may lead to standardization issues affecting efficient and timely certification. In addition, the qualification and certification data generated during the FAA fuel testing program by the FAA Tech Center is intended to support certification approval for engines/aircraft to operate on the new fuel. This data will be generated using specialized test procedures and processes and the applicability or scope of certification for unleaded AVGAS approvals will be based on the resulting test data. Local geographic FAA offices will not be familiar with the specialized procedures used to generate data in the FAA test program and fleet-wide approaches to issuing approvals which may also lead to standardization issues affecting efficient and timely certification related to unleaded AVGAS projects.

> 4) *The UAT ARC recommends* the FAA establish a centralized certification office with sufficient resources to support unleaded aviation gasoline projects.

4.5. Establish Piston Aviation Fuels Initiative (PAFI) to Implement UAT ARC Recommendations

The UAT ARC has strived to identify the key issues and obstacles to the development, certification and deployment of an unleaded AVGAS with least impact upon the existing piston-engine aircraft fleet and develop recommendations to overcome those obstacles. While each of these recommendations has independent value in addressing the barriers to transitioning the industry to an unleaded-aviation gasoline, the UAT ARC recognizes that the best chance for success lies in a coordinated approach to implementation.

5) *The UAT ARC recommends* the establishment of a collaborative industry-government initiative referred to as the Piston Aviation Fuels Initiative (PAFI) to implement the UAT ARC recommendations in this report designed to facilitate the development and deployment of an unleaded AVGAS with the least impact on the existing piston-engine aircraft fleet. The overall objective of this initiative is to identify candidate unleaded aviation gasolines, to provide for the generation of qualification and certification data on those fuels, and to support fleet-wide certification of the most promising fuels.

4.6. Develop AVGAS Assessment & Qualification Guidance and Procedures

As discussed previously, the civil aviation industry has evolved to rely on a very limited number of well-proven, conventional fuels for the design, operation and certification of aircraft and engines. The AVGAS production and distribution system, controlled by industry consensus-based ASTM standards, and FAA safety regulations also evolved to rely on these available aviation fuels. All existing standards and corresponding assessment and qualification methodologies and guidance are structured to ensure that new aviation products can be safely operated using an existing aviation fuel. However, additional procedures and guidance for the assessment and qualification of the existing fleet of aircraft/engines to operate on a non-drop-in alternative to 100LL is needed to facilitate the development and deployment of an unleaded AVGAS. In addition, guidelines are needed to assess the viability of a candidate unleaded AVGAS from both a fleet impact perspective and fuel production and distribution perspective.

4.6.1. ASTM Fuel Properties and Performance

Aviation fuels are produced and handled as bulk commodities with multiple producers sending fuel through the distribution system to airports and aircraft. These fuels are defined and controlled by industry consensus-based fuel specifications; ASTM International D1655 for jet fuel and ASTM D910 for leaded aviation gasoline. These ASTM aviation fuel production specifications define the properties, performance, and composition necessary to provide a level of control to support large-scale production, distribution, and the conduct of commerce for use in aircraft.

6) *The UAT ARC recommends* the use of a consensus standard peer review process as an integral and required element of the UAT ARC's recommendations. ASTM is the historically accepted consensus body for aviation fuels and is the practicable and accepted means to universally produce and distribute aviation gasoline as a commodity.

4.6.1.1. *ASTM Standard Practice for the Evaluation of New Aviation Gasolines*

At present there are no ASTM guidelines or procedures for the development and qualification of a new aviation gasoline intended to be used by the existing fleet of aircraft as an alternative to ASTM D910 and/or 100LL. This situation results in significant uncertainty, business risk, and cost impact for potential unleaded AVGAS fuel developers.

In response to recommendations by industry, ASTM is currently developing a "*Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives*" which provides procedures to develop data for use in research reports to support the development and issuance of new or revised AVGAS specifications. The procedures, tests, selection of materials, engines and aircraft detailed in the standard practice document have been collaboratively developed by industry and the FAA reflecting their respective expertise in these specialized areas. This standard is intended to be used by developers or sponsors of new aviation gasolines or additives as an aid to determining and standardizing the data requirements necessary to support the review and qualification of these new products by ASTM members.

The draft standard describes laboratory and aircraft equipment test requirements to evaluate a new aviation gasoline intended to be used by an existing fleet of aircraft that was designed and certified to operate using another aviation gasoline (i.e. 100LL). It includes requirements that address the following subjects:

- Basic specification properties
- Fit-for-purpose properties (see below)
- Materials Compatibility
- Compatibility with other aviation gasolines and aviation piston-engine lubricants
- Aircraft component bench or rig testing
- Engine test cell evaluation
- Aircraft flight test evaluation

Of particular importance for the evaluation of a non-drop-in alternative to 100LL are the requirements for fit-for-purpose properties relating to engine and aircraft operability and performance as well as properties relating to fuel handling and distribution. These properties

are characteristics of an aviation fuel that are not controlled by the fuel specification or specification properties, but that are necessary for evaluation in addition to the specification properties to provide a comprehensive assessment of the suitability of an aviation fuel for use on aircraft and aircraft engines. The data generated during this testing should be compared to corresponding data for ASTM D910 100LL fuel properties and differences reconciled in the Research Report. See Appendix K for background on ASTM.

7) *The UAT ARC recommends* the completion of the new ASTM "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives". This standard will significantly reduce the uncertainty, risk, timeline and cost to developers or sponsors of new unleaded aviation gasolines by describing the test and analysis requirements necessary to generate data to support the development of a new ASTM specification.

4.6.2. FAA Specialized Test Procedures & Certification Guidance

FAA certification relative to aviation fuels is designed to evaluate the airworthiness of specific engine and aircraft models when operating on the candidate fuel, whereas the ASTM process described above is designed to evaluate the properties of the candidate fuel under prescribed conditions. The UAT ARC recognized the synergy between the two processes when a common set of technical data is generated to support both evaluations.

For example, the airworthiness standards for aircraft engines in 14 CFR Part 33 require that performance, operability, durability, and safety be evaluated throughout the full envelope of extreme conditions the engine is expected to encounter in service, including extreme cold/hot temperatures and altitudes. Fuel properties such as vapor pressure, freeze point and distillation curve directly affect these engine performance envelopes. The most important performance indicator for an engine is horsepower and the safety critical limiting factor is detonation. The octane level of AVGAS is a measure of protection against the onset of detonation so the higher the octane the higher the horsepower that is possible from a particular engine and vice-versa. While octane is evaluated during the ASTM qualification process, a specific regulation (14 CFR 33.47) requires a test program to ensure that an aircraft engine can operate without destructive detonation throughout its full range of operation.

Similar to engines, the airworthiness standards for aircraft in 14 CFR Part 23 and rotorcraft in 14 CFR Part 27/29 require demonstration of minimum aircraft performance requirements such as takeoff runway length, climb, speeds and distance over a range of conditions such as maximum weight/payload, maximum outdoor temperatures and airport altitudes up to 10,000 feet. The critical performance envelopes and operational safety limitations for an aircraft established by these tests are directly dependent upon the engine and its associated performance, which in turn is dependent upon the fuel properties.

In addition, 14 CFR parts 33, 23 and 27/29 require materials compatibility testing to substantiate that the fuel is compatible with all engine and aircraft materials to ensure that there are no safety and airworthiness impacts upon components and parts such as pistons, valves, turbochargers, carburetors, pumps, hoses, gaskets, seals, fuel tanks, structure, sealants etc. Materials compatibility will be dependent upon the fuel composition, which is evaluated by ASTM.

Just like the ASTM evaluation process, the certification procedure and testing requirements to approve an engine/aircraft to operate on a new fuel is progressive and iterative in nature, determined by the fuel properties, characteristics and test results revealed at each successive stage. The scope of applicable certification basis requirements and extent of testing that may be necessary grows with increasing degree of divergence from the properties, performance, and experience with existing 100LL. As discussed previously, a high octane unleaded AVGAS that is intended to meet the needs of the existing fleet is not expected to be a drop-in and, therefore, will likely have some differences in properties, performance and/or composition from 100LL. Aviation fuel has a direct and significant impact upon both the engine and aircraft performance and, therefore, compliance with the applicable FAA safety standards.

Consequently, great efficiencies could be realized by developing one portfolio of tests that could provide data to support both the ASTM process and FAA certification process. This requires that the new ASTM Standard Practice and the FAA regulations and guidance be reviewed to identify where common tests and/or analyses can satisfy both sets of requirements. Test procedures will then be developed for both the common tests and unique tests for use by the FAA Tech Center under the centralized testing concept.

Of particular importance are detonation issues related to octane and the differences in behavior of anti-knock performance between leaded and unleaded fuels. The existing guidance in AC 33.47-1 for detonation testing is based on outdated test equipment and analyses methods. The FAA Tech Center detonation measurement methods and associated instrumentation should be correlated with industry test facilities, and there is industry interest in further investigation of the thresholds used to define limiting detonation levels (i.e. acceptable versus unacceptable).

8) *The UAT ARC recommends* development of specialized test procedures to support centralized testing of candidate unleaded aviation gasolines. The specialized test procedures will be used by the FAA Technical Center to generate fuel property data and engine/aircraft performance data necessary to support ASTM specification development and certification approval of existing engines and aircraft that can operate transparently using a new unleaded aviation gasoline.

In addition, template versions of FAA certification compliance plans will need to be developed that reflect the new test procedures and analyses. These template compliance plans can then be used for all candidate fuel projects.

9) *The UAT ARC recommends* the development of specialized certification guidance to support the centralized certification of unleaded aviation gasoline. The certification guidance should define the applicable certification basis and compliance requirements for Part 33 reciprocating aircraft engines, Part 23 airplanes, and Part 27/29 rotorcraft and should provide acceptable methods of compliance to assess and qualify expected differences in fuel properties, performance and composition from 100LL.

10) *The UAT ARC recommends* that the FAA Centralized Certification Office coordinate with the FAA Technical Center to develop certification test plans, conformity requirements, and test witnessing protocols that are acceptable for certification of unleaded aviation gasoline/s participating in the centralized

4.7. Impact Assessment of Candidate Unleaded Aviation Gasoline

The viability of a candidate unleaded AVGAS to be deployed as an alternative to 100LL depends upon the total impact upon the existing fleet of aircraft, fuel production and distribution infrastructure, and environment.

4.7.1. Aircraft Fleet

An unleaded AVGAS is expected to be transparent for large portions of the current aircraft fleet. It should have no physical impact or change in the design, operation or performance of engines and aircraft other than to list the new fuel specification in the operating limitations. These engines and aircraft are referred to as the transparent fleet. However, it is not expected to be a drop-in which means there will be some differences in certain fuel properties, performance or composition compared with 100LL that will impact certain portions of the fleet and require modification in order to operate safely using the new fuel. These engines and aircraft are referred to as the non-transparent fleet. However, there is no defined methodology to assess the impact of a candidate unleaded AVGAS upon the existing fleet of aircraft.

11) *The UAT ARC recommends* that methods and/or guidelines be developed to assess the impact of a candidate unleaded aviation gasoline on the existing fleet, including the need for proposed aircraft/engine modifications that could mitigate those impacts.

4.7.2. AVGAS Production & Distribution Infrastructure

As discussed previously, an unleaded AVGAS is expected to have a different composition than 100LL due to the need for specialty chemicals to compensate for the absence of lead. This raises potential materials compatibility issues and possible impact upon the production and distribution infrastructure. However, there is no defined methodology to assess the impact of a candidate unleaded AVGAS upon the existing AVGAS production and distribution infrastructure.

> 12) *The UAT ARC recommends* that methods and/or guidelines be developed to assess the impact of a candidate unleaded aviation gasoline on the existing production and distribution infrastructure.

4.7.3. Environment & Toxicology

The potential use of specialty chemicals raises potential environmental and toxicological issues. There are no existing FAA or EPA regulatory requirements for piston aircraft emissions. It is important that a candidate unleaded fuel does not introduce any new or more harmful emissions or environmental impact than the current leaded 100LL.

> 13) *The UAT ARC recommends* the identification of appropriate environment and toxicological issues that a candidate unleaded aviation gasoline should be assessed against.

4.8. FAA Support for Fleet-Wide Certification Approval

Each new make and model of engine and aircraft introduced into the fleet was specifically designed, tested and FAA certificated using 100LL (or equivalent ASTM D910 leaded AVGAS). It is not practical or even possible to re-certify each and every individual make and model engine and aircraft in the entire fleet to operate on a new unleaded fuel. Although there are a large number of different engine and aircraft make/models with broad ranges of configurations and performance, there are many key characteristics from a design and safety perspective that would allow for large groups of "like" engines and aircraft to be assessed, qualified and approved for operation on an unleaded fuel.

> 14) *The UAT ARC recommends* the FAA develop specialized policy and procedures to facilitate the most efficient approach possible for fleet-wide approval of aircraft and engines to use a new aviation gasoline. Fuel qualification and certification data from the centralized FAA fuel test program would support fleet-wide approval of the "in-scope" fleet of aircraft that can operate transparently on an unleaded aviation gasoline.

The following summarizes UAT ARC discussion on some of the fleet impact considerations and provisions necessary to address both the certificated and non-certificated aircraft categories. It also includes possible approval mechanisms and actions that could be considered.

4.8.1. Type-Certificated Aircraft

An unleaded AVGAS that is not drop-in will require some form of FAA approval to operate in each airplane and engine. These approvals could range from some type of FAA issued fleet-wide approval for the transparent portion of the fleet, to a change in type design for entire make/model series by a TC or STC DAH, to aircraft specific design changes or alterations. The most effective and efficient approaches would include support from the original equipment manufacturer of the aircraft and engine that hold certification and test data across the broadest range of make/models. However, as discussed previously, there are significant business risk factors that affect the potential level of DAH involvement in making application for and/or directly supporting approvals or design changes. Beyond economic interests and whether there is a potential return on investment, there is an ongoing regulatory responsibility for the continued airworthiness of any design approval along with product liability for 18 years. Since fuel is such an integral component to engine and aircraft performance and operation, the product liability risk exposure and associated insurance and litigation costs would likely be significant.

Therefore, it is anticipated that original equipment manufacturer DAHs will not likely be able to make application for and/or directly participate in unleaded AVGAS determination and recertification without some mechanism for liability protection. This could include approaches whereby the DAH can fully support FAA issuance of fleet-wide approvals, third-party STCs, field approvals, etc.

> *15) The UAT ARC recommends* that a mechanism be developed to mitigate the liability exposure of design approval holders (DAH) due to modification of the type design of their products in approving a new aviation gasoline.

In addition, there are many make/model engines and aircraft that are not supported by an original equipment manufacturer DAH because the type certificates and supplemental type certificates are orphaned, abandoned or otherwise unsupported. Various approval mechanisms as well as industry and FAA support activities will need to be considered in order to support the broadest possible range of type-certificated products.

Approval Mechanisms - Type-certificated fleet transition approval mechanisms for use of a new unleaded AVGAS may involve one or more of the following.

- Manufacturer DAH change to type certificate for in-production aircraft/engines
- Manufacturer DAH approval via Service Bulletins for legacy fleet
- FAA methods to provide some form of fleet-wide/blanket approval of engines and airplanes

- FAA Supplemental Type Certificate approval by industry sponsors
- FAA field approval of an aircraft/engine alteration

Industry Support - may include but is not limited to the following.

- Lobbying by industry members at Federal and state government levels for tax incentives and financial support to aid in technical and legal transition
- Providing available technical data to potential third-party solution providers (STC/field approval) to reduce work required and accelerate time to market

FAA Support - may include but is not limited to the following.

- Provide information and assist in fleet certification and approvals
- Make FAA Tech Center available to help conduct standardized tests needed to derive solutions and obtain group STC approval.

Fuel Developer Support - may include but is not limited to the following.

- Provide test fuel for development and testing
- Provide baseline fuel test and certification data to potential solution provider

4.8.2. Special Light Sport Aircraft (S-LSA)

In recent years a new category of manufactured recreational aircraft, Special Light Sport Aircraft (S-LSA), have evolved that do not hold type certificates in the traditional sense but rather are shown by the manufacturer to conform to industry consensus standards. The FAA uses manufacturer's certification as the basis for FAA issuance of an airworthiness certificate. These aircraft are unique in the sense that they cannot be legally modified by the owner/operator or third parties and therefore it falls solely on the manufacturer to approve the use of a new fuel in these aircraft. Changes cannot be legally accommodated by STC or other means of FAA approval. In instances where there is no longer a manufacturer supporting in-service S-LSA aircraft, the aircraft lose their S-LSA airworthiness certification status and are placed in the experimental category (E-LSA) with all of the attendant operational limitations that accompany experimental certification. At this point the aircraft is treated like any other aircraft certificated in the experimental category (such as amateur-built) and modifications, including fuel use, are at the discretion of the owner/operator.

Most S-LSA aircraft are certificated to operate on low octane unleaded fuels as well as 100LL so these aircraft are not expected to be significantly impacted by a transition to a future unleaded fuel. The primary considerations for this fleet will likely not be performance but rather materials compatibility assurance and an appropriate method for final approval for use.

Approval Mechanisms - S-LSA fleet transition approval mechanisms for use of a new unleaded AVGAS may involve one or more of the following.

- Engine manufacturers provide approval for use of the new unleaded fuel for their respective engine models

- Aircraft manufacturers address specific aircraft design and field aircraft solutions and approvals leveraging available test data derived for the type certificated fleet

S-LSA Industry Support - may include but are not limited to the following

- Coordinate fleet transition effort on Light Sport Aircraft and similar models certificated in other categories with support from stakeholder groups
- Coordinate with user groups and type clubs to provide info and better develop group solutions for similar types of aircraft
- Coordinate fleet transition with ASTM Committee F37

FAA Fuel Developer Support - may include but are not limited to the following.

- Provide information and test results generated to support approval of the TC products that can be communicated by the FAA to the S-LSA fleet.

4.8.3. Non-Certificated Fleet

There are a large number of non-type certificated aircraft in the fleet that are not supported by an original equipment manufacturer (OEM). These aircraft are certificated in the Experimental category and can include former military aircraft that were not designed and type certificated under civilian standards as well as amateur-built aircraft, some foreign aircraft, and those placed within this category for research, testing, and other purposes. This fleet is wide ranging in terms of performance, octane requirement, size, age and materials. Experimental aircraft have no regulatory requirement to operate on a particular fuel provided the owner determines the fuel to be suitable.

Experimental Fleet Assessment - the following are principle assessments that should be performed relative to evaluation of use of a new fuel in the experimental fleet.

- Composition and size of the experimental fleet
- Technical challenges in operating these airplanes with a new unleaded fuel
- FAA fleet data (group of engines) should be made available to the end user (amateur-built category) and type clubs to enable determination of impact by the user
- Economic impact on the experimental fleet should be included in the total aviation industry economic impact assessment

Experimental Fleet Approval Mechanisms - Experimental fleet approval mechanisms for use of a new unleaded AVGAS may involve one or more of the following.

- FAA provides specific guidance in the form of an AC or SAIB based upon type certificated products for owners of experimental aircraft to evaluate the impact (performance, materials compatibility, etc.) of the unleaded fuel on their individual aircraft and make informed decisions about its use

- SAIBs issued by FAA in support of the type-certificated fleet may be supportive of the amateur-built and other experimental aircraft impact determinations

Industry Support – may include but are not limited to the following.

- Engine manufacturers provide approval for use of the new unleaded fuel for their respective engine models (TC and non-TC)
- Provide applicable technical data to enable assessment of impact by users and type clubs
- Type Club coordination with FAA, manufacturers and fuel developer to provide data and information to the experimental community enabling assessment of any new fuel and approval means for the experimental fleet

FAA Fuel Developer Support - Provide information and test results generated to support approval of the TC products that can be communicated by the FAA to the experimental fleet.

4.8.4. Aircraft/Engine Modification Testing Approval

The UAT ARC recognizes that an unleaded AVGAS that completes the qualification and certification process will most likely not meet the full range of performance demands or be fully compatible with the entire fleet of existing piston-powered aircraft. Therefore, some portion of the fleet will not be able to operate safely using a new unleaded AVGAS without some form of aircraft and/or engine modifications. These are referred to as "out-of-scope" aircraft and engines.

> *16) The UAT ARC recommends* that the centralized FAA test program and the centralized FAA Certification Office support the approval of key aircraft and/or engine modifications that will allow the largest portions of "out-of-scope" aircraft and engines to operate with a new unleaded aviation gasoline. The FAA would have to develop procedures/guidance to facilitate certification of the out-of-scope aircraft/engines requiring modifications.

4.9. Development of Unleaded AVGAS Deployment Strategy

A clearly defined transition plan from 100LL to a replacement unleaded AVGAS is necessary to provide a common timeline to all stakeholders including manufacturers, operators, FAA, EPA, industry associations, etc. The UAT ARC Recommendations are designed to facilitate the development and deployment of an unleaded AVGAS and provide this transition plan. Implementation of the UAT ARC recommendations and the associated transition plan will ensure the continued safety and viability of general aviation. The Recommendations lay out three stages of the transition; Preparatory, Project and Deployment with significant detail provided for the first two stages. The Preparatory and Project stages address the development of an ASTM fuel specification, FAA approval and certification policy as well as the economic

viability of a candidate unleaded AVGAS. These stages represent a significant portion of the UAT ARC Recommendations.

The *Deployment stage* is, however, as critical as the first two Stages in managing the impact of a transition to an unleaded AVGAS. The Deployment Stage addresses the introduction of the unleaded AVGAS into the field and the eventual phase out of 100LL. The UAT ARC understands the need to provide the FAA with a recommendation for the framework and milestones to address the transition of the fleet to an unleaded fuel. At this time, the UAT ARC cannot recommend a specific timeline beyond the Preparatory and Project Stages of the recommendations due to the unknown impact of an unleaded fuel on the existing fleet.

Another important consideration in this discussion is the timeline by which alternatives are implemented and ultimately brought to market. An alternative that has a substantial impact, including the devaluation of a portion of the fleet, would require a significantly longer implementation timeline, perhaps decades, to allow for the consumption of the remaining life of the airframes and engines. This will enable the natural retirement and attrition of this portion of the fleet. The challenge with this approach is that the industry presently keeps heavy utilization aircraft active for decades. These aircraft are flying missions in support of critical roles and are difficult, expensive or in many cases, impossible to replace due to a lack of new aircraft produced that can fit the mission profile. The average age of the General Aviation piston fleet exceeds 39 years. This highlights the need for an extended transition for any alternative fuel that would otherwise significantly devalue or limit the capability of the existing fleet.

Another key consideration for a viable unleaded AVGAS replacement for 100LL is the economic impact. This includes both the upfront costs to transition to an unleaded AVGAS as well as the long term cost impact of operating on a new fuel. The EPA's Advance Notice of Proposed Rulemaking on Lead Emissions from Piston-Engine Aircraft recognized that converting in-use aircraft/engines to operate on unleaded aviation gasoline would be a significant logistical challenge, and in some cases, a technical challenge as well. As discussed previously, a change to the approved AVGAS or modifications to engines and aircraft require FAA certification to ensure compliance with applicable airworthiness standards necessary for safety. The FAA certification process is comprehensive and requires significant investment of resources, expertise and time to complete. The cost and resource impact upon both industry and government can be significant depending upon the level of effort and number of modifications that may be necessary to support a transition of the in-use fleet to an unleaded AVGAS. However, the closer the physical and performance properties of an unleaded AVGAS to 100LL, the less upfront economic impact there would be, particularly with respect to octane rating. This is a critical fuel property for aircraft engines to maintain rated horsepower that in turn is crucial for high performance aircraft to meet their performance limitations. Another potentially significant upfront cost for an unleaded AVGAS is the impact upon the fuel production and distribution infrastructure and level of modifications/investment that may be necessary. Long-term economic impacts that should be considered are the cost of unleaded AVGAS per gallon and any potential impact on aircraft/engine operating and maintenance costs. These are ongoing costs incurred by entire in-use fleet for the foreseeable future.

4.9.1. Milestones and Timeline

It is imperative to understand that at this time the UAT ARC is only able to discuss major milestones that are expected to be necessary for the Deployment Stage. Timelines for these milestones can only be established once a potentially viable unleaded AVGAS has been identified and the industry has an understanding of the impact upon the existing fleet and production and distribution infrastructure. The UAT ARC also highlights the importance of understanding that the milestones may also represent decision points. Once a milestone is reached, all information available to that point must be evaluated. Future milestones may need to be altered, adjusted or completely reevaluated as information about new fuels becomes known.

The following summarizes some of the key milestones necessary for deployment of an unleaded AVGAS once a potentially viable unleaded AVGAS with least impact upon the piston-engine aircraft fleet has been identified:

- **Identification of an Unleaded AVGAS with Least Impact Upon Existing Fleet**
  - ASTM production specification to support commercial acceptance
  - FAA qualification and certification test data to support maximum fleet approval
  - Aircraft fleet impact assessment and potential modification data
- **New Aircraft Certified for Unleaded AVGAS Capability**
  - New production engines/aircraft certified to operate on unleaded AVGAS
    - Only affects engine/airplane certification and not current operations
    - Would require dual certification for unleaded AVGAS and 100LL
  - Consideration of some type of regulatory mandate may be necessary
- **Transition to Unleaded AVGAS**
  - Applies to fuel availability and operations of all General Aviation aircraft
  - Transition timeline dependent upon impact of unleaded AVGAS
    - Level of FAA certification required for fleet-wide approvals
    - Development and implementation of modifications (i.e. overhaul cycle)
    - Level of change to AVGAS production and distribution infrastructure
  - Consideration of special case
    - Portions of fleet that cannot transition (i.e., cargo operations in remote areas, public safety operations, historic aircraft, etc.)
  - Consideration of some type of regulatory mandate may be necessary

17) The UAT ARC recommends that the FAA, working with industry, develop a deployment and transition plan and timeline only after unleaded aviation gasoline(s) with least impact upon the piston-engine aircraft fleet has been identified and a process for fleet-wide approval to use the new fuel in aircraft has been clearly established. Any FAA action should support the efforts of the industry to transition to unleaded aviation gasoline(s) in a safe and orderly manner.

4.9.2. Consideration of Regulatory Action

The UAT ARC recognizes that an ultimate transition to unleaded aviation gasoline for general aviation is not likely to occur due to market forces alone and accordingly some form of regulatory action may be required to effect a permanent and complete change from leaded to unleaded AVGAS. However, given the uncertainties surrounding what a future fuel might look like relative to its performance, safety and economic impact it is premature for the UAT ARC to recommend any form or regulation or timeline. We only acknowledge that such an action may need to occur once a satisfactory replacement has been identified and approved

18) The UAT ARC recommends that the FAA and EPA continue to coordinate closely with stakeholders and take into consideration implementation of the UAT ARC's recommendations in any potential rulemaking efforts. Consideration must be given to safety, costs, and the ability and time needed to implement new technology.

4.9.3. Funding for Piston Aviation Fuels Initiative (PAFI)

This implementation of the proposed PAFI will require an estimated $57.5M of public funds and $13.5M of industry in-kind support over 11 years. Specifics for the estimated funding are addressed in Section 5.5.

19) The UAT ARC recommends the FAA establish a line item in its annual 2013-2020 budget requests to fully support the UAT ARC recommendations for a Piston Aviation Fuels Initiative (PAFI) which includes centralized FAA fuel testing to support the development of an ASTM unleaded aviation gasoline specification and fleet-wide certification approval.

5. Implementation of UAT ARC Recommendations

The implementation concept recommended by the UAT ARC relies upon both a process and an organization called the Piston Aviation Fuel Initiative (PAFI) formed by the FAA and an industry-government coalition. The overall objectives of this initiative are to identify candidate unleaded aviation gasolines, to provide for the generation of qualification and certification data for those fuels, and to support the qualification and certification of the most promising fuels. The elements of PAFI will be an FAA Test Program, centralized certification office, a FAA review board, and a PAFI Steering Group (PSG) (refer to Figure 6.0). The FAA test program will test candidate fuels at the FAA William J. Hughes Technical Center (FAA Tech Center) to generate data that can then be used by the fuel developer to support ASTM specification development and FAA certification. The PSG will facilitate, coordinate, expedite, promote, and oversee the PAFI process that is identified throughout this report. The PSG will consist of an Executive Director and a coalition of industry associations and government representatives who will engage subject matter experts (SMEs) as necessary (refer to Figure 7.0). The PSG will provide input to candidate fuel developers to facilitate the process to result in an unleaded fuel that would have the least impact to the existing fleet and distribution system.

A secondary objective of PAFI will be to support the testing and approval of key aircraft/engine modifications that would have a significant impact on compatibility of the existing fleet with new unleaded AVGAS.

The following roles, responsibilities, resources, funding, and scheduling requirements are designed to support these objectives. In addition, a description of the integration of PAFI with the FAA fuel testing program and with the prospective AVGAS developers who participate in that program is also provided.

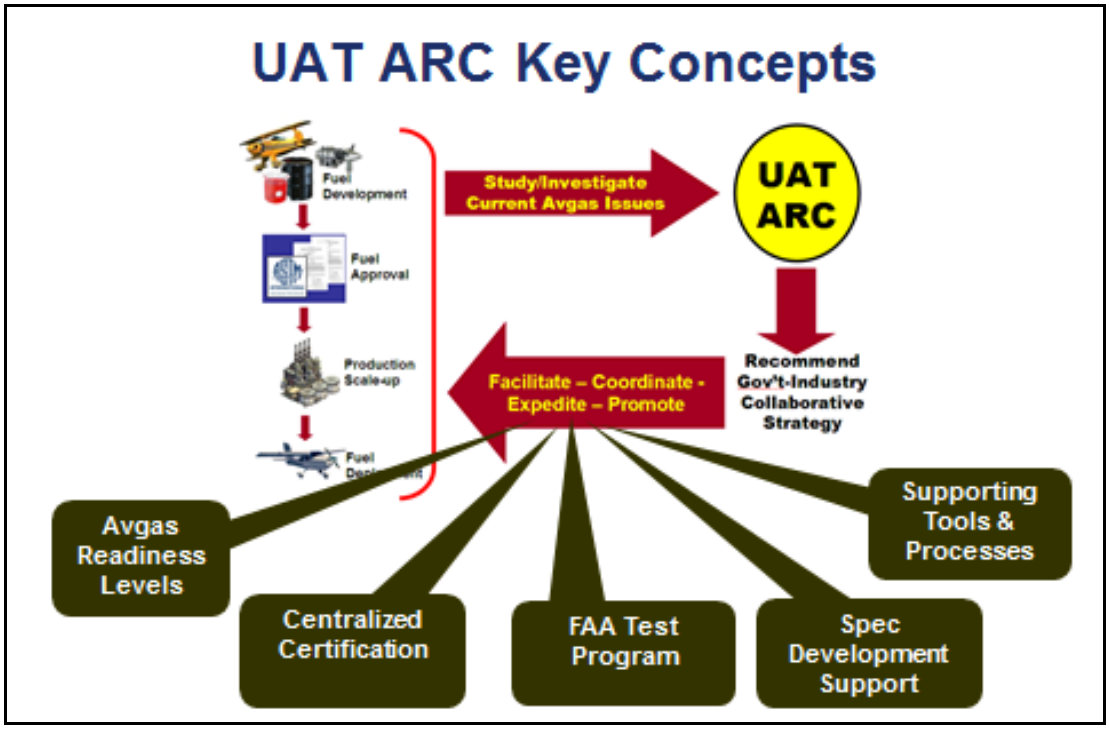


Figure 6.0 – UAT ARC Key Concepts

5.1. PAFI Organization

It is recommended that PAFI be organized as an industry-FAA coalition; similar to the structure of the existing FAA sponsored Commercial Aviation Alternative Fuels Initiative (CAAFI); see Appendix D for a description of CAAFI. It is also recommended that the FAA fund and provide administrative support for a PAFI Director, and fund other consultants as required. This administrative support would include the establishment and maintenance of a web site for the PAFI organization. The membership of PAFI would be comprised of stakeholders from the General Aviation community including aviation trade and other directly involved industry trade and membership associations, and the FAA as illustrated in the following Figure 7.0. The members would be expected to provide in-kind support to perform the tasks necessary for PAFI to perform its role as described in this report. Members would allocate resources to support unique PAFI tasks, such as the generation of job aids and to support industry tasks related to development and approval of unleaded AVGAS, such as ASTM Task Forces.

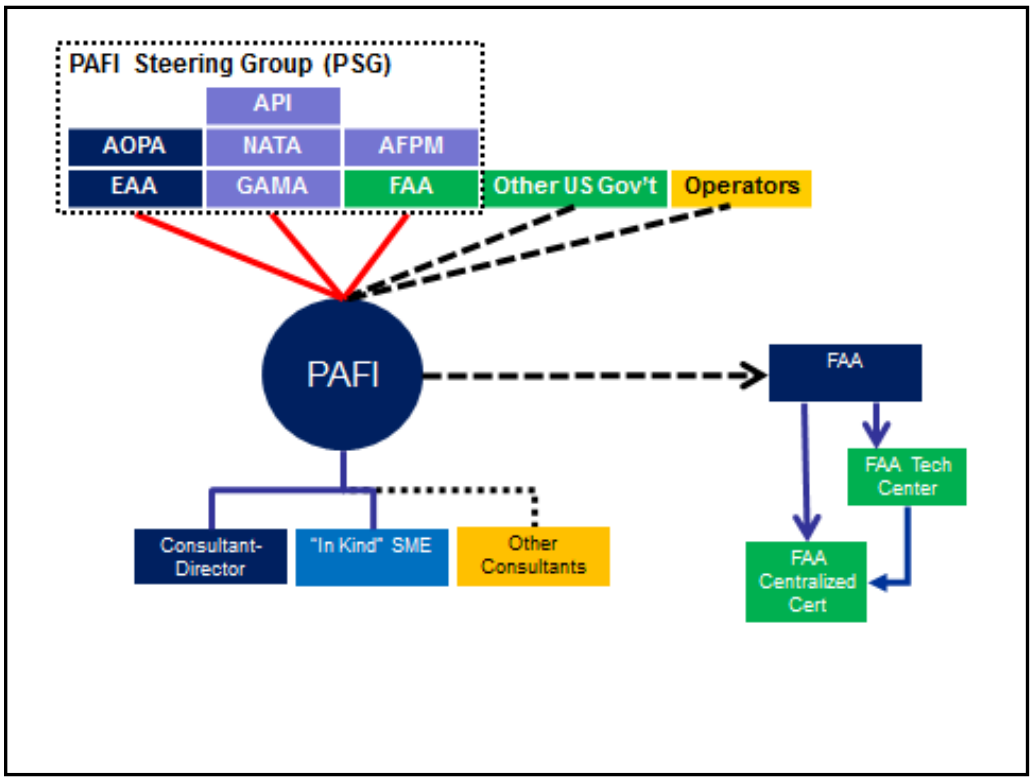


Figure 7.0 – PAFI Organization

5.2. The PAFI Process

5.2.1. PAFI Fuel Development Stages

The PAFI roles, responsibilities, resources, funding and schedule requirements are presented for three distinct stages which are structured to facilitate the integration with FAA fuel testing program and the AVGAS development process (see Figure 8.0).

Preparatory Stage

This stage precedes the start of the FAA fuel testing program and associated testing of candidate fuels. Job Aids will be developed during this stage by PAFI to support the subsequent stages. These job aids will include technical, logistical, economic and other AVGAS-related industry information that are necessary for the FAA Tech Center to conduct testing in support of the FAA fuel testing program. These job aids will also provide reference information for prospective fuel producers, potential investors, and government agencies that may play a future role in the commercialization of unleaded AVGAS. It is recommended that the FAA establish an aviation fuel centralized certification office during this stage.

Project Stage

The FAA will issue a solicitation for prospective unleaded AVGAS producers to submit fuel for testing for the FAA fuel testing program during this stage. The FAA will select a limited number of the most promising fuels for testing at the FAA Technical Center. The data generated from this testing will support the concurrent ASTM specification development and FAA certification activity during this stage. As appropriate, PAFI members may also advocate for and promote both private and government financing opportunities to support this initiative.

Deployment Stage

This stage commences upon the completion of fuel testing, specification development, and FAA certification activities. PAFI provides expert support to facilitate the production, distribution, and initiation of fleet-wide operations of the new unleaded aviation gasolines.

A more detailed overview of the PAFI activities in each of these stages is provided in Section 5.7 PAFI & FAA Work Scope.

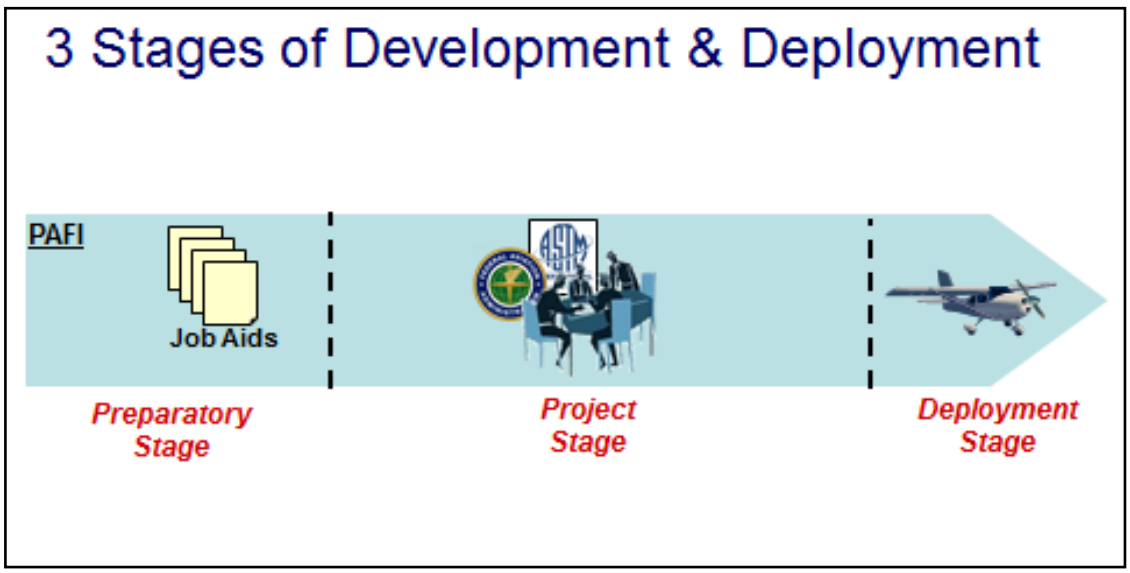


Figure 8.0 - PAFI Fuel Development & Deployment Stages

5.2.2. FAA Integration

During the Preparatory Stage, the PSG will facilitate the development of job aids that the FAA will use to support screening and testing of candidate fuels. The FAA will use the job aids to develop "Request for Proposals" (RFPs) to solicit new fuels to undergo testing at the FAA Tech Center. This FAA Test Program will generate data that can be used by the applicant to support fuel approval. The FAA will establish an FAA Review Board that will use the job aids to screen candidate fuels for admittance to the FAA Test Program (see Section 5.2.5). The FAA Review Board will require the technical expertise necessary to evaluate fuel property and composition data to determine the feasibility of the candidate fuel. In addition, the FAA will establish a centralized certification office (see Section 5.2.4). During the Project Stage, the fuel testing program will be conducted at the FAA Tech Center. See Figure 9.0.

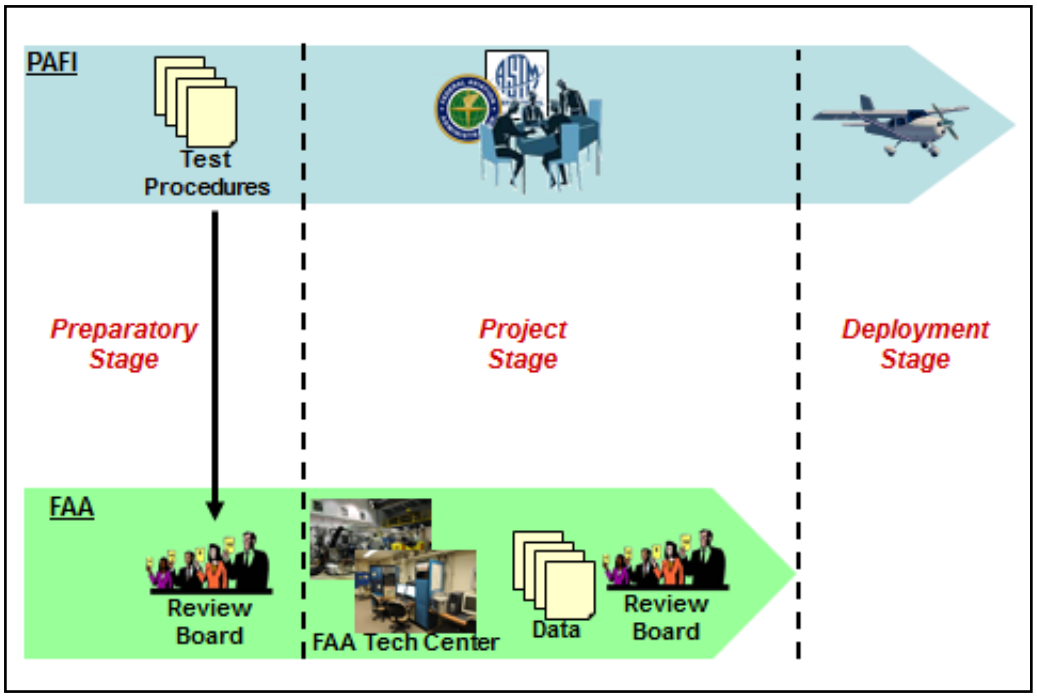


Figure 9.0 - FAA Integration

5.2.3. Fuel Developer Integration

Both the PSG and the FAA will be working closely with the prospective fuel developers during the Project and Deployment Stages. The fuel developers will need to provide test fuel to the FAA Test Center for conduct of the testing. The data generated during the testing at the FAA Tech Center will be used by the fuel developer to support specification development and FAA certification. The fuel developer will progress through the AVGAS Readiness Levels (ARLs) during the development and deployment of the fuel. The PSG will support the fuel developer during the project and deployment stages to facilitate the specification issuance, certification approvals, and distribution and deployment of the approved fuel. See Figure 10.0.

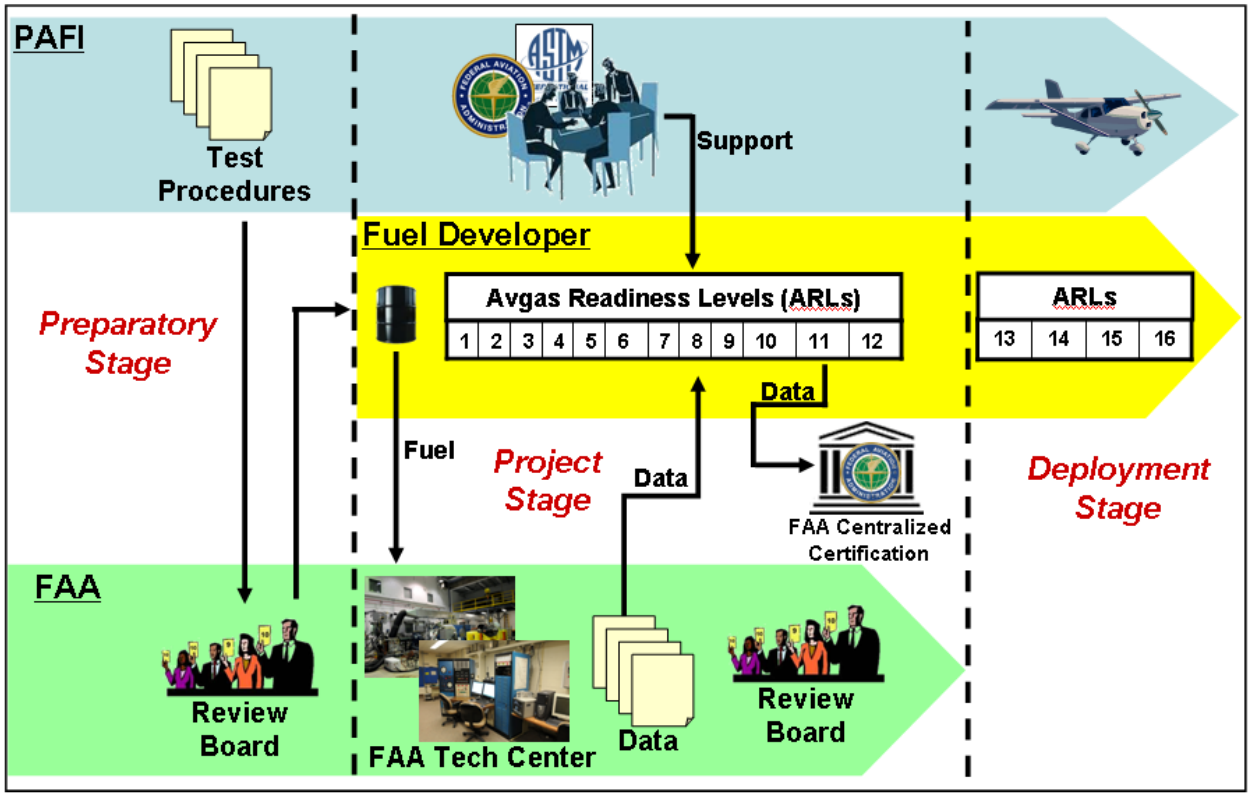


Figure 10.0 - PAFI & FAA fuel testing program Integration with Fuel Developer

5.2.4. FAA Centralized Certification

In accordance with the UAT ARC recommendations, the FAA will establish a centralized certification office for aviation fuel projects. The PSG will coordinate with the centralized certification office and with the FAA Tech Center to develop test procedures and conformity and test witnessing protocols that are acceptable for certification. The data generated during the FAA fuel testing program by the FAA Tech Center is provided to the candidate fuel developer. The fuel developer can then submit this data to the FAA Centralized Certification office as certification data. The applicability or scope of certification will be based on the test results and will be reflected in the application to the centralized FAA certification office. See Figure 10.0.

5.2.5. FAA Testing Program Overview

The FAA fuel testing program will occur during the Project Stage of the PAFI fuel development process (see Figure 10.0). The program will be managed by the FAA and will offer the incentive of government funding and industry in-kind contribution to test the fuel at the FAA Tech Center. The program consists of a screening phase that the fuel candidate conducts to measure key fuel properties. The fuel developer will then provide the fuel property data when responding to the FAA RFP. If selected by the FAA Review Board, the fuel developer will then be required to provide specified quantities of fuel that will be subjected to Phase 1 testing under the FAA test program. The FAA Review Board will then select a limited number of

candidate fuels to continue on to Phase 2 testing upon receipt of an additional specified quantity of fuel from the fuel developer (see Figure 11.0).

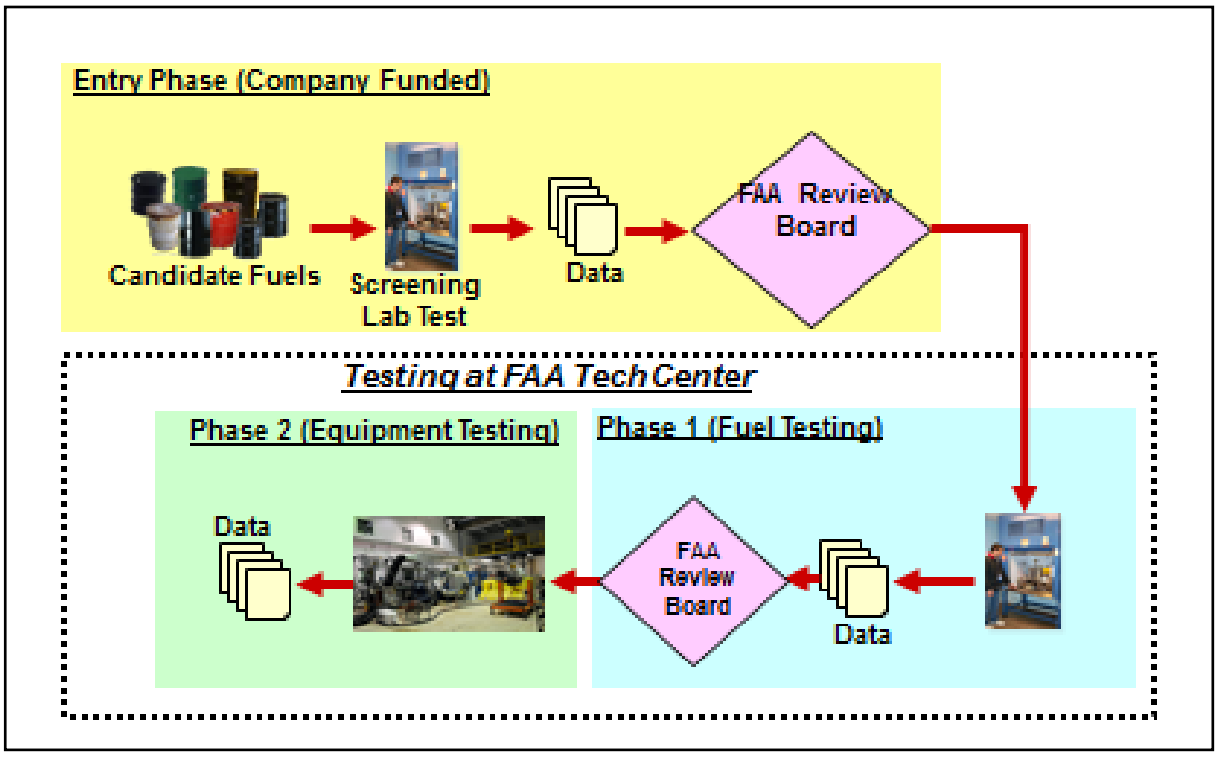


Figure 11.0 - FAA Fuel Testing Program

The FAA Testing Program is described separately; the following is a short overview of the anticipated structure of the program.

Entry Phase

The fuel developer will send on the order of 10 gallons (final quantity TBD) of the candidate fuel to a laboratory designated by the FAA during the evaluation period defined in the RFP. The lab will perform initial testing to measure fuel properties. The fuel developer will submit the data to the FAA Review Board for review. The best performing fuels will be admitted to Phase 1 of the program.

Phase 1

If the fuel passes the screening phase, the fuel developer will send on the order of 100 gallons (final quantity TBD) of the candidate fuel to the FAA Tech Center for expanded fuel properties testing. The test data will be submitted to the FAA Review Board for review. The best performing fuels will be admitted to Phase 2 of the program.

Phase 2

The fuel developers of the candidate fuels selected after Phase 1 testing will send on the order of 10,000 gallons of the candidate fuel (final quantity TBD) to the FAA Tech Center for engine and aircraft testing. The final test data will be provided to the fuel producer to support ASTM specification development and FAA certification. A final report or appropriate information will be provided to the PSG with an assessment of the scope of the transparent fleet to aid the fuel developer and FAA centralized certification office to facilitate subsequent ASTM and certification approval.

This recommended program includes both the conduct of testing and the provision of data that can be used to support development of ASTM International fuel specifications and for FAA certification (see Figure 12.0). Availability of test data to persons other than the fuel developer when using public funds needs to be further evaluated and addressed by the PSG. The PSG will coordinate with the FAA Fuel Testing Program, the FAA Tech Center, and PSG member companies to facilitate the ASTM specification development process. PSG will also coordinate with the FAA Tech Center and the FAA centralized certification office to facilitate the FAA certification process.

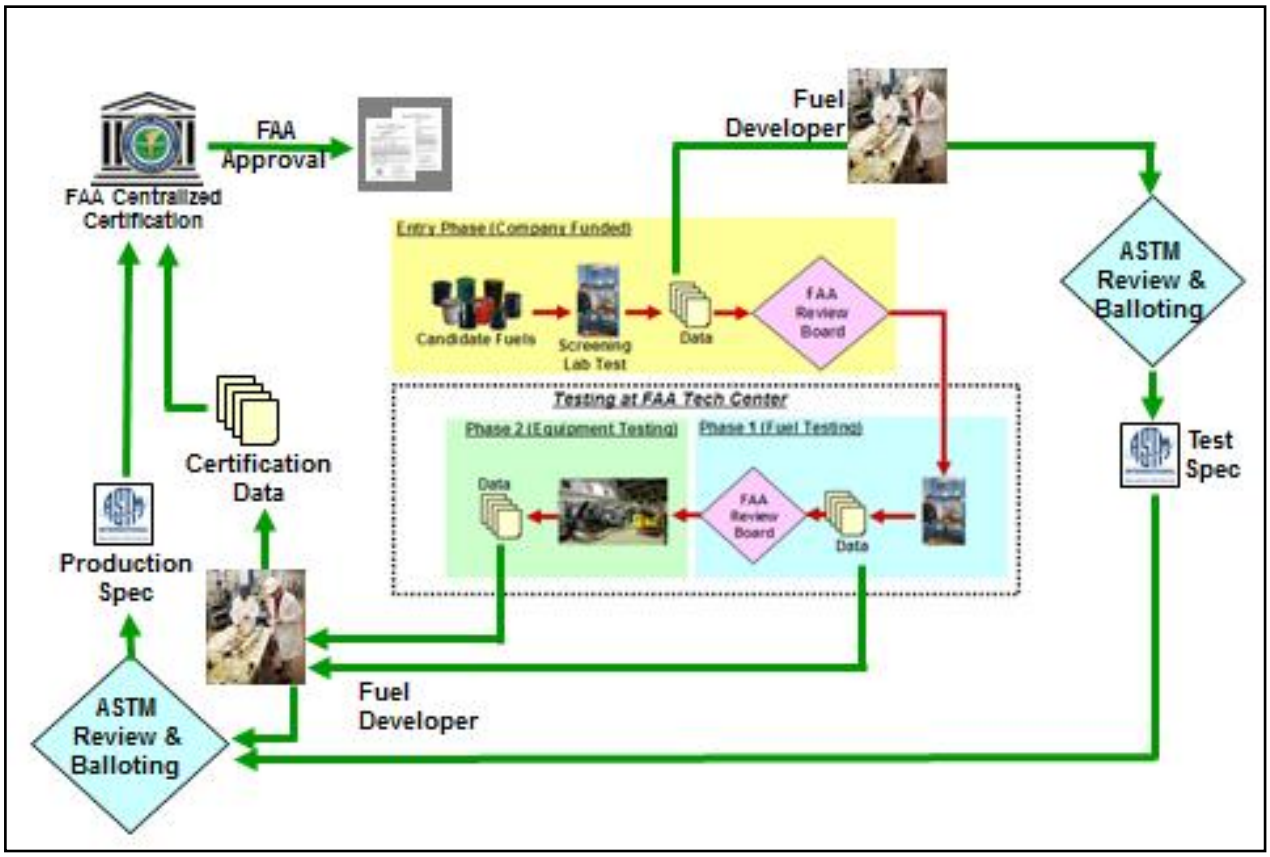


Figure 12.0 - Integration of FAA Fuel Testing Program with ASTM and FAA

5.2.6. FAA Technical Center Support

The FAA Tech Center has established itself as the leading expert for testing of candidate aviation gasolines. The FAA fuel testing program will utilize the FAA Tech Center to perform fuel property testing in Phase 1 and equipment (engine and aircraft) testing in Phase 2 of the program. All the candidate fuels will be tested in the same manner using the same equipment, instrumentation and test facilities. This will allow for accurate comparisons of the results, and also for standardized data to be used in the ASTM specification development process and in the FAA certification process. This will provide for a more efficient and expeditious overall approval process.

5.2.7. AVGAS Readiness Levels (ARLs)

The UAT ARC applied the CAAFI concept of jet "FRLs" to the unique needs of AVGAS development. The ARLs are designed to reflect the fuel developer's progression through the FAA fuel testing program, ASTM specification development, FAA certification, and deployment as shown in Figure 10.0. The ARLs will be used to develop the screening criteria to be used by the FAA Review Board to select fuels for each of the respective phases of the FAA Test Program. The ARLs are color coded in Figure 13.0 to identify where they apply during the project stage and deployment stage (ARLs are not applicable to the preparatory stage). Within the project section, they are further divided into screening phase, Phase 1 and Phase 2, to correlate with the FAA fuel testing program concept shown in Figure 11.0. Figure 14.0 provides a detailed description of the ARLs developed by the UAT ARC.

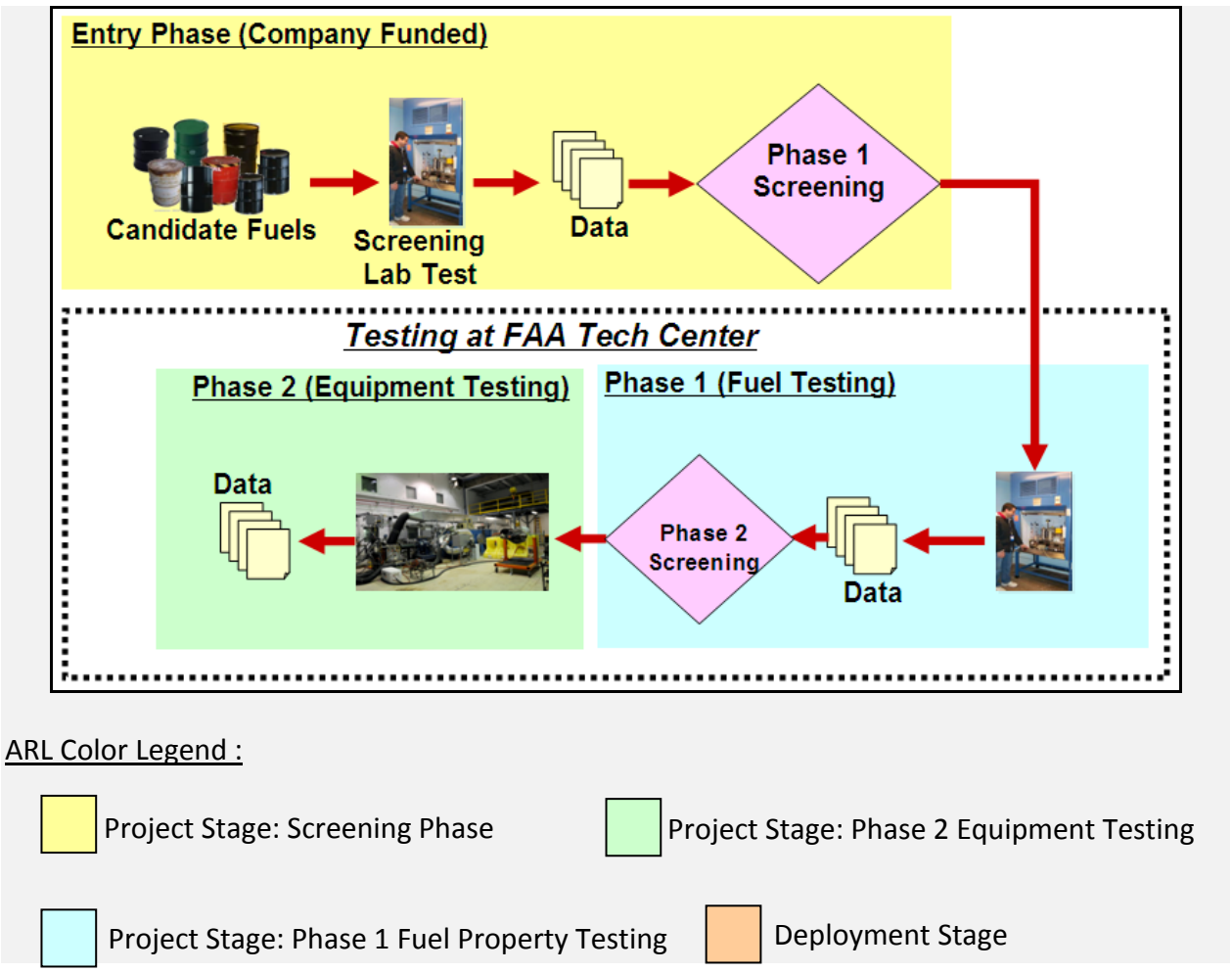


Figure 13.0 – ARL Color Coding

Figure 14.0
AVGAS Readiness Levels

ARL	Title	Description	Deliverable (Informational / Data / Regulatory)	Fuel Qty Guidance
1	Fuel Definition	Utilize data developed during experimentation phase to establish process elements and parameters (such as reactor hardware and catalyst materials) and fuel compositional definition by GC analysis.	Fuel sample and report including process flow diagram and fuel compositional analysis	4 Liters
2	Material Safety Review	Initial review of candidate fuel composition relative to published guidance on material safety with respect to environmental and safe handling considerations. Develop material safety data sheet (MSDS).	MSDS and other data as needed	
3	Basic Fuel Properties and Composition Iterative process	Intended to support initial engagement with ASTM to form Task Force. Lab analysis of fuel sample to identify composition and measure key Fit-For-Purpose properties per test methods defined in ASTM International Standard Practice , "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives": ▪ Motor Octane Number (detonation) ▪ Vapor Pressure (starting, vapor lock) ▪ Freezing Point (high-altitude operation) ▪ Corrosion, copper strip (metal fuel system components) ▪ Oxidation stability (gumming) ▪ Water reaction (hygroscopic effect) ▪ Electrical conductivity (fuel handling) ▪ Distillation curve ▪ Initial material compatibility testing	Independent lab analysis report(s), report how the fuel was produced (blending purchased components, lab scale production, etc.)	20 to 50 Liters Minimum
4	Preliminary ASTM Research Report	Compile data derived from laboratory analysis of candidate fuel in accordance with Section 6.2 of ASTM International Standard Practice, "Standard Practice for the Evaluation of New	Preliminary ASTM Research Report	200 – 400 liters minimum

		Aviation Gasolines and New Aviation Gasoline Additives". This data will include: ▪ Basic Specification properties ▪ Compositional analysis ▪ Preliminary Fit-For-Purpose (FFP) Properties ▪ Preliminary Materials Compatibility Assessment ▪ Information from preceding ARLs		
5	ASTM Test Specification	ASTM Test Specification defines the properties of the fuel for subsequent testing and analysis.	Issued ASTM Test Specification	
6	Preliminary Feasibility Assessment	Prepare the following reports to assess the potential viability of the candidate fuel concurrent with the previous ARLs 1-5.		
6.1	Preliminary Production and Distribution Assessment	Analyze current AVGAS production and distribution infrastructure to identify gaps in current system and develop preliminary plan to address gaps and to scale-up production and distribution to commercially viable volumes.	Report	
6.2	Environmental & Toxicology Assessment	Review candidate fuel composition with consideration to use and handling from an environmental perspective, including OSHA, EPA and other regulatory entities.	Report with compositional data, MSDS, environment and toxicology assessment, and other relevant environmental data.	
6.3	Preliminary Business Plan	Provide a business plan that addresses the following: a) Scope of Solution: Describe the fuel, engine/aircraft hardware and operational concept proposed. If hardware or operational changes are proposed summarize and characterize in accordance to CFRs as minor, major or model changes. b) Production Concept: Describe how the candidate fuel composition can be scaled up and commercialized. Include summary of fuel production process flow and related hardware c) Applicability: Define fleet	Report	

		satisfaction concept relative to either actual aircraft cross section as defined in the FAA Aviation Fuels Reciprocating Engine Aircraft Fleet Fuel Distribution Report or BMEP/detonation propensity as defined by TBD document. d) Cost: Describe market cost of proposed solution inclusive of recurring cost/volume and non-recurring associated with hardware or operational limitation changes. e) Implementation: Describe defined or to-be-defined strategic partnerships, financing strategies, infrastructure leveraging opportunities, distribution strategies and other relevant details facilitating path to market. f) Deployment Concept: Describe whether the proposed fuel is miscible and fungible with 100LL. Does the solution require a separate distribution and control system? g) Intellectual Property: Declare IP associated with the Scope of Solution and how stated IP is protected or public domain considerations.		
7	Initial Pilot Production Capability	Scale-up lab production capability, and define production process flow and hardware for novel production capability requirements.	Fuel sample produced by the defined process	400 liters minimum, or as needed to support ARL 8
8	Final ASTM Research Report			
8.1	Final ASTM Research Report – Part 1	Compile data derived from laboratory analysis and of candidate fuel in accordance with Section 6.3 of ASTM International Standard Practice, "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives". This data will include: ▪ Final Fit-For-Purpose (FFP) Properties	Report	

		▪ Final Materials Compatibility Assessment		
8.2	Final ASTM Research Report – Part 2	Compile data derived from equipment testing of candidate fuel in accordance with Section 6.3 of ASTM International Standard Practice, "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives". This data will include: ▪ Engine Testing ▪ Aircraft Testing	Final ASTM Research Report	
9	ASTM Production Specification	ASTM Production Specification defines the properties of the fuel and other criteria necessary for high-volume production and distribution.	Issued ASTM Production Specification	
10	Pilot Production Capability	Scale-up initial pilot production capability, using the production process flow from the initial pilot production capability requirements (ref: ARL 7). Demonstrate the ability to produce at least 10,000 gals/yr (40,000 liters/yr).	Production Process Demonstration	10,000 gals (40,000 liters) minimum, or as needed to support ARL 11
11	Airworthiness Certification			
11.1	Engine Certification Testing	Completion of all rig, component and engine certification tests in accordance with compliance program established by the cognizant airworthiness regulatory authority.	Certification Test Reports	
11.2	Engine Certification	Obtain certification approval from cognizant airworthiness regulatory authority.	Issued Amended or Supplemental Type Certificate(s)	
11.3	Aircraft Certification Testing	Completion of all ground and flight testing in accordance with compliance program established by the cognizant airworthiness regulatory authority.	Certification Test Reports	
11.4	Aircraft Certification	Obtain certification approval from cognizant airworthiness regulatory authority.	Issued Amended or Supplemental Type Certificate(s)	
12	Final Feasibility Assessment	Prepare the following reports to assess the potential viability of the candidate fuel concurrent with the previous ARLs 7-11.		
12.1	Final Production and Distribution Assessment	Update preliminary report based on data and information developed during the fuel development.	Report	

12.2	Final Environmental & Toxicology Assessment	Update preliminary report based on data and information developed during the fuel development. This may include testing for baseline emission data.	Report and MSDS	
12.3	Final Business Plan	Update preliminary report based on data and information developed during the fuel development.	Report	
13	Initial Production Capability	Scale-up pilot production capability, using the production process flow from the pilot production capability requirements for the large-scale (ref: ARL 10). . Establish production capability to produce at least 100,000 gals/yr (400,000 liters/yr).	Fuel inventory	
14	Initial Limited-Scale Fleet Operations	Introduce fuel on a regional basis to gain experience with commercial operations.	Coordinated plan with fuel distributors and fleet operators to demonstrate operational use of fuel	
15	Production Scale-up	Construct facilities to produce at least 10,000,000 gals/yr (40,000,000 liters/yr).	Fuel inventory	
16	Wide-Scale Fleet Operations	Fuel availability and usage over several geographic regions.	Coordinated plan to transition production, distribution, and use on a regional basis	

5.3. Aircraft/Engine Modification Testing and Approval

The UAT ARC recognizes that unleaded aviation gasolines that complete the above described PAFI process will most likely not meet the performance demands of, or not be compatible with the entire fleet of existing piston-powered aircraft. Therefore, this implementation plan includes tasks to support the testing at the FAA Tech Center and approval of aircraft and/or engine modifications that will allow a portion of the non-transparent fleet to operate with a new unleaded AVGAS. This recommendation will include the following key elements (see Figure 15.0).

- The FAA will maintain the FAA Review Board to review proposed aircraft/engine modifications.
- Prospective aircraft/engine modifiers will submit proposed modifications to the FAA Review Board.

- The FAA Review Board will select those modifications that will enable the greatest number of aircraft in the non-transparent fleet to operate safely with a new unleaded AVGAS.
- Once selected, the modifier will provide the modification hardware to the FAA Tech Center.
- The FAA Tech Center will test the hardware to test plans developed with the FAA Centralized Certification Office
- The test data will be provided to the modifier who will then work with the FAA Centralized Certification Office to approve the modification.
- A final report or appropriate information will be provided to PSG with an assessment of the applicability of the proposed modification to aid the fuel developer and FAA centralized certification office to facilitate subsequent certification approval.

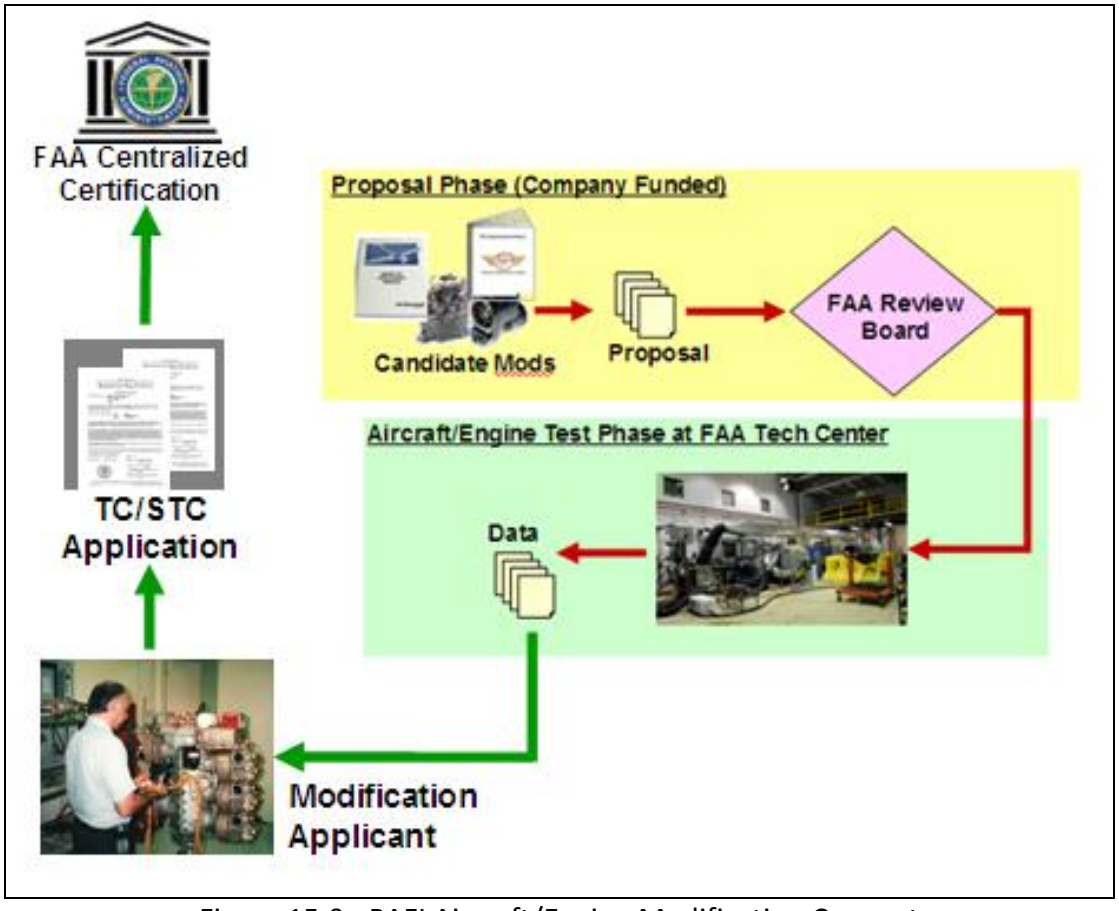


Figure 15.0 - PAFI Aircraft/Engine Modification Concept

5.4. PAFI Management

The PSG is envisioned to be a coalition, rather than a formalized legal entity. The FAA fuel testing program will perform the selection and testing of the candidate fuels separately from the PSG. The role of the PSG will be limited to providing supporting data, and coordinating the activities of member organizations to provide the necessary project and deployment support.

The recommended organization for PAFI is modeled after CAAFI. Like CAAFI, it is proposed that the FAA fund a full-time consultant to act as the PAFI Director, other consultants as required, and that the FAA provide administrative support for the Director. In addition, like CAAFI, it is recommended that the FAA fund the construction, maintenance, and updating of a web site for the PAFI organization. It is expected that both the PAFI Director and PAFI members will need to participate in dedicated PAFI meetings and perform other tasks unique to the PAFI organization.

PAFI management is projected as being an on-going program management function throughout the Preparatory, Project, and Deployment stages. The PAFI Executive Director, reporting to the FAA and the PSG, will act as the program manager monitoring, directing, and coordinating overall PAFI activities and interfaces with industry, government, and candidate fuel developers. The PAFI Executive Director will represent PAFI at industry meetings and will interface with government agencies, PAFI members, and other external organizations as directed by the PSG. The PAFI Executive Director will act as a champion and advocate for the PAFI program. PAFI management tasks and associated work scope are illustrated in Figure 16.0.

A cost estimate for the PAFI management-function and associated overhead is provided in Figure 17.0. Included in the cost estimate are subcontract costs for the director, administrative support, travel, PAFI website maintenance, and other direct costs (ODC). Other direct costs provides for miscellaneous costs such as expenses and small service subcontracts. This cost estimate is presented as an annual cost that covers PAFI management and overhead tasks such as Program Management, Advocacy, PAFI Meetings, and Communications. It is envisioned that the PAFI Executive Director will report to the FAA and the PSG of which the FAA is a member.

Note that Figure 17.0 does not included cost of specific subcontracts to SME and other specialists as required to support the specific FAA-PAFI tasking and work scope of Section 5.7; these subcontract costs are included in the total program cost estimates of Figure 18.0. It is anticipated that Industry will provide SME as in-kind-resources similar to commitments currently made to ASTM, Coordinating Research Council (CRC) and other standardization bodies.

Figure 16.0
PAFI Leadership & Management
Tasks & Work Scope

Task No.	Task	Work Scope	Cost Estimate	Schedule
PREPARATORY, PROJECT, & DEPLOYMENT STAGES				
O&C-1	Program Management	Active on-going program management: Monitoring, directing, and coordination of PAFI activities and interfaces with industry, government, and fuel developers. Reports directly to the PSG.	See Figure 17.0	On-going
O&C-2	Advocacy	Represent PAFI at industry meetings, interface with government agencies and offices.	See Figure 17.0	On-going
O&C-3	PAFI Meetings	Plan, organize, coordinate, and convene PAFI meetings. Issue meeting reports.	See Figure 17.0	On-going
O&C-4	Communications	Provide communications regarding status and progress to users and General Aviation industry. Provide reports at industry meetings. Provide and coordinate input to PAFI website.	See Figure 17.0	On-going

Figure 17.0
PAFI Management & Overhead
Estimated Cost

Year	Director Labor	Admin Support	Travel	Web Site	ODC	FAA Cost	Industry Cost	Total FAA + Industry
1	$150K	$26K	$21K	$10K	$2K	$209K	$360K	$569K
2	$150K	$26K	$21K	$2K	$2K	$201K	$360K	$561K
3	$150K	$26K	$21K	$2K	$2K	$201K	$360K	$561K
4	$150K	$26K	$21K	$2K	$2K	$201K	$360K	$561K
5	$150K	$26K	$21K	$2K	$2K	$201K	$360K	$561K
6	$150K	$26K	$21K	$2K	$2K	$201K	$360K	$561K
7	$150K	$26K	$21K	$2K	$2K	$201K	$360K	$561K
8	$75K	$13K	$10K	$2K	$1K	$101K	$180K	$281K
9	$75K	$13K	$10K	$2K	$1K	$101K	$180K	$281K
10	$75K	$13K	$10K	$2K	$1K	$101K	$180K	$281K
11	$75K	$13K	$10K	$2K	$1K	$101K	$180K	$281K
					Totals	$1.82M	$3.24M	$5.06M

Notes:
1) The above represents management and overhead cost only and does not include subcontracts to SME and other external specialists.
2) Industry in-kind estimate based upon assumption of 8 PSG members + 4 SME

5.5. PAFI Program Estimated Cost

The following Figure 18.0 identifies estimated program cost for the total FAA-PAFI program as proposed within the context of the recommendations presented within this report. For planning purposes, the cost estimate is based upon the assumption of 11 years of funding (subject to change). It is not possible at this point to project funding beyond 11 years. The estimated cost is segregated into categories of FAA, PAFI, and industry in-kind participation.

Figure 18.0
Estimated Total Cost
Cumulative FAA-PAFI Work Scope

		Estimated Cost				
		FAA Direct Funding	**FAA Funding of PAFI**	**FAA Total**	**Industry In-Kind Support**	**Total Funding**
PAFI PREPARATORY – PROJECT – DEPLOYMENT STAGES						
1	Certification & Qualification (C&Q)	$3.85M	$0	$3.85M	$236K	$4.09M
2	Test & Evaluation (T&E)	$51.22M	$0	$51.22M	$9.65M	$60.9M
3	Production & Distribution (P&D)	$0	$8K	$8K	$182K	$0.19M
4	Impact & Economics (I&E)	$0	$300K	$300K	$210K	$0.51M
5	Environment & Toxicology (E&T)	$300K	$0	$300K	$0	$0.30M
6	PAFI Management & Overhead (O&C)	$0	$1.82M	$1.82M	$3.24M	$5.06M
	Total Funding	$55.37M	$2.13M	$57.5M	$13.52M	**$71M**

Notes:
1. See Figure 17.0 for PAFI Management & Overhead Annual Cost Estimate
2. See Figures 19.0 & 19.1 for FAA Direct Funding of PAFI Annual Cost Estimate

Caution *– the industry in-kind participation represents support furnished to the FAA Test & Evaluation Program and does not include industry non-recurring engineering costs. An estimate of industry DAH non-recurring engineering costs is included in Appendix M.*

5.5.1. Industry In-Kind Participation

Industry in-kind participation does not reflect the total cost to transition to new fuel(s). The total PAFI Estimated Cost of $71 million dollars as shown in Figure 18.0 reflects only the direct industry in-kind support of $13.5 million that will be provided to PAFI during the Preparatory and Project stages. It does not reflect, nor does this report attempt to estimate, the actual cost and in-kind support that industry will bear during basic research conducted by fuel sponsors

prior to entering the PAFI process or transition of the fleet to a new fuel during the Deployment Stage. The Deployment Stage represents the potential for the largest impact to all segments of the industry and is the most difficult to estimate without knowing the properties and composition of the fuel. The impact and cost to the industry of the Deployment Stage can only be determined and estimated as the impact of the potential candidate fuels becomes apparent. Fuels necessitating significant changes to production, distribution, aircraft operations, or that require aircraft modifications will result in additional costs to segments of the industry. These impacts cannot be quantified or shown at this time and are not reflected in the industry in-kind support. However, consideration must be given to these significant economic impacts, when contemplating contributions of the stakeholders in this effort. The collaborative effort presented in this report relies on the FAA funding of a significant portion of the upfront cost of the PAFI program as reflected in this report, but also on the potentially much larger costs that industry will incur to transition the existing fleet and future production aircraft and engines to a new fuel or fuels.

5.5.2. Industry Deployment Stage Costs Not Reflected in In-Kind Support

Examples of potential industry costs which may be encountered during the Deployment Stage but are not reflected in the industry in-kind support cost estimate include the following.

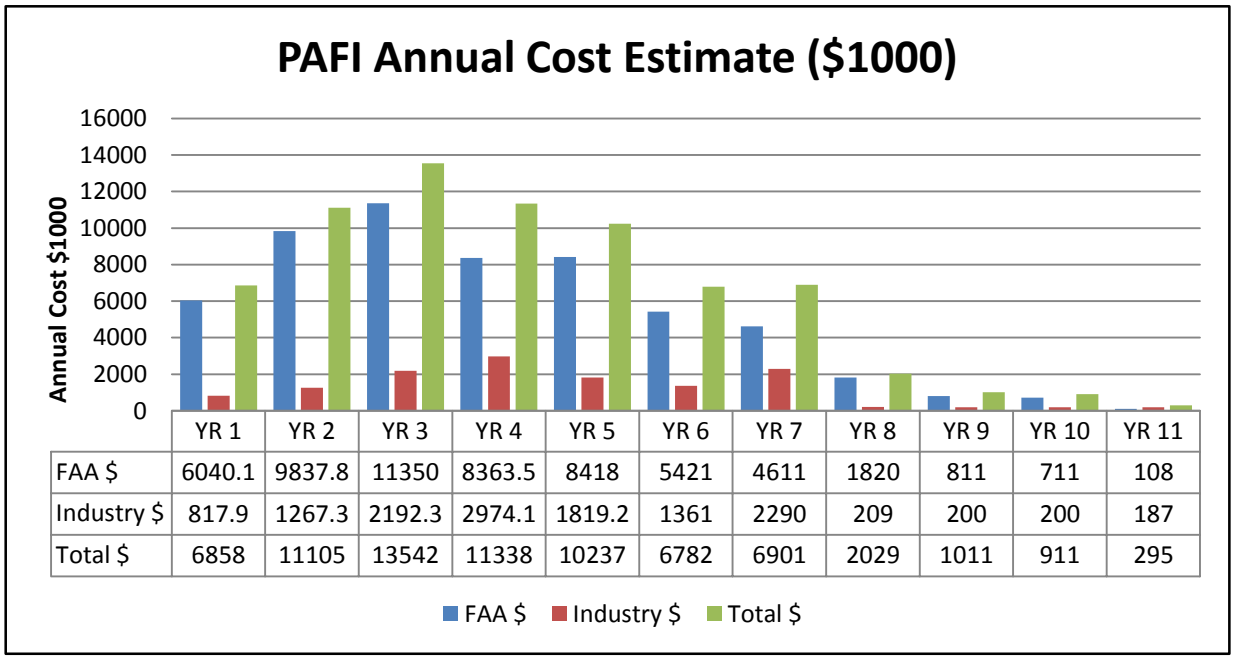
Production and Distribution – It is anticipated that new unleaded fuels will require some change to the production and distribution systems currently used for avgas. These changes are likely to include physical infrastructure changes to accommodate new fuels, including the need for new production facilities and changes to distribution infrastructure materials to accommodate new chemicals. Facilities that produce, transport, store and dispense these fuels will, at a minimum, likely need to change product labeling, educate staff on handling characteristics, and potentially make changes to dispensing equipment and practices.

Aircraft Operations - New fuels may require changes to aircraft operations. While it is the intent of the UAT ARC recommendations and subsequently PAFI to minimize these impacts, any change will have a subsequent effect on some portion of the fleet. That portion of the fleet that may see operational changes will experience an economic impact that will affect the entire industry.

Aircraft Modifications – This report recommends FAA support of some key aircraft modifications to lessen the impact of a new fuel on the non-transparent fleet. However, the incorporation of these aircraft modifications after approval will still have a significant economic impact on industry. These modifications may vary from minor changes to the aircraft operating limitations, Pilot Operating Handbook (POH), and placards to hardware modifications necessary to accommodate a new fuel. Even what may appear to be a simple modification such as placarding or a POH update will result in costs to owners and operators. Depending on the size of the non-transparent fleet, these costs may be significant when compared to the overall PAFI costs presented in this report.

5.5.3. PAFI Annual Cost Estimate

The following figures 19.0 through 19.3 identify the estimated PAFI annual funding requirements. Figure 19.1 provides a breakdown for the annual FAA funding requirements for the PAFI tasks. Similarly, Figure 19.2 provides an indication of the annual Industry In-Kind funding requirements. Figure 19.3 identifies PAFI annual subcontract cost estimates.



	YR 1	YR 2	YR 3	YR 4	YR 5	YR 6	YR 7	YR 8	YR 9	YR 10	YR 11
FAA $	6040.1	9837.8	11350	8363.5	8418	5421	4611	1820	811	711	108
Industry $	817.9	1267.3	2192.3	2974.1	1819.2	1361	2290	209	200	200	187
Total $	6858	11105	13542	11338	10237	6782	6901	2029	1011	911	295

Figure 19.0 – PAFI Annual Cost Estimate FAA & Industry In-Kind

Figure 19.1
FAA Funding Annual Cost Estimate
PAFI Tasks

Year	C&Q	T&E	P&D	I&E	E&T	PAFI Mgt & OH	PAFI Subcon	Total
1	$74.1K	$5277K	$0	$0	$300K	$209K	$180K	$6040.1K
2	$34.8K	$9572K	$0	$0	$0	$201K	$30K	$9837.8K
3	$139.5K	$11009K	$0	$0	$0	$201K	$0	$11349.5K
4	$139.5K	$7963K	$0	$0	$0	$201K	$60K	$8363.5K
5	$36K	$8178K	$0	$0	$0	$201K	$3K	$8418K
6	$12K	$5208K	$0	$0	$0	$201K	$0	$5421K
7	$395K	$4008K	$0	$0	$0	$201K	$7K	$4611K
8	$1712K	$0	$0	$0	$0	$101K	$7K	$1820K
9	$703K	$0	$0	$0	$0	$101K	$7K	$811K
10	$603K	$0	$0	$0	$0	$101K	$7K	$711K
11	$0	$0	$0	$0	$0	$101K	$7K	$108K
Totals	$3848.9K	$51215K	$0	$0	$300K	$1819K	$308K	$57490.9K

Notes:
1) The above identifies FAA annual funding requirements for each PAFI task including PAFI management and overhead. See Figures 29.9 – 39.0 for PAFI Task Descriptions and Appendices E – G for PAFI Task Cost Estimates. See Figure 19.3 for PAFI Annual Subcontract Cost Estimate.

Figure 19.2
Industry In-Kind Annual Cost Estimate
PAFI Tasks

Year	C&Q	T&E	P&D	I&E	E&T	PAFI Mgt & OH	Total
1	$57.4K	$175K	$75.5K	$150K	$0	$360K	$822.9K
2	$1.8K	$853K	$52.5K	$0	$0	$360K	$1267.3K
3	$45.3K	$1787K	$0	$0	$0	$360K	$2192.3K
4	$44.1K	$2510K	$0	$60K	$0	$360K	$2974.1K
5	$19.2K	$1425K	$15K	$0	$0	$360K	$1819.2K
6	$12K	$989K	$0	$0	$0	$360K	$1361K
7	$12K	$1910K	$8K	$0	$0	$360K	$2290K
8	$21K	$0	$8K	$0	$0	$180K	$209K
9	$12K	$0	$8K	$0	$0	$180K	$200K
10	$12K	$0	$8K	$0	$0	$180K	$200K
11	$0	$0	$7K	$0	$0	$180K	$187K
Totals	$236.8K	$9649K	$182K	$210K	$0	$3240K	$13517.8K

Notes:
1) The above identifies industry annual in-kind cost estimates for each PAFI task. See Figures 29.9 – 39.0 0 for PAFI Task Descriptions and Appendices E – G for PAFI Task Cost Estimates.
2) PAFI industry in-kind support estimate based upon 8 PSG member + 4 SME

Figure 19.3
PAFI Annual Subcontract Cost Estimate
PAFI Tasks

Year	C&Q	T&E	P&D	I&E	E&T	Total
1	$0	$0	$0	$180K	$0	$180K
2	$0	$0	$0	$30K	$0	$30K
3	$0	$0	$0	$0	$0	$0
4	$0	$0	$0	$60K	$0	$60K
5	$0	$0	$3K	$0	$0	$3K
6	$0	$0	$0	$0	$0	$0
7	$0	$0	$1K	$6K	$0	$7K
8	$0	$0	$1K	$6K	$0	$7K
9	$0	$0	$1K	$6K	$0	$7K
10	$0	$0	$1K	$6K	$0	$7K
11	$0	$0	$1K	$6K	$0	$7K
Totals	$0	$0	$8K	$300K	$0	$308K

Notes:
1) The above identifies annual cost estimates for PAFI subcontracts required to support PAFI tasks. See Figures 29.9 – 39.0 for PAFI Task Descriptions and Appendices E – G for PAFI Task Cost Estimates.

5.6. PAFI Program Estimated Schedule

It is recommended that PAFI begin operating by June 2012. Operations are estimated to continue for at least 11 years from the initial authorization of funding to support development and approval of candidate fuels. In addition, it is anticipated that PAFI activities will continue through the deployment phase. Master schedules for the PAFI preparatory, project, and deployment phases are shown in the following Figures 20.0 through 22.0

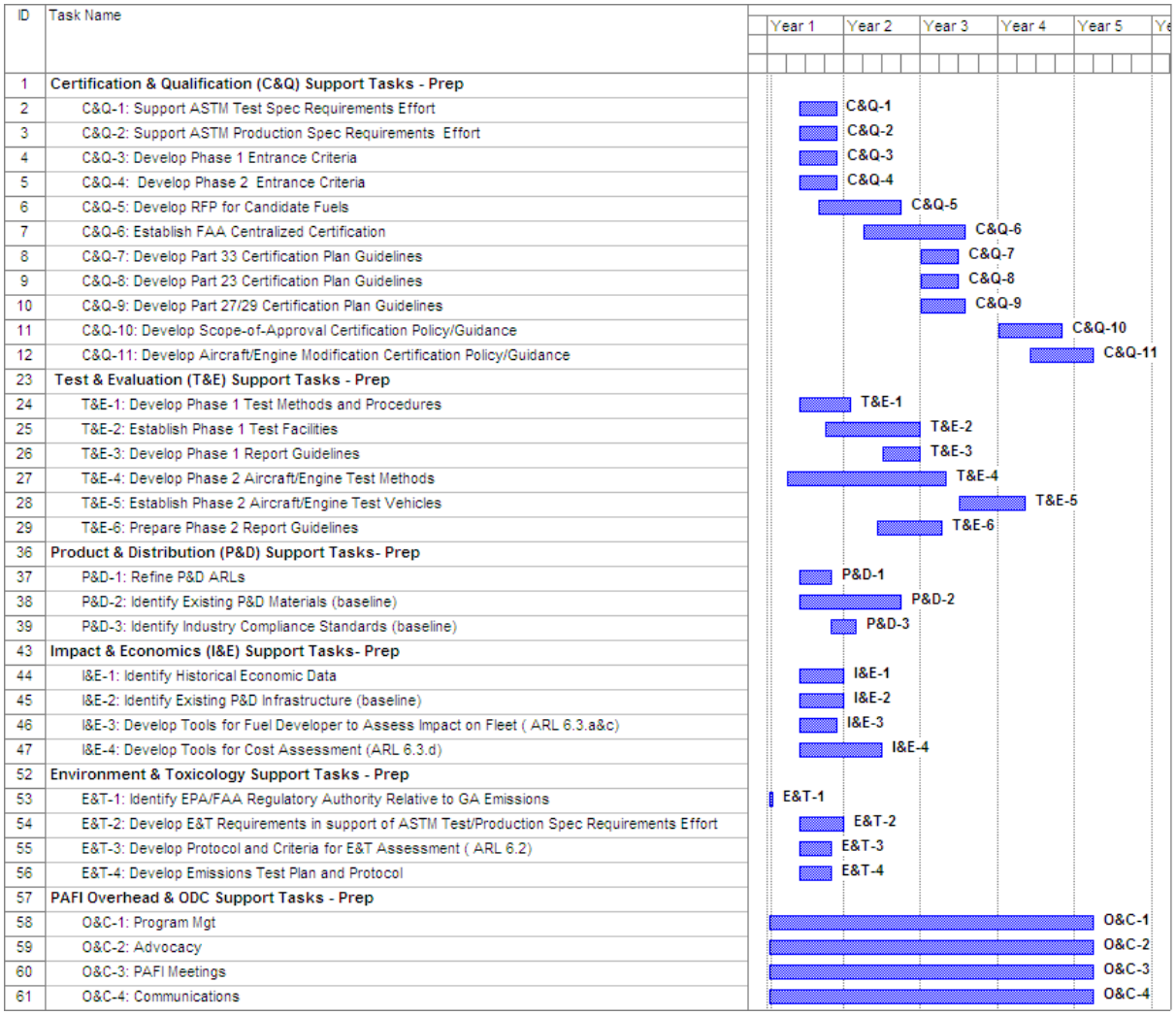


Figure 20.0 – Master Schedule PAFI Preparatory Phase

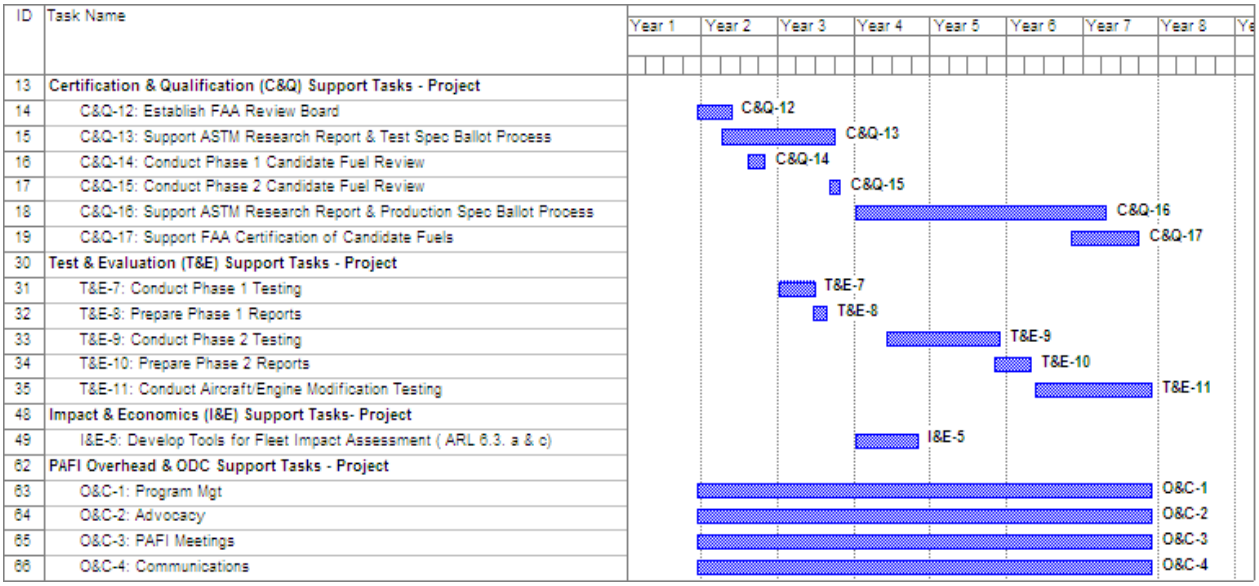


Figure 21.0 – Master Schedule PAFI Project Phase

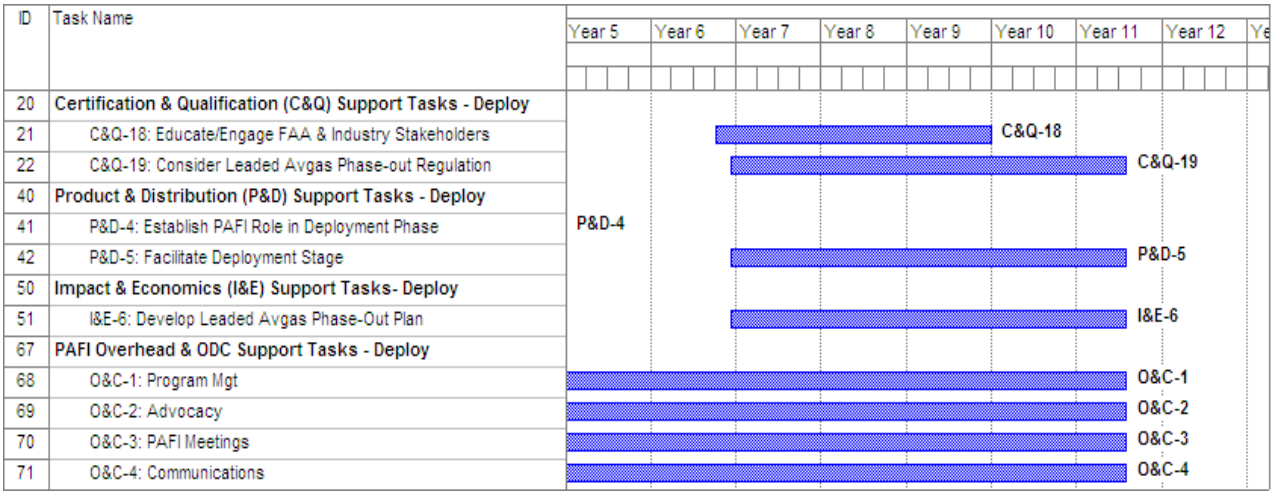


Figure 22.0 – Master Schedule PAFI Deployment Phase

5.7. PAFI and FAA Work Scope

The following describes the PAFI and FAA work scope for each of the three stages - Preparatory, Project, and Deployment. Within each stage, PAFI and the FAA will perform tasks designed to facilitate, incentivize, subsidize, and promote the approval and deployment of candidate unleaded aviation gasolines. For each stage, the UAT ARC developed work scope tasks and associated resource and schedule requirements are identified. Specific tasking is segregated into five major support functions that are illustrated in Figure 23.0.

The PAFI and FAA work scope for each of the three stages is described in the following sections 5.7.1, 5.7.2 and 5.7.3; there are a total of 45 tasks identified. The following Figures 24.0 – 28.0 identify the upper level PAFI work tasks grouped for each of the five major support functions shown in Figure 23.0. The PAFI management and leadership work scope was addressed in Section 5.4.

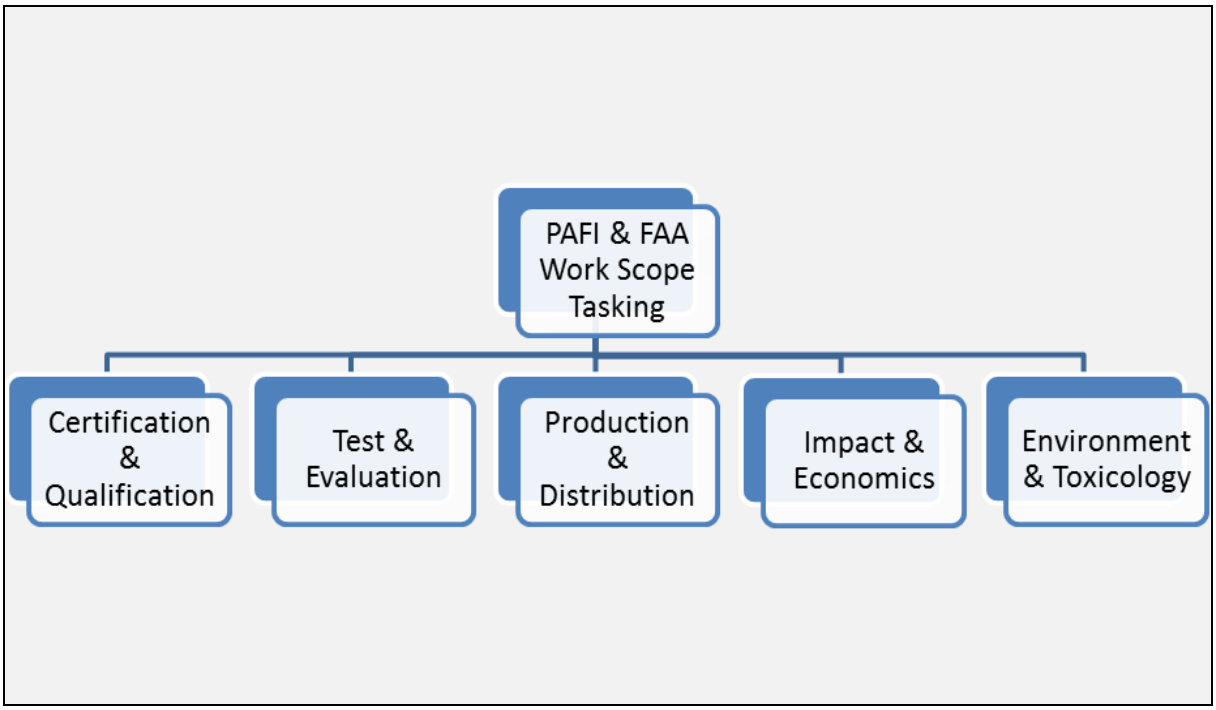


Figure 23.0 – PAFI & FAA Work Scope Tasking

PAFI Certification & Qualification Tasks

- PAFI Certification & Qualification Preparatory Stage Support
  - C&Q-1 – Support ASTM Test Spec Requirements Effort
  - C&Q-2 – Support ASTM Production Spec Requirements Effort
  - C&Q-3 – Develop Phase 1 Entrance Criteria
  - C&Q-4 – Develop Phase 2 Entrance Criteria
  - C&Q-5 – Develop RFP for Candidate Fuels
  - C&Q-6 – Establish FAA Centralized Certification
  - C&Q-7 – Develop Part 33 Certification Plan Guidelines
  - C&Q-8 – Develop Part 23 Certification Plan Guidelines
  - C&Q-9 – Develop Part 27/29 Certification Plan Guidelines
  - C&Q-10 – Develop Scope-of-Approval Certification Policy/Guidance
  - C&Q-11 – Develop Aircraft/Engine Modification Certification Policy/Guidance
- PAFI Certification & Qualification Project Stage Support
  - C&Q-12 – Establish FAA Review Board
  - C&Q-13 – Support ASTM Research Report and Test Spec Ballot Process
  - C&Q-14 – Conduct Phase 1 Candidate Fuel Review
  - C&Q-15 – Conduct Phase 2 Candidate Fuel Review
  - C&Q-16 – Support ASTM Research Report & Production Spec Ballot Process
  - C&Q-17 – Support FAA Certification of Candidate Fuels
- PAFI Certification & Qualification Deployment Stage Support
  - C&Q-18 – Educate/Engage FAA & Industry Stakeholders
  - C&Q-19 – Consider Leaded AVGAS Phase-Out Regulation

Figure 24.0 – PAFI Certification & Qualification Tasks

PAFI Test & Evaluation Tasks

- PAFI T&E Preparatory Stage Support
  - T&E-1 - Develop Phase 1 Test Methods & Procedures
  - T&E -2 - Establish Phase 1 Test Facilities
  - T&E -3 - Develop Phase 1 Report Guidelines
  - T&E -4 - Develop Phase 2 Engine/Aircraft Test Methods
  - T&E -5 - Establish Phase 2 Engine/Aircraft Test Articles
  - T&E -6 - Prepare Phase 2 Report Guidelines
- PAFI T&E Project Stage Support
  - T&E -7 - Conduct Phase 1 Testing
  - T&E -8 - Prepare Phase 1 Reports
  - T&E -9 - Conduct Phase 2 Testing
  - T&E -10 - Prepare Phase 2 Reports
  - T&E -11 – Conduct Aircraft/Engine Modification Testing

Figure 25.0 – PAFI Test & Evaluation Tasks

PAFI Production & Distribution Tasks

- PAFI P&D Preparatory Stage Support
  - P&D-1 – Refine Production & Distribution ARLs
  - P&D-2 – Identify Existing Production & Distribution Materials
  - P&D-3 – Identify Industry Compliance Standards (Baseline)
- PAFI P&D Deployment Stage Support
  - P&D-4 – Establish PAFI Role in Deployment Phase
  - P&D-5 – Facilitate Deployment Phase

Figure 26.0 – PAFI Production & Distribution Tasks

PAFI Impact & Economics Tasks

- PAFI I&E Preparatory Stage Support
  - I&E-1 – Identify Historical Economic Data (Baseline)
  - I&E-2 – Identify Existing Production & Distribution Infrastructure (Baseline)
  - I&E-3 – Develop Tools for Fuel Developer to Assess Impact on Fleet (ARL 6.3.a & c)
  - I&E-4 – Develop Tools for Cost Assessment (ARL 6.3.d)
- PAFI I&E Project Stage Support
  - I&E-5 – Develop Tools for Fleet Impact Assessment (ARL 6.3.a & c)
- PAFI I&E Deployment Stage Support
  - I&E-6 – Develop Leaded AVGAS Phase Out Plan

Figure 27.0 – PAFI Impact & Economics Tasks

PAFI Environment & Toxicology Tasks

- PAFI E&T Preparatory Stage Support
  - E&T-1 – Identify EPA/FAA Regulatory Authority Relative to GA Emissions (Completed; See Appendix I, Background on Environmental Regulations Related to AVGAS)
  - E&T-2 - Develop E&T Requirements in Support of ASTM Test/Production Spec Requirements Effort
  - E&T-3 – Develop Tools for E&T Assessment (ARL 6.2)
  - E&T-4 – Develop Emissions Test Plan and Protocol

Figure 28.0 – PAFI Environment & Toxicology Tasks

5.7.1. Preparatory Stage Work Scope

PAFI will develop job aids and screening criteria during this stage to support the activities in the subsequent Project and Deployment stages. The FAA will prepare for the testing and approval of candidate fuels by developing the FAA RFP and defining the concept for the FAA Centralized Certification Office. A summary of each task in the preparatory stage is provided in Figures 29.0 - 33.0. Refer to Figure 20.0 for the estimated schedule associated with each preparatory stage task. Implementation plans that include a detailed description and associated cost estimate for each preparatory stage task are provided in Appendix E.

5.7.1.1. Certification & Qualification Prep Stage Work Scope

Figure 29.0 PAFI Certification & Qualification Preparatory Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
PREPARATORY STAGE		
PREP-C&Q-1	Support ASTM Test Spec Requirements Effort	Support ASTM Task Force effort to develop Standard Practice.
PREP-C&Q-2	Support ASTM Production Spec Requirements Effort	Support ASTM Task Force effort to develop Standard Practice.
PREP-C&Q-3	Develop Phase 1 Entrance Criteria	Define criteria used to rate candidate fuel.
PREP-C&Q-4	Develop Phase 2 Entrance Criteria	Define criteria used to rate candidate fuel.
PREP-C&Q-5	Develop RFP for Candidate Fuels	FAA PAFI RFP Document specifying criteria for selection of candidate unleaded fuels for participation in the FAA Tech Center testing program.
PREP-C&Q-6	Establish FAA Centralized Certification	Define applicant & FAA responsibilities, FAA scope of support, deliverables, The UAT ARC respectfully submits the recommendations contained in this report and eagerly awaits your feedback and questions. FAA organizational support.
PREP-C&Q-7	Develop Part 33 Certification Plan Guidelines	Define applicable FARs and compliance requirements that are compatible with PAFI fuel development concept.
PREP-C&Q-8	Develop Part 23 Certification Plan Guidelines	Define applicable FARs and compliance requirements that are compatible with PAFI fuel development concept.
PREP-C&Q-9	Develop Part 27/29 Certification Plan Guidelines	Define applicable FARs and compliance requirements that are compatible with PAFI fuel development concept.
PREP-C&Q-10	Develop Scope-of-Approval Certification Policy/Guidance	Develop policy to facilitate the fleet wide approval of aircraft & engine sub-population based on non-model parameters.
PREP-C&Q-11	Develop Aircraft/Engine Modification Policy/Guidance	Develop procedures/guidance to facilitate certification of out-of-scope aircraft/engines requiring modifications.

5.7.1.2. Test & Evaluation Program Prep Stage Work Scope

Figure 30.0 PAFI Test & Evaluation Preparatory Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
PREPARATORY STAGE		
PREP-T&E-1	Develop Phase 1 Test Methods and Procedures	FAA Tech Center works with PAFI members to develop methods/procedures based on ASTM document guidance.
PREP-T&E-2	Establish Phase 1 Testing Faculties	FAA Tech Center procures necessary equipment and contracts to support Phase 1 testing.
PREP-T&E-3	Develop Phase 1 Report Guidelines	FAA Tech Center works with other PAFI members to standardize report content and format.
PREP-T&E-4	Develop Phase 2 Engine/Aircraft Test Methods	FAA Tech Center works with PAFI members to develop methods & procedures based on ASTM document guidance.
PREP-T&E-5	Establish Phase 2 Engine/Aircraft Test Articles	FAA Tech Center procures necessary equipment to support Phase 2 testing.
PREP-T&E-6	Prepare Phase 2 Report Guidelines	FAA Tech Center works with PAFI members to standardize report content and format.

5.7.1.3. Production & Distribution Prep Stage Work Scope

Figure 31.0 PAFI Production & Distribution Preparatory Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
PREPARATORY STAGE		
PREP-P&D-1	Refine Production & Distribution ARLs	Refine ARL's relating to production & distribution, including defining criteria for meeting an individual ARL step.
PREP-P&D-2	Identify Existing P&D Materials	Prepare report summarizing component materials used in existing P&D system for use by candidate fuel developer.
PREP-P&D-3	Identify Industry Compliance Standards (Baseline)	Prepare list of applicable industry compliance standards for use by candidate fuel developer (UL, AFPM, EI, etc.).

5.7.1.4. Impact & Economics Prep Stage Work Scope

Figure 32.0 PAFI Impact & Economics Preparatory Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
PREPARATORY STAGE		
PREP-I&E-1	Identify Historical Economic Data	Prepare market analysis & historical trends for AVGAS. Develop historical information regarding the industry reaction to price fluctuations. Analysis of historic price & consumption elasticity. Assess market size and future demand for unleaded AVGAS. Information will assist developers in making market assessments and in developing business plans. Data to also be used in the analysis-audit-validation tool in PREP-I&E-4.
PREP-I&E-2	Identify Existing Production & Distribution Infrastructure (Baseline)	Prepare summary of existing fuel production & distribution infrastructure. Provide fuel developer with useful data regarding existing fuel production infrastructure to help in understanding of existing capabilities when developing cost analysis. Data to also be used in the analysis-audit-validation tool in PREP-I&E- 4.
PREP-I&E-3	Develop Tools for Fuel Developer to Assess Impact on Fleet (ARL 6.3.a & c)	Develop tools and guidelines for assessment of impact of changes to fleet. Data to also be used in the analysis-audit-validation tool in PREP-I&E- 4.
PREP-I&E-4	Develop Tools for Cost Assessment (ARL 6.3.d)	Prepare an analysis-audit-validation tool to enable assessment of fuel developer's economic assumptions & factors for economic claims. Will use data generated in PREP-I&E-1 through -3.

5.7.1.5. Environment & Toxicology Prep Stage Work Scope

UAT ARC deliberations identified the roles of both the EPA in regulating lead emissions and the FAA in its authority to regulate fuel composition; the results of which are included in Appendix I. Consideration is being given to inclusion of environmental and toxicology requirements in ASTM International Standard Practice DXXXX, "Standard Practice for the Evaluation of New Aviation Gasolines and New Aviation Gasoline Additives".

During the preparatory stage, a consultant will review the composition of candidate fuels to assess any environmental or toxicological properties relative to current fuels in the widespread market in order to identify any potential regulatory (EPA, OSHA, etc.) concerns associated with their adoption, handling, and use. This information will then be used to develop an emissions test plan that can be implemented during engine testing at the FAA Tech Center in the Test and Evaluation Project Phase, Phase 2 (PROJ-T&E-9).

Figure 33.0 PAFI Environment & Toxicology Preparatory Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
PREPARATORY STAGE		
PREP-E&T-1	Identify EPA/FAA Regulator Authority Relative to General Aviation Emissions	Document FAA & EPA authority, and obligations as related to General Aviation emissions. Completed & included in UAT ARC Final Report Part II , Appendix I.
PREP-E&T-2	Develop E&T Requirements in Support of ASTM Test/Production Spec Requirements Effort	Add environmental and toxicology requirements in ASTM TF responsible for dev of ASTM New Fuel Standard Practice.
PREP-E&T-3	Develop Protocol & Criteria for Environ-ment & Toxicology Assessment (ARL 6.2)	Develop protocol & Criteria for environmental & toxicological properties relative to current AVGAS.
PREP-E&T-4	Develop Emissions Test Plan and Protocol	Develop input & guidance to PAFI to develop a test plan and protocol for exhaust emissions testing.

5.7.1.6. Fuel Developer Integration in Preparatory Stage

There is minimal integration with the prospective fuel developers during this stage.

5.7.1.7. FAA Integration in Preparatory Stage

PAFI will coordinate with the FAA to establish the centralized certification office. PAFI will develop template compliance plans with the office to establish a common understanding of the certification compliance requirements for AVGAS approvals. PAFI will also facilitate the upfront acceptance of conformity and testing procedures to be conducted at the FAA Tech Center. The FAA will develop and issue the RFP to solicit candidate fuels for testing and the FAA Tech Center will be establishing facilities and test equipment to support the testing.

5.7.2. Project Stage Work Scope

Candidate fuels that are accepted into the FAA Test & Evaluation Program will be tested at the FAA Tech Center during this stage. PAFI will monitor and track the fuel developer's progress through the ARLs. The ARL deliverables will be integrated into the FAA review process and will need to be submitted to the FAA Review Board, but they can also be used to support other activities. The ARL deliverables can support ASTM specification development, FAA certification, and investor requests.

PAFI members will support the progression of the candidate fuels through the ASTM specification development and FAA certification processes. In addition, members will also

support meetings with government agencies, private investors, financial institutions, and other stakeholders interested in commercialization of unleaded AVGAS.

A summary of each task in the project stage is provided in Figures 34.0-36.0. Refer to Figure 21.0 for the estimated schedule associated with each project stage task. Implementation plans that include a detailed description and associated cost estimate for each project stage task are provided in Appendix F.

5.7.2.1. Certification & Qualification Project Stage Work Scope

Figure 34.0
PAFI Certification & Qualification
Project Stage Tasks & Work Scope

Task No.	Issue/Task	Work Scope
PROJECT STAGE		
PROJ - C&Q-12	Establish FAA Review Board	Identify, recruit and contract technical specialists to serve on the FAA Review Board to review candidate unleaded fuels for acceptance into FAA Tech Center test.
PROJ - C&Q-13	Support ASTM Research Report and Test Spec Ballot Process	Support ASTM Task Force effort to ballot report and spec and to address ballot.
PROJ - C&Q-14	Conduct Phase 1 Candidate Fuel Review	FAA Review Board reviews and selects candidate unleaded fuels for Phase 1 testing.
PROJ - C&Q-15	Conduct Phase 2 Candidate Fuel Review	FAA Review Board reviews and selects candidate unleaded fuels for Phase 2 testing.
PROJ - C&Q-16	Support ASTM Research Report and Production Spec Ballot Process	Support ASTM Task Force effort to ballot report and spec and to address ballot comments.
PROJ- C&Q-17	Support Certification of Candidate Fuels	Review Tech Center reports and other data submitted by applicant and issue certification approval for in-scope fleet.

5.7.2.2. Test & Evaluation Program Project Stage Work Scope

Figure 35.0 PAFI Test & Evaluation Project Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
PROJECT STAGE		
PROJ-T&E-7	Conduct Phase 1 Testing	Test fuel samples using lab & rig equipment.
PROJ-T&E-8	Prepare Phase 1 Reports	Compile data and prepare report.
PROJ-T&E-9	Conduct Phase 2 Testing	Test fuel in engines & airframes.
PROJ-T&E-10	Prepare Phase 2 Reports	Compile data and prepare report.
PROJ-T&E-11	Conduct Aircraft & Engine Modification Testing	Selective testing of aircraft and engine modifications only for fuels that exceed specified threshold of fleet coverage.

5.7.2.3. Production & Distribution Project Stage Work Scope

There are no "Production and Distribution" related tasks defined at this time in support of the PAFI Project Stage.

5.7.2.4. Impact & Economics Project Stage Work Scope

Figure 36.0 PAFI Impact & Economics Project Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
PROJECT STAGE		
PROJ-I&E-5	Develop Tools for Fleet Impact Assessment (ARL 6.3.a & c)	PAFI oversight and advocacy role. In its advocacy role PAFI will develop tools and methods needed to enable the FAA Review Board to assess the potential adverse impact to the fleet which is not supported by a candidate proposed fuel solution. Impact assessment and mitigation is not within PAFI scope.

5.7.2.5. Environment & Toxicology Project Stage Work Scope

There are no "Environment & Toxicology" related tasks defined at this time in support of the PAFI Project Stage.

5.7.2.6. Fuel Developer Integration in Project Stage

The fuel developer progresses through the project ARLs during this stage and provides the necessary reports and data to demonstrate successful completion of each ARL step. PAFI members will assist the fuel producer in this progression through participation in ASTM Task Forces established for AVGAS specification development, support of proposed AVGAS specification balloting and deliberations at ASTM, and will coordinate with the FAA centralized certification office to facilitate the approval of the fuel. It is anticipated that these activities will be iterative in nature, and require frequent communications between the parties involved.

5.7.2.7. FAA Integration in Project Stage

The FAA plays three key roles during the Project Stage. First, the FAA Review Board will review data submitted by candidate fuel developers and select the best performing fuels for testing. Next, the FAA Tech Center performs the fuel property and aircraft equipment testing necessary to generate the data for the FAA test program, ASTM specification development, and FAA certification. Lastly, the FAA centralized certification office will coordinate with PAFI and the fuel producer to apply a standardized procedure to the review and approval of that data.

5.7.3. Deployment Stage Work Scope

The deployment stage will begin upon FAA certification approval of the first candidate unleaded AVGAS. PAFI members will support the fuel producer's efforts to establish the production and distribution infrastructure necessary for commercialization of the unleaded AVGAS. This will include providing expertise and counsel when dealing with investors, government agencies, local environmental organizations, equipment manufacturers, and other regulatory entities. Once an unleaded AVGAS with least impact on the fleet has been identified, the FAA may consider both short-term and long-term regulatory action to facilitate the transition to unleaded AVGAS in consultation with the EPA. The FAA & EPA will coordinate as appropriate under their respective authorities & obligations.

A summary of each task in this stage is provided in Figures 37.0 – 39.0. Refer to Figure 22.0 for the estimated schedule associated with each deployment stage task. Implementation plans that include a detailed description and associated cost estimate for each deployment stage task are provided in Appendix G.

5.7.3.1. Certification & Qualification Deployment Stage Work Scope

Figure 37.0 PAFI Certification & Qualification Deployment Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
DEPLOYMENT STAGE ARL 13-16		
DEPLOY-C&Q-18	Educate/Engage FAA & Industry Stakeholders	Communicate new fuel certifications and field approval requirements.
DEPLOY-C&Q-19	Consider Leaded AVGAS Phase-out Regulation	Once an unleaded AVGAS with least impact on the fleet has been identified, the FAA may consider both short term and long term regulatory action to facilitate the transition to unleaded AVGAS in consultation with the EPA.

5.7.3.2. Test & Evaluation Deployment Stage Work Scope

There are currently no “Test & Evaluation” tasks defined at this time in support of the PAFI Deployment Stage.

5.7.3.3. Production & Distribution Deployment Stage Work Scope

Figure 38.0 PAFI Production & Distribution Deployment Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
DEPLOYMENT STAGE		
DEPLOY-P&D-4	Establish PAFI Role in Deployment Phase	Identify the role PAFI may play in facilitating deployment of fuel.
DEPLOY-P&D-5	Facilitate Deployment Phase	Interface with applicable industry organizations to facilitate compliance with non-ASTM standards, codes, &requirements.

5.7.3.4. Impact & Economics Deployment Stage Work Scope

Figure 39.0 PAFI Impact & Economics Deployment Stage Tasks & Work Scope		
Task No.	**Issue/Task**	**Work Scope**
DEPLOYMENT STAGE ARL 13-16		
Deploy-I&E-6	Develop Leaded AVGAS Phase-Out Plan	PAFI advocacy role. Facilitate deployment by working with FAA to plan phase out of leaded AVGAS & transition to unleaded AVGAS. FAA & EPA coordinate as appropriate under their respective authorities & obligations.

5.7.3.5. Environment & Toxicology Deployment Stage Work Scope

There are no "Environmental & Toxicology" tasks defined at this time in support of the PAFI Deployment Stage.

5.7.3.6. Fuel Developer Integration in Deployment Stage

The fuel producer will be utilizing the PAFI and the FAA resources to accelerate the commercialization of the approved fuel.

5.7.3.7. FAA Integration in Deployment Stage

PAFI will need to coordinate with the FAA Flight Standards and Airports organizations to ensure a smooth transition to fielding of the new unleaded AVGAS.

6. References

(1) ASTM D910, "Standard Specification for Aviation Gasolines", American Society for Testing and Materials.

(2) "Aviation Fuels Research Reciprocating Engine Aircraft Fleet Fuel Distribution Report", DOT/FAA/AR-TN11/22, dated November 2011.

(3) CRC Report No. 657, "Investigation of Reduced TEL Content in Commercial 100LL AVGAS", Rev A dated May 09, 2011.

(4) CRC Report AV-7-07, "Research Results Unleaded High Octane Aviation Gasoline", June 17, 2010.

(5) FAA Advisory Circular 20-24C, "Approval of Propulsion Fuels and Lubricating Oils", July 29, 2011.

(6) FAA ARM Committee Manual ARM 001-015, Revision 36, July 27, 2009.

(7) Orr, M., "The History, Specification, Production, Use and Evaluation of Unleaded Aviation Gasoline", Report by the ASTM D910 Task Force of D02.J.02.

(8) "Review of Certificates of Analysis and Test Data of Aviation Gasoline for Current Ranges of Lead Additive", DOT/FAA/AR-TN11/20, dated October 2011.

(9) ASTM Subcommittee J on Aviation Fuels Operating Procedures, Annex A6, "Guidelines for the Development and Acceptance of a New Aviation Fuel Specification for Spark-Ignition Reciprocating Engines", approved June 2002

(10) General Aviation Statistical Databook & Industry Outlook 2010, General Aviation Manufacturers Association

(11) U.S. Energy Information Administration, http://www.eia.gov

– End of Report Part I Body –

Note: See UAT ARC Final Report Part II Appendices for Appendices A – M.

HARE Leaded Fuel Subcommittee

DEQ PATS Lead Modeling, Follow-Up Studies, and Technical Background Information

October 28, 2013

Attachments:

1) **Ambient lead concentration maps from PATS study (DEQ)**
2) **Hillsboro Airport Lead Study (Camp, Dresser & McKee; Port of Portland)**
3) **Hillsboro Airport Lead Fact Sheet (DEQ)**
4) **Summary of lead issues at HIO, provided to FAA for HIO Parallel Runway Supplemental EA (Port of Portland)**
5) **Summary of Transportation Research Board leaded fuels roadmap May 13 – 14, 2013 (Port of Portland)**
6) **Leaded AvGas Use in General Aviation Aircraft fact sheet (Port of Portland)**

Ambient lead concentration maps from PATS study

(DEQ)

HIO LEAD MODELING RESULTS AND THE NATIONAL AMBIENT AIR QUALITY STANDARD

The USEPA has adopted National Ambient Air Quality Standards (NAAQS) for the criteria pollutants, including lead. These standards are set by USEPA and are designed to protect public health and welfare with an adequate margin of safety and with consideration given to sensitive populations. As noted by USEPA:

"The Clean Air Act, which was last amended in 1990, requires EPA to set National Ambient Air Quality Standards (40 CFR part 50) for pollutants considered harmful to public health and the environment. The Clean Air Act identifies two types of National Ambient Air Quality Standards. Primary standards provide public health protection, including protecting the health of "sensitive" populations such as asthmatics, children and the elderly. Secondary standards provide public welfare protection, including protection against decreased visibility and damage to animals, crops, vegetation, and buildings." (hppt://www.epa.gov/air/criteria.html)

Washington County has been designated by USEPA as attainment for all of the NAAQS and has no history of violating USEPA air quality standards. The area around Hillsboro Airport currently meets, and is expected to continue to meet, all of the NAAQS, including the lead NAAQS to protect public health and welfare.

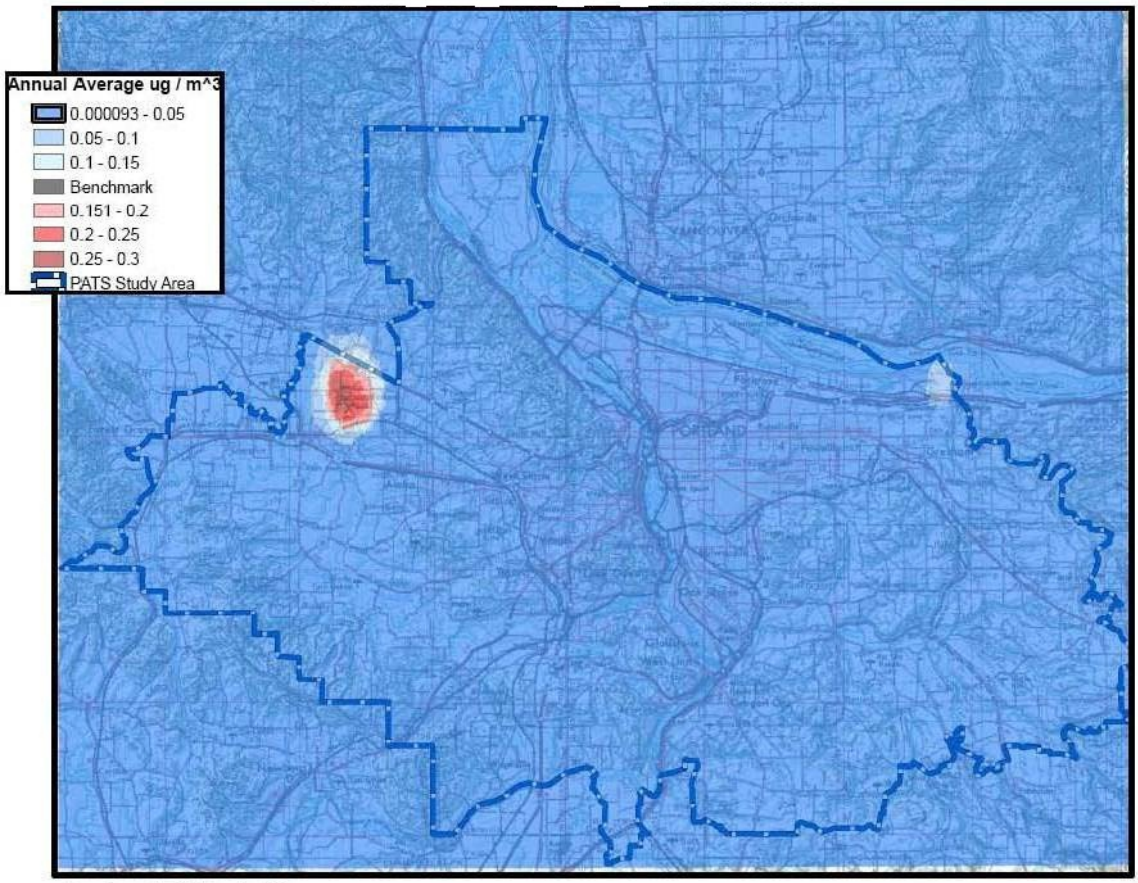
As part of the Portland Air Toxics Solutions project, ODEQ modeled lead concentrations along with other air toxics within the Portland-Vancouver air shed using the CALPUFF atmospheric dispersion modeling system. This model is most often used to assess dispersion over long distances, from tens to hundreds of kilometers. The lead emission inputs to ODEQ screening modeling analysis were based on the emissions from 2005 operations at Hillsboro Airport. The results of a screening level model run showed an area around the Airport that had the potential to have ambient lead concentrations greater than the NAAQS of 0.15 µg/m3 (calendar quarter average). This initial screening level model run, however, incorporated all lead emissions at Hillsboro Airport as a ground-level area source and did not account for dispersion effects from aircraft in flight and operating beyond the airport boundary. The model was subsequently refined by ODEQ by adjusting the emission release parameters to more accurately simulate emissions from actual flight operations. The refined model showed a maximum predicted concentration of 0.00331 µg/m3 at "receptor" level (ground level), well below the NAAQS.

In the fall of 2010, a study was prepared by CDM, on behalf of the Port, in response to the ODEQ's initial evaluation of lead emissions. The Port retained CDM to model lead emissions associated with Hillsboro

Airport's 2007 operations using the FAA's required model, the Emission & Dispersion Modeling System (EDMS). EDMS uses the AERMOD atmospheric dispersion model to complete the dispersion analysis. AERMOD is the model recommended by EPA for near-field lead dispersion analysis. CDM conducted several evaluations using different modeling approaches, assumptions, and sensitivity analyses. The maximum modeled concentration for lead around the Airport perimeter was 0.00405 µg/m3, closely approximating the results of DEQ's refined model.

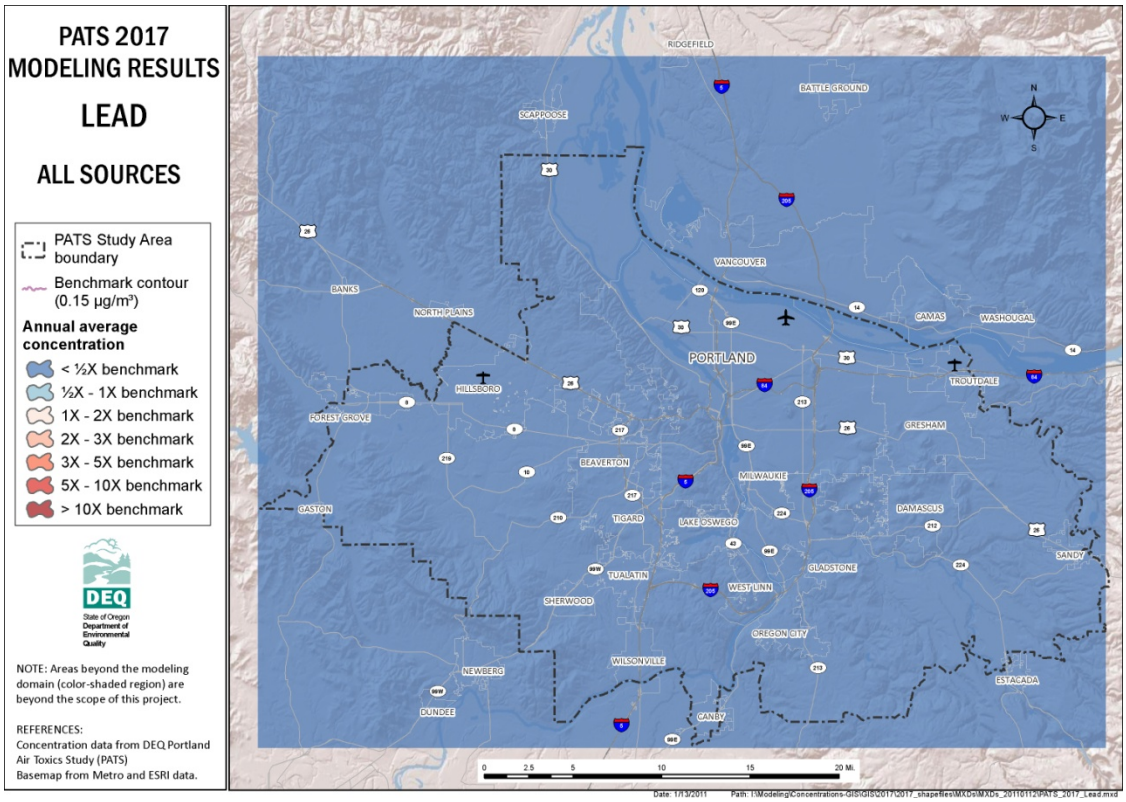
That 2010 study provides an indication of how emissions from Hillsboro Airport can be compared with the NAAQS. The maximum modeled concentration of lead emissions, 0.06567 µg/m3, is less than 50% of the lead NAAQS. It should be noted that this maximum concentration was produced from a model sensitivity analysis in which all of the emissions associated with the airport (e.g., airborne and ground-level emissions) were concentrated into the ground-level source representing the runways and taxiways.

PATS 2005 Lead Modeling (Screening Level Analysis)



Benchmark: 0.15 ug/m^3

PATS 2017 Lead Modeling (Refined Approach Analysis)



Hillsboro Airport Lead Study

(Camp, Dresser & McKee; Port of Portland)

Section 1
Executive Summary

The Oregon Department of Environmental Quality (ODEQ) recently completed an analysis of lead emissions from airports located in the state. Dispersion modeling was then completed using the CALPUFF model, a non-steady-state dispersion model that simulates the effects of long distance pollutant transport. The results indicated that a high concentration of lead that could exceed the National Ambient Air Quality Standard (NAAQS) was located over Hillsboro Airport (HIO). As a result, the Port of Portland requested that a parallel study be completed to evaluate lead emissions and dispersion using the Federal Aviation Administration's (FAA's) required model, the Emission & Dispersion Modeling System (EDMS). EDMS uses the AERMOD modeling system, a steady-state plume model, to complete dispersion.

An emissions inventory for lead was completed for existing conditions (2007) using aircraft operation information from the Draft Hillsboro Airport Parallel Runway 12L/30R Environmental Assessment. EDMS estimate lead emissions to be approximately 0.632 tons per year for piston aircraft; all turbine aircraft were excluded from the study. Further review of the data indicated that approximately five percent of the airport's emissions are from ground-level sources associated with taxiing and idling at the airport. It would therefore be overly conservative to consolidate all of an airport's emissions into a ground-level source because emissions would disperse differently at a higher release height.

EDMS typically generates several hundred emission sources for a given airport. ODEQ requested that these sources be simplified into no more than ten sources, which could then be imported into the CALPUFF model. Several dispersion analyses were completed to accomplish the following goals:

1. Complete dispersion modeling using EDMS directly to serve as a comparison for the simplified AERMOD dispersion.

2. Complete modeling using the simplified sources for eventual use in CALPUFF.

3. Complete sensitivity analyses to evaluate how modifying the sources affects the modeling.

    a. Evaluate the effects of lower the release heights of the emission sources.

    b. Evaluate the effects of merging all of the emission sources into a ground-level source, equal to the area of the taxiways and runways.

The simplified modeling indicate that the average modeled concentration was approximately 17 percent less than the EDMS model, whereas the maximum concentration was approximately four percent less than EDMS. The maximum concentration from the ODEQ's CALPUFF modeling, however, was found to be approximately 60 times greater than the peak concentration from the EDMS modeling. The results indicate that the CALPUFF modeling is overly conservative and that the lead emissions from HIO should not exceed the NAAQS level of 0.15 $\mu g/m^3$, based on a three-month rolling average.

The results of the modeling are provided in Table 1-1.

Table 1-1
Results of EDMS and AERMOD Air Dispersion Modeling

Scenario	Concentration ($\mu g/m^3$)	Difference (Compared to EDMS) ($\mu g/m^3$)	Percentage Difference
Maximum Concentration			
EDMS	0.00405	n/a	n/a
Simplified AERMOD Run	0.00389	-0.00016	-4%
Adjusted Release Height	0.00766	0.00361	89%
Ground-Based Sources	0.06567	0.61620	1,521%
Average Concentrations			
EDMS	0.00082	n/a	n/a
Simplified AERMOD Run	0.00068	-0.00014	-17%
Adjusted Release Height	0.00104	0.00022	26%
Ground-Based Sources	0.01007	0.00925	1,127%

Key:
$\mu g/m^3$ = micrograms per cubic meter
AERMOD = AMS/EPA Regulatory Model
AMS = American Meteorological Society
EDMS = Emission & Dispersion Modeling System
EPA = Environmental Protection Agency

Section 2
Overview

The Oregon Department of Environmental Quality (ODEQ) recently completed an inventory of lead emissions from airports located in the State. Air dispersion modeling was then completed using the CALPUFF modeling system to evaluate if there were any localized concentrations of lead in the state. The dispersion modeling completed by ODEQ suggested that a high concentration of lead could be centered near Hillsboro Airport (HIO). Figure 2-1 shows the results of the modeling completed by ODEQ. Although the maximum concentration determined by ODEQ is not explicitly provided, based on the results of the figure, it appears as though a high concentration of lead (approximately 0.25 $\mu g/m^3$) is centered over HIO.

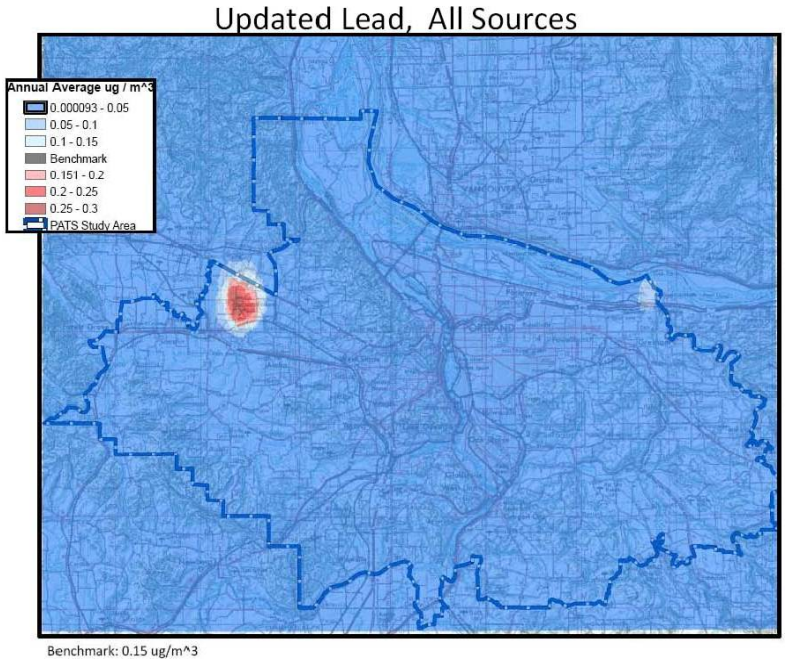


Figure 2-1. Results of ODEQ modeling (provided by ODEQ).

An updated emissions inventory and refined dispersion modeling was completed using the Federal Aviation Administration's (FAA's) Emission & Dispersion Modeling System (EDMS) to compare to the ODEQ CALPUFF results. EDMS uses the Environmental Protection Agency's (EPA's) preferred refined dispersion model, AERMOD. Since EDMS will typically create several hundred or thousand emission sources for a typical airport, the emission sources were simplified so that the model would contain no more than ten emission sources. The results of the simplified model were then compared to the full EDMS model to verify the results.

Section 3
Methodology

This section describes the methodology used to complete the lead emissions inventory for the airport and to complete the air dispersion modeling.

3.1 Model Selection

The Federal Aviation Administration's (FAA's) Emission & Dispersion Modeling System (EDMS) was used to estimate emissions of lead from general aviation aircraft operations at Hillsboro Airport (HIO). EDMS uses the Environmental Protection Agency's (EPA's) AERMOD modeling system to complete the air dispersion element of the study. AERMOD is the EPA's recommended refined air dispersion model in 40 CFR 51, Appendix W. EDMS is also the FAA's required model for air quality analyses for aviation sources and was therefore selected for use in this study.

3.2 User-Created Aircraft

By default, EDMS creates emission inventories of criteria pollutants, including carbon monoxide (CO), volatile organic compounds (VOC), nitrogen oxides (NOx), sulfur oxides (SOx), and particulate matter (PM_{10} and $PM_{2.5}$). To estimate emissions of lead (Pb) directly in EDMS, it was necessary to define user-created aircraft that specified a lead emissions index (EI).

The lead EI was calculated using the maximum lead content allowed in aviation gas (avgas) (0.56 grams per liter) and the average density of avgas (6 pounds per gallon). The lead EI is then calculated as approximately 0.78 grams of lead per kilogram of avgas (lead content divided by density).

The consolidated aircraft fleet mix for 2007 existing operations contained in Appendix C to the Draft Hillsboro Airport Parallel Runway 12L/30R Environmental Assessment ("Draft EA") was used as a starting point for the creation of user-specific aircraft. Each combination of representative aircraft and engine types was used to define the user-created aircraft; all turbine aircraft (turboprop, turbojet, and helicopter turbine) were excluded from further analysis. Table 3-1 identifies the user-created aircraft and associated landing/takeoff operations (LTOs) and touch-and-go operations (TGOs).

Table 3-1 Fleet Mix for Hillsboro Airport (HIO) Lead Study					
Representative Aircraft	**Representative Engine**	**EDMS User-Created Aircraft Name**	**TGOs**	**LTOs**	**Total**
Cessna 150 Series	O-200	HIO-FP-o 235	5,474	4,259	9,733
Cessna 172 Skyhawk	O-320	HIO-FP-o 320	18,042	14,037	32,079
Cessna 182	IO-360B	HIO-FP-o 360	2,770	2,156	4,926
Cessna 210 Centurion	TIO-540-J2B2	HIO-FP-tio 540	3,759	3,117	6,873
Raytheon Beech Bonanza 36	TIO-540-J2B2	HIO-VP-io 360	2,912	3,348	6,260
Cessna 337 Skymaster	IO-360B	HIO-MEP-o 360	293	1,557	1,850
Cessna 310	TIO-540-J2B2	HIO-MEP-tio 540	238	1,263	1,501
Robinson R22	IO-360-B	HIO-HP-o 360	35,145	10,177	45,322
Robinson R44 Raven	TIO-540-J2B2	HIO-HP-io 540	1,849	536	2,385
Total			**70,479**	**40,450**	**110,929**

The aircraft were created by defining the fuel flow rates and flight profiles as being equivalent to the representative aircraft/engine combinations. The emission indices for the specific engine were zeroed out with the exception of PM, which was changed to be equal to the calculated lead EI. Figure 3-1 shows a typical data entry screen for the user-created aircraft used in the study.

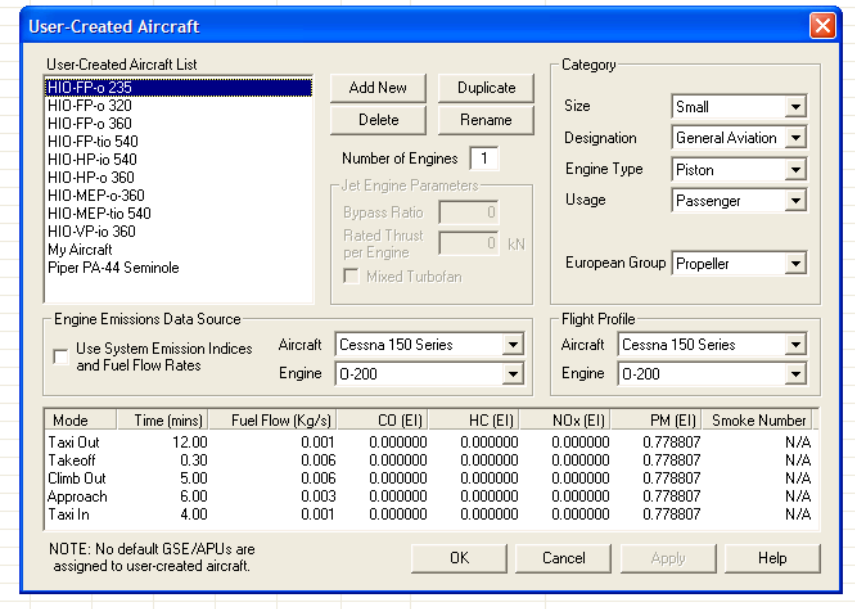


Figure 3-1. Screenshot of example user-created aircraft data entry.

3.3 Airport Layout and Configuration

A simplified airport layout, adapted from Figure 1-1 of the Draft EA, was developed for EDMS. The airport layout was simplified to only include the Main Apron; Runway 12/30; Taxiways A, A1, and A8; and Charlie Helipad. The cross-runway 2/20 was not included in the analysis because of its limited use. The runway use percentages were derived from Table 1AA of the HIO Master Plan and were adjusted to reflect runway use assuming that only Runway 12/30 was operational. The runway usage by aircraft type was then averaged for input into the runway assignments section of EDMS. Table 3-2 summarizes the runway use percentages used in the modeling.

Table 3-2
Runway Use Percentages

Aircraft	Runway Usage	
	12	30
Itinerant Operations		
SEPF (Fixed Propeller)	7.29%	92.71%
SEPV (Variable Pitch Propeller)	7.29%	92.71%
MEP (Multi-Engine Piston)	18.95%	81.05%
Average	*11.18%*	*88.82%*
Local Operations		
SEPF (Fixed Propeller)	2.13%	97.87%
SEPV (Variable Pitch Propeller)	2.13%	97.87%
MEP (Multi-Engine Piston)	40.00%	60.00%
Average	*14.75%*	*85.25%*

EDMS requires the runway configuration to be identified for each size of aircraft (small, large, and heavy). In order to account for the proper runway configuration by aircraft type, it was necessary to complete two individual model runs for aircraft sources and for helicopters. Not doing so would result in an underestimation of emissions from the aircraft. For helicopter emissions on Charlie Helipad, all takeoffs were assumed to occur at the southeastern portion of the landing strip.

3.4 Receptors

Two main types of receptors were used in the modeling: plant boundary receptors and uniform polar grid receptors. A Cartesian plant boundary was placed along the property boundary of HIO. Intermediate receptors were then placed every 100 meters along the property boundary. A uniform polar grid was centered over the airport emission sources and extended approximately 2,000 meters from the airport boundary. Direction radials were spaced in increments of 10 degrees around the airport, while each spoke on the polar grid had 100-meter spacing. All receptors located on the airport property were removed from modeling. Figure 3-2 identifies the receptors that were used in the modeling.

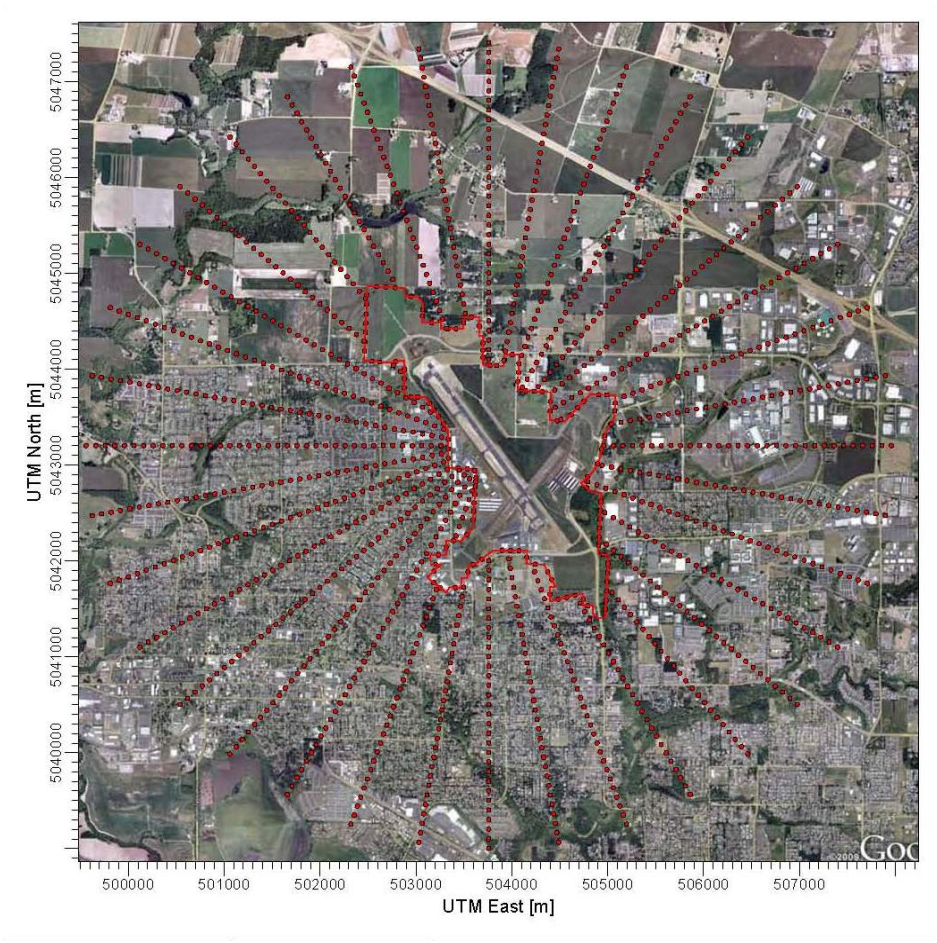


Figure 3-2. Uniform polar grid and Cartesian plant boundary receptors used in modeling.

A review of the 7.5-minute series Hillsboro Quadrangle from the United States Geological Survey (USGS) indicates that the area surrounding the airport is relatively flat. Although there are hills to the northeast of the airport, they are not within the modeled flight path and receptors for the airport and would not affect the modeling. The terrain was therefore modeled as flat and elevation data was not imported into the model.

3.5 Meteorological Data

Representative meteorological data is required to complete the necessary air dispersion modeling. Portland International Airport (ID No. 24229) was determined to be the closest representative surface weather station to HIO and was selected for use in the model. Salem McNary Field (ID No. 24232) was identified as the closest upper air weather station to HIO. Data was downloaded from the WebMET website (http://www.webmet.com), a source of free meteorological data. The most recent year of data available, 1990, was used in the analysis.

3.6 Emission Sources

EDMS models aircraft activity that occurs during six modes of operation. The following modes in an LTO cycle are identified as follows:

- Approach – Airborne segment of an aircraft's arrival extending from the start of the flight profile to touchdown on the runway.
- Taxi-in – The landing roll segment of an arriving aircraft and the taxiing from the runway exit to a gate.
- Startup – Aircraft main engine startup at the gate. Since this mode is only applicable to International Civil Aviation Organization (ICAO) engines, emissions at the gate were not modeled because piston engines are not ICAO certified.
- Taxi-out – Taxiing from the gate to a runway end.
- Takeoff – Segment that extends from the start of the ground roll on the runway through the airborne portion of the ascent during which the aircraft operates at maximum thrust.
- Climb Out – Segment from engine cutback at maximum thrust to the end of the flight profile or mixing height (whichever is lower)

3.6.1 EDMS Sources

EDMS generated over 1,100 sources to represent aircraft activity at the airport. In addition, it creates an hourly emission rate (HRE) that specifies emissions for every source and hour of the day. For the HIO modeling, the HRE file contained over 10 million lines of data and was approximately 500 megabytes.

EDMS creates a series of area sources to represent aircraft emissions. Ground-based emission sources, such as taxiing, have a release height of 12 meters, which is the approximate height of an engine. Airborne sources, such as approach and takeoff operations, are shown as a series of elevated area sources that rise from approximately 22 meters to 619 meters, or the maximum height of the flight profile.

3.6.2 Simplified Sources

To evaluate how to consolidate the EDMS-generated sources to a simplified AERMOD dispersion run, the distance of each source from the runway end was plotted against its height above ground. Release heights of 100 meters, 300 meters, and 500 meters were selected to represent the airborne emissions associated with the airport. The plots of the arrival and departure sources indicated that the airborne sources generally overlap at the same distance from the runway end at these elevations. As a result, the arrival and departure operations were consolidated into a single area source for each release height. The length of each area source was taken as the distance from the runway end for all of the EDMS sources at each of the release

heights. The width of the emission source was taken as the distance between Runway 12/30 and Charlie Helipad.

A total of seven source groups were consequentially created to represent the aircraft: three elevated sources from Runway 12, three elevated sources from Runway 30, and one ground-level source to represent aircraft movements on the runway and taxiways. To further simplify the model, aircraft and helicopter emissions were also merged into each of the sources; Charlie Helipad was not explicitly included in the model as a source.

3.6.3 Emission Rates

A goal of the simplified modeling was also to avoid the large HRE file that is created by EDMS; rather, an average annual emission rate was used for each of the sources. Emissions from each source type in the HRE file were converted to emissions of tons per year using a Microsoft Access Query. Emissions were found to be slightly less than the emissions inventory developed directly by EDMS; therefore, emissions for the sources were adjusted to equal the EDMS emission inventory. Emissions were then divided by the total area of all of the sources, as determined by EDMS, to create an average emission rate for entry into the models. The aircraft were assumed to be operating continuously at 8,760 hours to per year to develop an average annual emission rate. The emission rates for each main source category are provided in Table 3-3.

Table3-3
AERMOD Emission Rates (Average Annual)

Source	Emissions		Area	Model Emission Rate
	(tpy)	(g/sec)	(m^2)	(g/(s-m^2))
Takeoff 30/Approach 12	0.328	9.42E-03	3,216,000	2.93E-09
Takeoff 12/Approach 30	0.270	7.75E-03	3,264,000	2.38E-09
Taxiways	0.035	9.97E-04	240,000	4.25E-09
Total[a]	**0.632**	**1.82E-02**	**6,720,000**	**2.70E-09**

Notes:

[a] Total emission rate identified for "Model Emission Rate (g/(s-m^2))" is the weighted average of the other modeled emission rates, rather than an additive total.

Key:

tpy = tons per year

g/sec = grams per second

m^2 = square meters

g/(s-m^2) = grams per second per square meter

Section 4
Emission Inventory Results

An emissions inventory was completed for lead emissions from aviation gas-fueled aircraft (piston engines) at HIO. The user-created aircraft described in Section 2 were entered into EDMS for the number of LTOs and TGOs identified in the Draft EA for existing conditions. Table 4-1 summarizes the lead emissions and fuel consumption that was estimated by EDMS for piston aircraft operations at HIO.

Table 4-1
Summary of Emissions and Fuel Consumption

Mode	Lead Emissions		Fuel Consumption	
	(kg/yr)	(tpy)	(kg/yr)	(tpy)
Taxi-Out	3.177	0.004	4,079	4
Takeoff	56.969	0.063	73,149	81
Climb out	212.921	0.235	273,393	301
Approach	278.400	0.307	357,470	394
Taxi-In	21.648	0.024	27,796	31
Total	**573.114**	**0.632**	**735,887**	**811**

Key:
kg/yr = kilograms per year
tpy = short tons per year

To verify the lead emissions inventory that was generated by the model, the fuel consumption estimated by EDMS was multiplied by the lead EI that was entered into the model (0.78 grams lead per kilogram fuel). Annual emissions of lead were estimated to be 0.632 tons per year, which is equal to the lead emissions estimated by EDMS. The method used to estimate lead emissions and dispersion in EDMS was therefore confirmed and no further edits to the model were necessary.

4.1 Source Analysis

As is shown in Table 4-1, total emissions from ground-level sources (e.g., taxi-out and taxi-out) are approximately 0.028 tons per year (tpy). Ground-level source therefore represent less than five percent of the total emissions associated with the airport, as calculated by EDMS. Since the ground-based source represents a small percentage of total emissions at the airport, modeling all of the airports emissions at this level would be overly conservative because emissions would be focused on the ground. By concentrating the emissions at the ground, the ground-level concentrations would be higher than if the emissions were to be dispersed at the higher elevations from the airborne sources.

Section 5
Dispersion Results

The following section describes the results of the air dispersion modeling that was completed for HIO. Results from the full EDMS modeling and the simplified approach are both presented.

5.1 EDMS Dispersion Results

Air dispersion modeling was initially completed using the EDMS-generated sources and HRE files. Due to complications with runway assignments, it was necessary to create two files to model aircraft and helicopter emission sources separately. Modeling was completed using the Lakes Environmental graphical user interface (GUI) to AERMOD. Although sources can be modeled in EDMS directly, EDMS uses a local coordinate system. The files were modeled by Lakes in order to shift the sources to a NAD83 UTM coordinate system. The latest version of AERMOD, Version 09292, was used to complete the modeling.

The ground-level concentrations of lead from aircraft and helicopter emissions were added externally for each receptor. The maximum concentration of lead from aircraft was 0.00396 micrograms per cubic meter ($\mu g/m^3$), while the maximum concentration from helicopters was 0.00022 $\mu g/m^3$; however, these concentrations occurred at different receptors. The maximum combined concentration was 0.00405 $\mu g/m^3$, while the average combined concentration from all receptors was 0.00082 $\mu g/m^3$. Figure 5-1 shows the results of the dispersion modeling.

5.2 Simplified AERMOD Dispersion Results

Air dispersion modeling was also completed using the seven simplified area sources described in Section 2 and the average annual emission rates. Since aircraft and helicopter sources and emissions were combined for this study, only one model was created for the simplified approach. The maximum ground-level concentration of lead was estimated at 0.000389 $\mu g/m^3$ from this simplified approach. This value is approximately 0.0002 $\mu g/m^3$ less than the combined results of the EDMS modeling. The ground-level concentration is approximately four percent less than the EDMS modeling. The average lead concentration was 0.00068 $\mu g/m^3$, which is 17 percent less than the EDMS modeling. Figure 5-2 shows the results of the simplified AERMOD dispersion modeling.

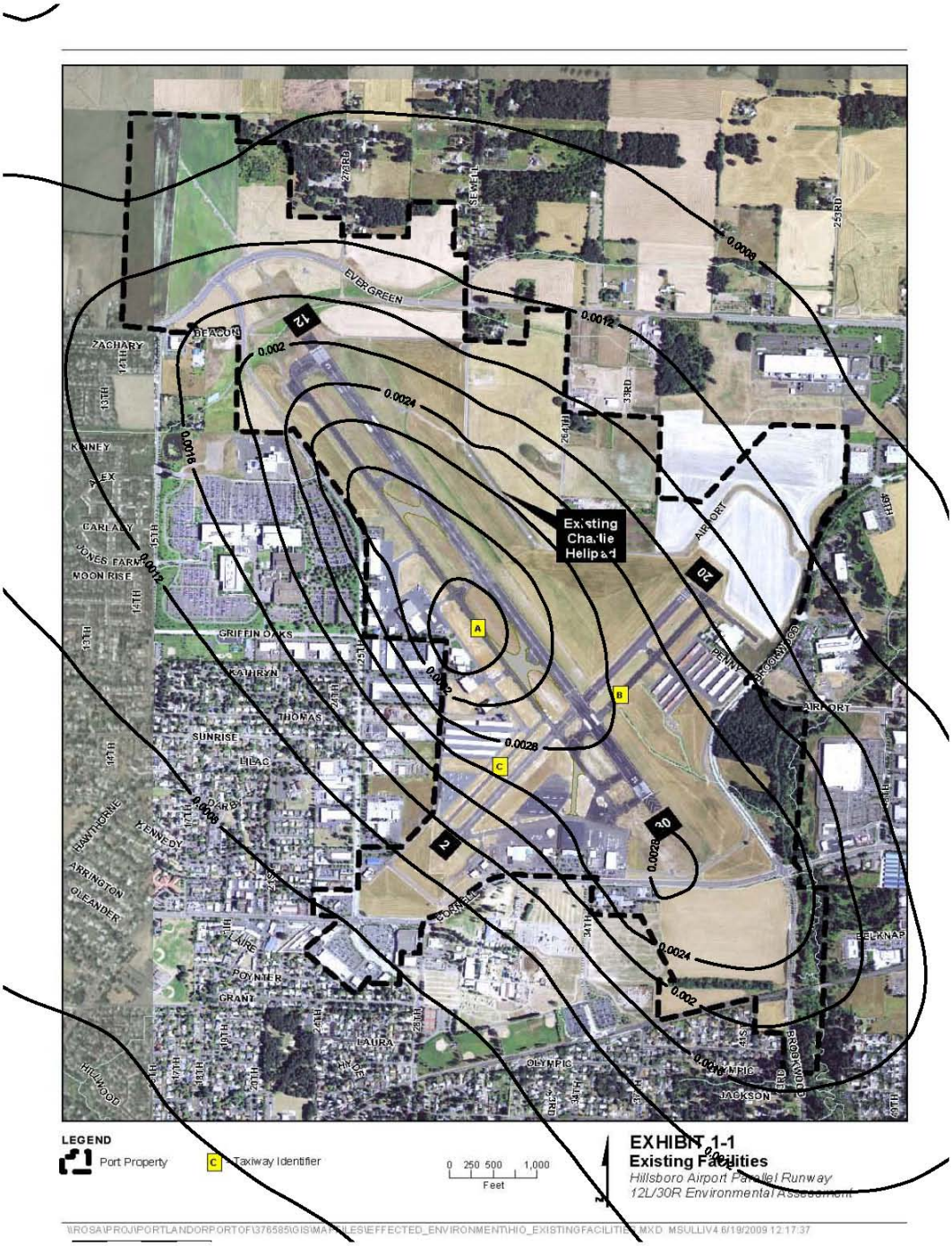


Figure 5-1. Lead concentrations from combined (aircraft + helicopter) EDMS modeling.

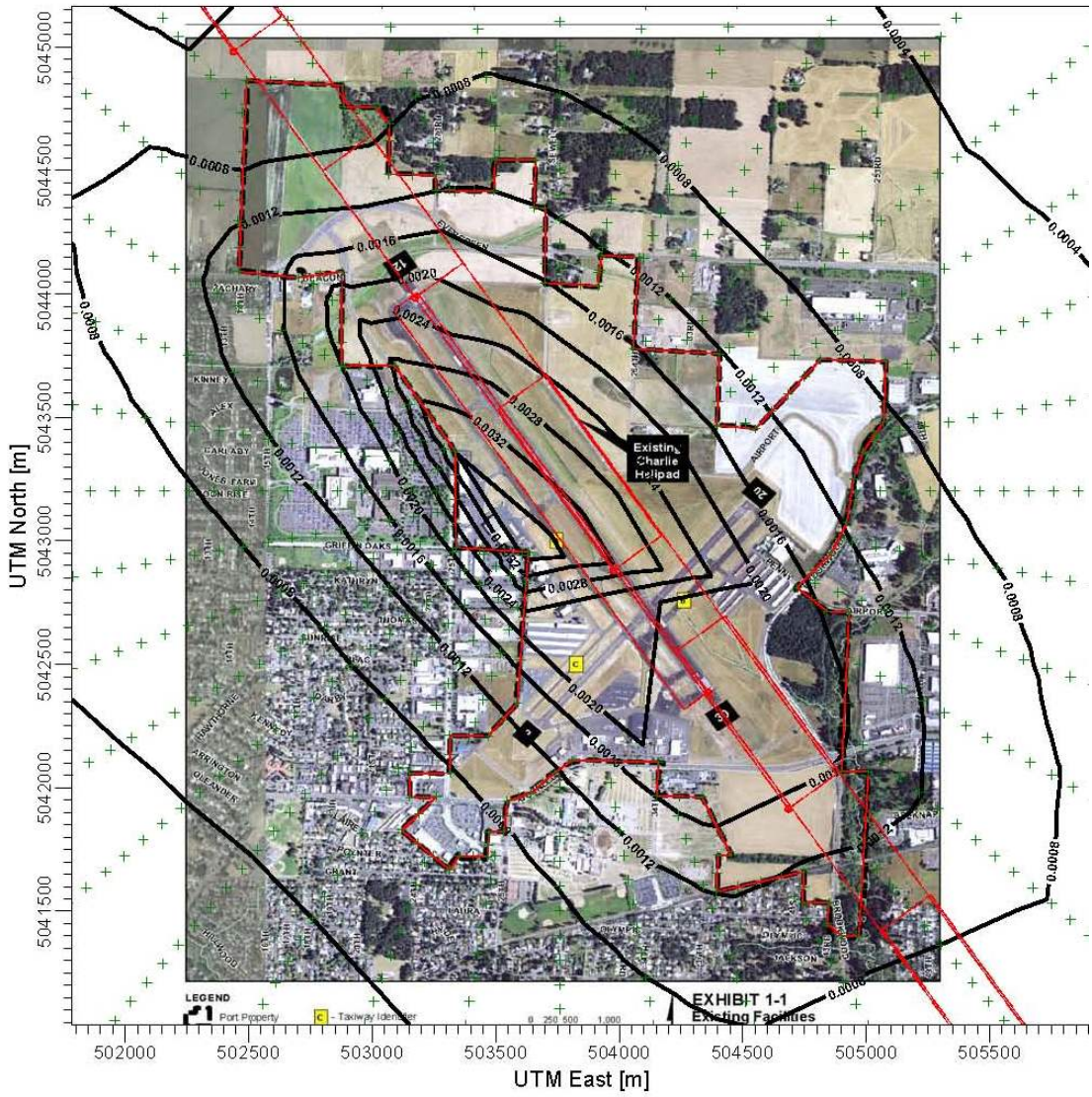


Figure 5-2. Lead concentrations from simplified AERMOD modeling.

5.3 Sensitivity Analysis

A sensitivity analysis was completed to evaluate how lead concentrations would be affected by different source scenarios.

5.3.1 Modified Source Release Height

An initial sensitivity analysis was completed by decreasing the height of the airborne release heights by 50 meters from the original simplified model. This resulted in airborne release heights of 50, 250, and 450 meters. The default release height for ground-level aircraft is 12 meters, which most closely represents the engine height of large jet aircraft. Since the only sources included in the modeling are small piston aircraft, the release height was estimated to be approximately half of the default height (6 meters).

The maximum ground-level concentration was estimated at 0.00766 $\mu g/m^3$, while the average concentration was estimated at 0.00104 $\mu g/m^3$. These values were found to be 89 percent and 26 percent higher, respectively, than the EDMS concentrations. Figure 5-3 shows the isopleths created with this model scenario.

5.3.2 Ground-Level Sources

A second sensitivity analysis was completed to evaluate the effect of concentrating all of the emissions associated with the airport (i.e., airborne and ground-level emissions) into the ground-based source for taxiing. The maximum ground-level concentration was estimated at 0.06567 $\mu g/m^3$, while the average concentration was estimated at 0.01007 $\mu g/m^3$. These values were found to be over 1,500 percent and over 1,100 percent higher, respectively, than the EDMS concentrations. Figure 5-4 shows the isopleths created with this model scenario.

5.4 Source Group Analysis

Source groups were used in the modeling to determining the contribution of an emission source to the overall concentration. The results of the simplified modeling indicate that on average airborne sources contribute 23 percent of the modeled concentration, whereas ground sources contribute the remaining 77 percent. The sensitivity analysis with the reduced release heights indicated that airborne sources represent 32 percent of the modeled concentration, whereas ground sources reflect 68 percent. The distribution of all source groups for the maximum concentration from the AERMOD models is provided in Figure 5-5.

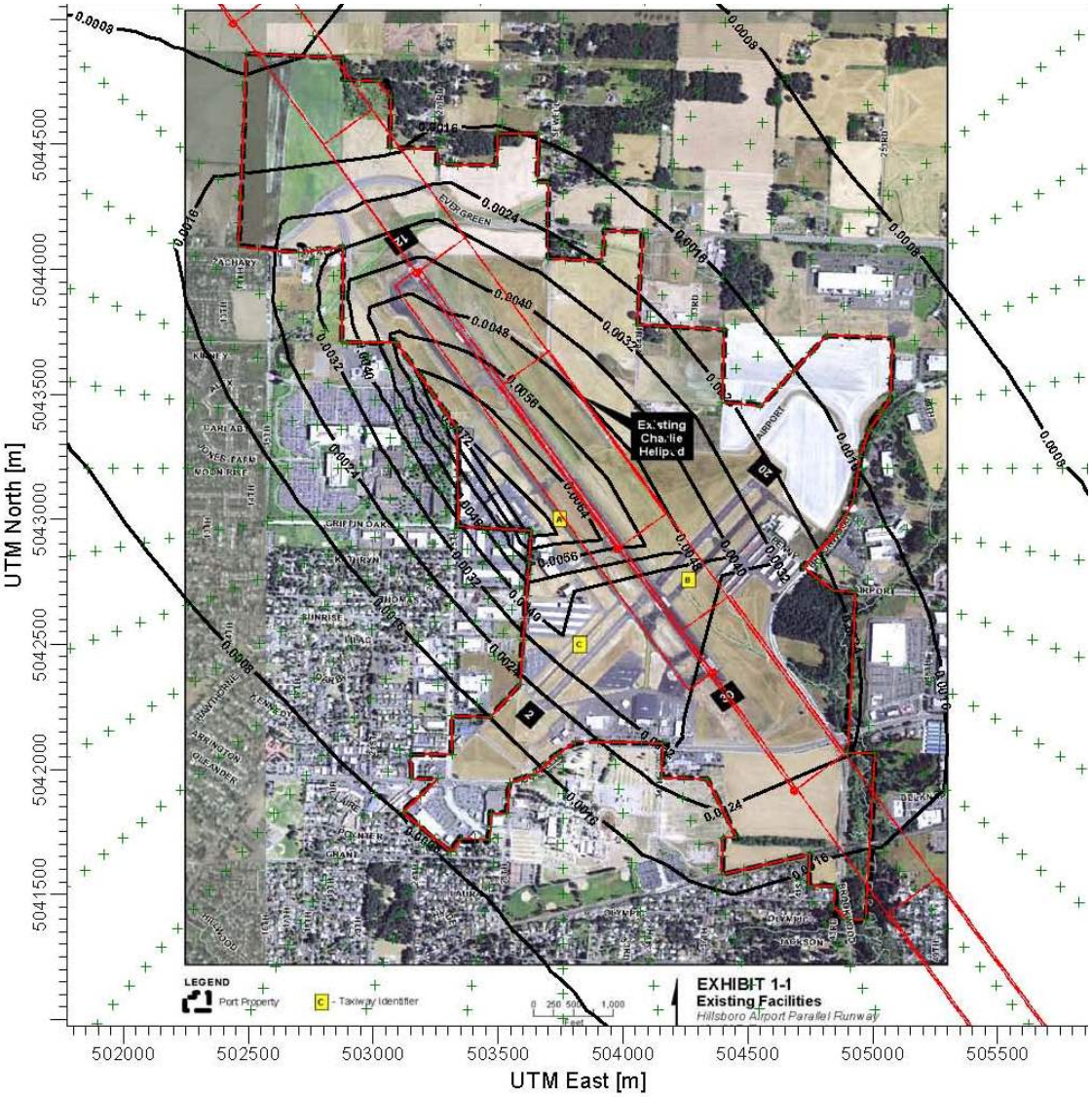


Figure 5-3. Sensitivity Analysis: Release height reduced by 50 meters for airborne sources and ground-based source release height reduced to 6 meters.

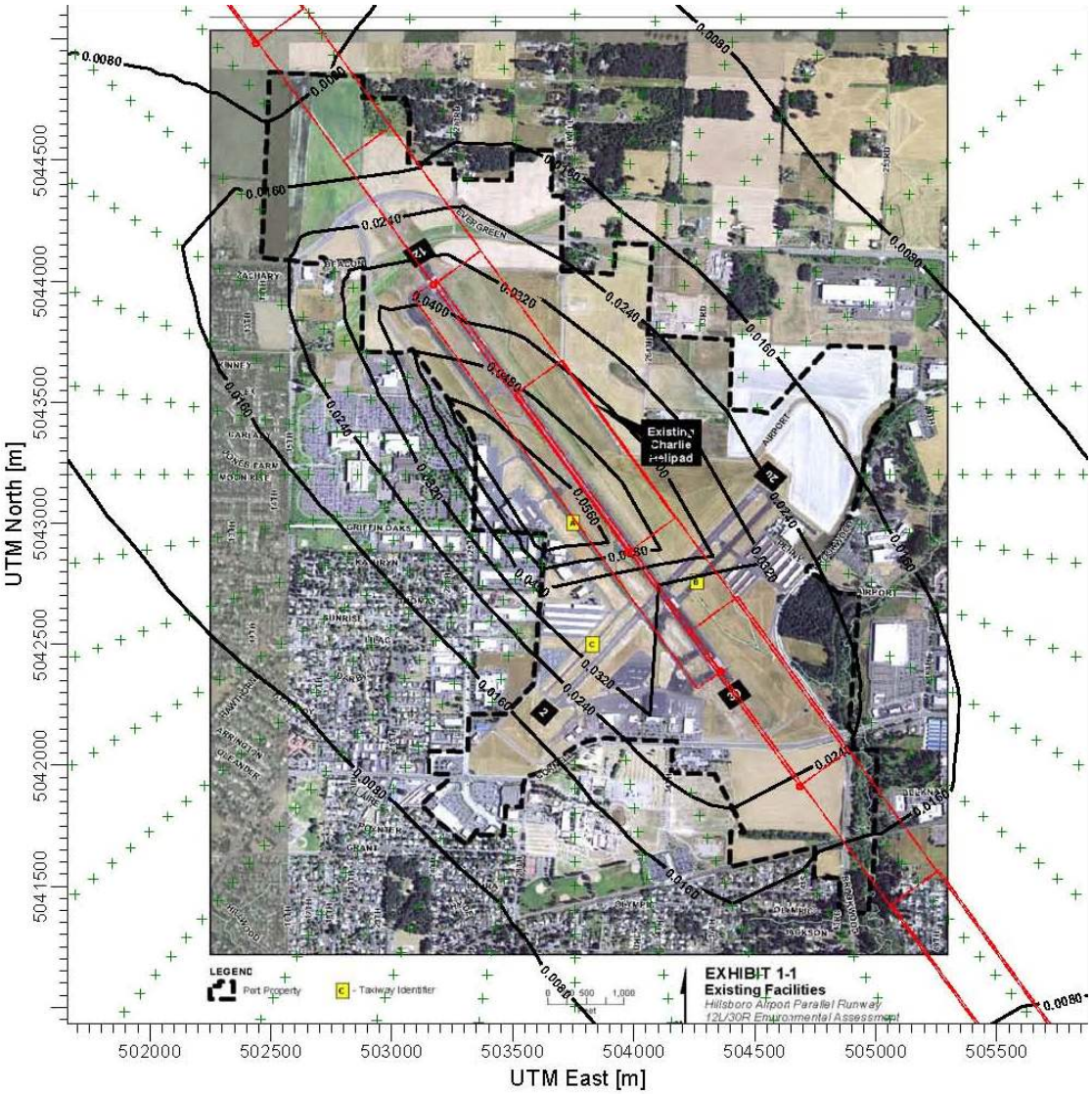
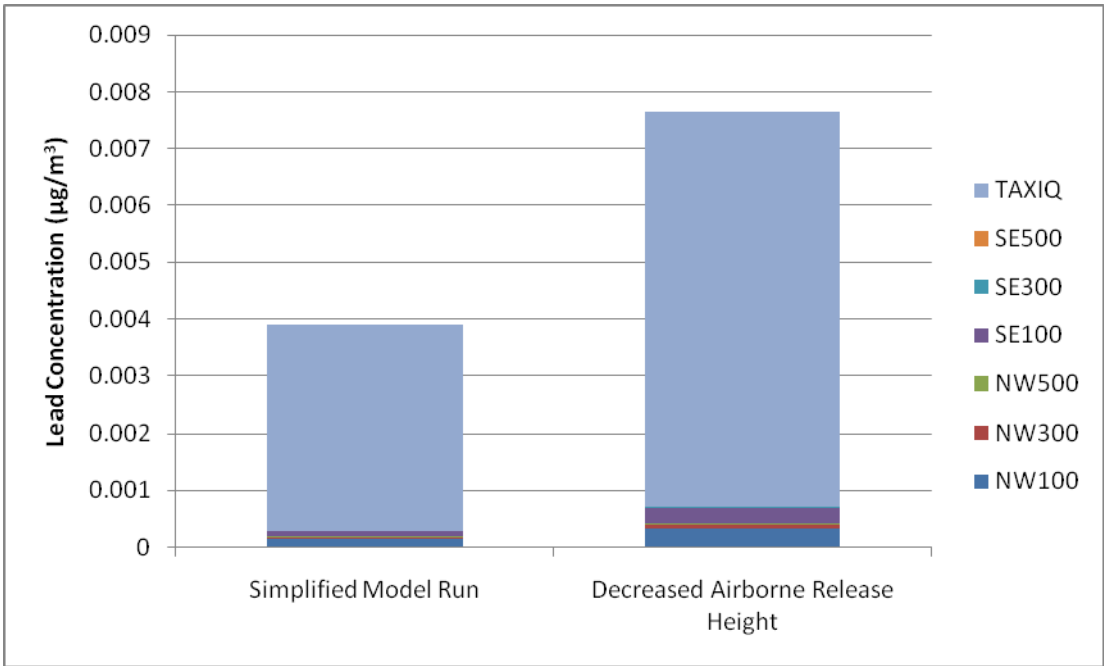


Figure 5-4. Sensitivity Analysis: Emission rates for all sources consolidated into ground-level source group.



Key:
TAXIQ = taxi/idle source group
SE500 = Takeoff (RW12) and Approach (RW 30) – 500/450 meter release height
SE300 = Takeoff (RW12) and Approach (RW 30) – 300/250 meter release height
SE100 = Takeoff (RW12) and Approach (RW 30) – 100/50 meter release height
NW500 = Takeoff (RW30) and Approach (RW 12) – 500/450 meter release height
NW300 = Takeoff (RW30) and Approach (RW 12) – 300/250 meter release height
NW100 = Takeoff (RW30) and Approach (RW 12) – 100/50 meter release height

Figure 5-5. Contribution of each source group to overall emissions (based on maximum lead concentration determined from modeling).

Hillsboro Airport Lead Fact Sheet

(DEQ)

Fact Sheet

Lead at Hillsboro Airport

Small aircraft flying in and out of Hillsboro Airport use lead-containing fuel to meet octane requirements and to reduce wear on engine parts. Lead is toxic at low concentrations. People are concerned that air near Hillsboro Airport may contain unhealthy levels of lead.

DEQ and Port of Portland computer models indicate that air lead levels at Hillsboro Airport are below both the national clean air standard and the Oregon health benchmark. The model is the best scientific information DEQ currently has.

DEQ will evaluate the results of EPA lead monitoring at Snohomish and Auburn, Washington airports and consult with EPA before considering the need to monitor in Oregon.

Copyright of the Port of Portland

What is EPA's new lead standard and what is Oregon's benchmark for lead?

In 2008, EPA implemented a much more protective health-based lead standard. The new standard, 0.15 micrograms per cubic meter of air, is 10 times stronger than the old standard. EPA changed the standard because they found that serious health effects occur at much lower levels of lead in blood than previously thought. Health effects of lead air pollution include neurological problems in children and cardiovascular disease in adults. Infants and young children are especially sensitive to low levels of lead, which may contribute to behavioral problems, learning deficits and lower intelligence.

In August 2010, DEQ adopted EPA's new, more protective lead standard as Oregon's benchmark. Oregon air toxics benchmarks are clean air goals that DEQ uses to identify, evaluate and address air toxics problems.

What are EPA's lead monitoring requirements?

EPA requires all airports that emit more than one ton of lead per year to assess whether they are meeting the new standard. EPA is also requiring a one-year monitoring study at 15 smaller airports that emit **less** than one ton of lead per year. This study will help determine whether lead emissions from smaller airports might cause unhealthy levels of lead in the air. Hillsboro Airport is not participating in this study in part because at 0.6 tons per year it ranks 21st nationally in amount of lead emitted. EPA is currently considering options for decreasing lead in general aviation fuel. This could include new regulations.

What has DEQ done to study lead at the Hillsboro Airport?

As part of the Portland Air Toxics Solutions Project, DEQ ran a computer model of 19 pollutants for the Portland region to identify pollutants above health-based benchmarks, emissions sources and potential emission reduction options. Working with a broad based advisory committee, DEQ used this model to prioritize sources of air toxics for reduction.

How does the Portland Air Toxics Solutions model work?

The Portland Air Toxics Solutions model uses emissions data from all known sources of air toxics in the Portland region. The model factors in topography and weather to produce concentration estimates of the 19 pollutants throughout the Portland area.

The modeling consisted of two phases. In the first phase, DEQ established estimated baseline emissions for 2005. In the second phase, DEQ projected estimated emissions to the year 2017. DEQ reached the 2017 projections by updating and increasing the 2005 emissions data to account for current conditions, regulatory requirements and economic growth.

The 2017 results are the most accurate estimates of the Portland Air Toxics Solutions model. Data improvements for the 19 pollutants included filling gaps where data was missing, removing emissions that no longer existed, improving emission factors to be more realistic, placing emissions in more accurate locations, and using modeling assumptions that better approximated actual conditions. To project to 2017 levels, which are our most accurate

State of Oregon
Department of Environmental Quality

Air Quality Division
811 SW 6th Avenue
Portland, OR 97204 Phone: (503) 229-5696 (800) 452-4011 Fax: (503) 229-6762
Contact: Sarah Armitage
Armitage.Sarah@deq.state.or.us

DEQ is a leader in restoring, maintaining and enhancing the quality of Oregon's air, land and water.

Last Updated: 08/09/2012
By: Sarah Armitage
DEQ 12-AQ-049

estimates of emissions, DEQ applied Metro's economic growth factors to the refined 2005 data.

How did DEQ model lead at the Hillsboro Airport?

DEQ modeled lead emissions as part of the Portland Air Toxics Solutions project. The primary sources of lead in the model are general aviation fuel and industrial metals production. For general aviation lead emissions, DEQ received activity data from the Port of Portland and applied EPA emission factors, or rates, and then used the dispersion model to predict concentrations. Estimated lead concentrations in the 2005 draft model were above the lead benchmark at Hillsboro Airport.

DEQ discussed the 2005 estimated lead results with the Port of Portland to check on the accuracy of emissions input and modeling for the Hillsboro Airport. While the emissions estimates on aviation activity were the most current data available from the Port, the 2005 assumptions on emission release height were inaccurate because they placed all general aviation fuel lead emissions at ground level instead of in a vertical distribution matching aircraft take off and landing patterns.

Applying the more realistic emission data for the releases of aircraft emissions based on a refined airport emissions model used by the Port, DEQ corrected its lead emissions data at the Hillsboro Airport and re-ran the model, including growth assumptions for 2017. The 2017 estimated concentrations for lead showed no modeled concentrations above the benchmark. This result was due to the greater mixing and dilution of lead emissions within the air column through which arriving and departing aircraft operate.

What is the Port of Portland doing to study lead at the Hillsboro Airport?

The Port of Portland's contractor, CDM, also conducted an air pollution model and produced a Hillsboro Airport Lead Study in September 2010. This study also estimated that lead emissions at the Hillsboro Airport are below the EPA standard and Oregon benchmark. The CDM Hillsboro Airport Lead Study used a model that is different and more complex than the model DEQ used for the Portland Air Toxics Solutions project.

For more information:

Portland Air Toxics Solutions Project
www.deq.state.or.us/aq/toxics/pats.htm

Alternative Formats

Alternative formats of this document can be made available. Contact DEQ's Office of Communications & Outreach for more information at (503) 229-5696.

Summary of lead issues at HIO, provided to FAA for HIO Parallel Runway Supplemental EA

(Port of Portland)

Summary of PATS Lead Analysis and CDM Lead Study at HIO

October 2, 2013

The USEPA has adopted National Ambient Air Quality Standards (NAAQS) for the criteria pollutants, including lead. These standards are set by USEPA and are designed to protect public health and welfare with an adequate margin of safety and with consideration given to sensitive populations. As noted by USEPA:

> "The Clean Air Act, which was last amended in 1990, requires EPA to set National Ambient Air Quality Standards (40 CFR part 50) for pollutants considered harmful to public health and the environment. The Clean Air Act identifies two types of National Ambient Air Quality Standards. Primary standards provide public health protection, including protecting the health of "sensitive" populations such as asthmatics, children and the elderly. Secondary standards provide public welfare protection, including protection against decreased visibility and damage to animals, crops, vegetation, and buildings." (hppt://www.epa.gov/air/criteria.html)

Washington County has been designated by USEPA as attainment for all of the NAAQS and has no history of violating USEPA air quality standards. The area around Hillsboro Airport currently meets, and is expected to continue to meet, all of the NAAQS, including the lead NAAQS to protect public health and welfare.

The Port or Portland has worked with DEQ to study lead dispersion, in a project unrelated to the HIO third runway proposal. As part of the Portland Air Toxics Solutions project, Oregon DEQ modeled lead concentrations along with other air toxics within the Portland-Vancouver air shed using the CALPUFF atmospheric dispersion modeling system. The lead emission inputs to DEQ screening modeling analysis were based on the emissions from 2005 HIO operations. The results of a screening level model run showed an area around HIO that had the potential to have ambient lead concentrations greater than the national ambient air quality standard (NAAQS) of 0.15 µg/m3 (calendar quarter average). This initial screening level model run, however, incorporated all lead emissions at HIO as a ground-level area source and did not account for dispersion effects from aircraft in flight and operating beyond the airport boundary. The model was subsequently refined by DEQ by adjusting the emission release parameters to more accurately simulate emissions from actual flight operations. The refined model showed a maximum predicted concentration of 0.00331 µg/ at "receptor" level (ground level), well below the NAAQS.

The Final Supplemental EA includes a study prepared by the Port in response to the ODEQ's initial evaluation of lead emissions performed in the fall of 2010. The Port separately retained CDM to model lead emissions associated with HIO 2007 operations using the FAA's required model, the Emission & Dispersion Modeling System (EDMS). EDMS uses the AERMOD atmospheric dispersion model to complete the dispersion analysis. The maximum modeled concentration for lead around the HIO airport was, 0.00405 µg/m^3, closely approximating the results of DEQ's refined CALPUFF model.

That 2010 Port study provides an indication of how emissions from Hillsboro Airport can be compared with the NAAQS. The lead NAAQS is 0.15 µg/m^3 evaluated as a calendar quarter average. Using 2007 activity levels (at 240,735 annual operations) the Port study evaluated aircraft lead emissions associated with aviation gasoline ("AvGas" or "100LL"). The Port conducted several evaluations using different modeling approaches and assumptions.

The highest modeled concentration of lead emissions was found to be 0.00405 µg/m^3, less than 3% of the lead NAAQS. The modeled concentration of 0.00405 µg/m^3 corresponds well to the emission inventory reported in the original EA at 0.622 tons of lead emitted per year. Thus, as the proposed project would result in either no increase in lead emissions, or an increase in lead emissions of 0.1 ton, relative to the No Action Alternative, no violation of the NAAQS is expected to result from the proposed runway construction.

Summary of Transportation Research Board leaded fuels roadmap May 13 – 14, 2013

(Port of Portland)

AVGAS Lead Technical Summary Sheet

- *Finding a safe, high octane substitute for leaded avgas is an ongoing technical challenge*. 190,000 GA aircraft in the fleet; only 1/3 of which can run on lower octane fuels. 250 M gallons of aviation fuel is produced per year versus automobiles which consume 360 M gallons/day. Consequently, there is a supplier side issue

- *Environmental and supply security issues will continue to drive the effort for an unleaded avgas*. A petition was filed in 2006 by environmental groups who wanted EPA to outright ban leaded fuels or conduct a study to determine if there is endangerment to human health and the public. Independent of this action; EPA looked at the National Ambient air Quality Standards (NAAQS) in 2008 and reduced the standard by a factor of 10.

- *EPA is getting a better understanding of aircraft lead emissions and potential exposure through monitoring, modeling, demographic and other studies*. EPA looked at all potential source of lead emissions, and determined that general aviation accounts for approximately 50% of lead emissions today; approximately 500 tons per year.

- *The modeling and monitoring will be used to make a determination of endangerment, but not until a late 2015 timeframe*. Lead monitoring at 17 general aviation airports is part of the process for EPA to fulfill its Clean Air Act obligation to determine if lead emissions from piston engine aircraft cause an endangerment to human health. There is concern that some of results from the studies may not be representative; such as San Carlos, where the ambient lead monitors where located just off the aircraft run-up area; are hit by prop-wash as the planes turn, and have a fence right behind the monitors which could create boundary effects. EPA is going to certify the data; which should be completed by May 2014. With the data EPA will continue to refine emissions inventories and improve modeling. They will study fate of lead around airports, look at case studies, demographics and determine whether lead exceeds NAAQS and presents an endangerment to the public.

  Update: June 19, 2013. EPA released an update providing a summary of data currently available on concentrations of lead at 17 U.S. airports. As of May 2013, states and local air authorities have collected and certified lead concentration data for at least 3 months from the 17 airports. Two airports have monitored lead concentrations that exceed the lead NAAQS. EPA is currently conducting the analytical work, including modeling and monitoring, to evaluate under section 231 of the Clean Air Act whether lead emissions from the use of leaded avgas in piston-engine aircraft cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare. There may be some

challenges to the findings with respect to data quality. For example, at San Carlos, the lead monitors are located on the airport immediately adjacent to the run up area and are directly impacted by prop wash as the planes turn onto the taxiway. Supplemental sampling is being conducted at these two airports to evaluate lead concentrations at additional locations at the near the airport. If EPA makes a final positive endangerment finding the agency would initiate rulemaking to establish standards concerning lead emissions from piston-engine aircraft. FAA would then be required to prescribe regulations to insure compliance with such standards, and prescribe standards for the composition of aircraft fuel to control or eliminate certain emissions.

On March 27 a U.S. District court ruled that the (EPA) should not be forced to rush the issuance of its report on the public health effects of lead emissions from general aviation aircraft. The ruling came in response to a March 2012 lawsuit filed by environmental group Friends of the Earth (FOE) that sought to force the EPA to issue an accelerated endangerment finding on GA emissions. The legal action followed a 2006 petition by the group that sought to force the agency to release those findings before their planned publication during the second half of 2015.

- *Short and Long Term Mitigation Strategies*.
  - Approximately 1/3 of the aircraft in the fleet could be safely powered on the 80 MON avgas as a short term mitigation effort. Would have to work through supply logistics and airport fueling infrastructure issues.
  - 100 VLL, fuel management and engine run-up politics could also be considered for short-term mitigation.
  - Install fueling vapor recovery systems; similar to at retail automobile fueling stations.
  - Relocation of run-up areas to add additional distance buffer to the general public.

- *The Unleaded Avgas Transition (UAT) Plan is FAA's long term mitigation strategy to find a replacement for leaded fuels*.
  - Implement a fuel development roadmap for Avgas readiness levels that identifies milestones in the aviation gasoline development process
  - Established centralized testing of candidate unleaded fuels which would generate standardized qualification and certification data.
  - Establish a solicitation and selection process for candidate unleaded aviation gasoline for the centralized testing program
    - Phase 1 test program (1 year); up to 10 fuels will be selected for rig and property testing

- On June 10, 2013, FAA issue a request for candidate fuel producers to submit unleaded fuel formulations to be evaluated.
    - Phase 2 test program; 2 fuels will be tested in engines and aircraft
  - Established a centralized certification office to support unleaded aviation gasoline projects
  - Establish a collaborative industry-government initiative called the Piston Aviation Fuels Initiative (PAFI) to implement the UAT PAF recommendations to facilitate the development and deployment of an unleaded avgas with the least impact on the existing piston engine aircraft fleet

- *EPA and FAA will continue to work together in efforts in communicating with airports, the aircraft industry, and the Public*

Leaded AvGas Use in General Aviation Aircraft fact sheet

(Port of Portland)

Leaded Fuel Use in General Aviation Aircraft

Air quality, and operations that affect air quality, are important topics to the community and the Port of Portland. The use of leaded fuel by some general aviation aircraft at Port facilities is consistent with general aviation practices nationwide, but one which continues to generate community interest.

Certain types of general aviation aircraft use aviation gasoline, called AvGas, which contains lead as an additive ingredient. Lead is a naturally occurring heavy metal used in a wide variety of products and industrial processes.

Lead is added to AvGas to help boost fuel octane, prevent knock, and prevent engine issues which could result in a subsequent loss of compression. Each of these is a safety consideration for piston-engine aircraft. Piston-engine aircraft are used at the Port's airports for personal transportation, instructional flying, corporate uses, air tours, and surveillance.

Lead was historically added to a variety of transportation fuels, including motor vehicle gasoline. In 1996, the Environmental Protection Agency completely phased out lead from highway vehicle fuels. This, in conjunction with some tighter controls on other lead sources (such as waste incineration and other stationary sources), resulted in average concentrations of lead in air decreasing by 91 percent between 1980 and 2008.

Regulatory Considerations

The Clean Air Act establishes the Environmental Protection Agency's authority to regulate air pollutant emissions from aircraft, and directs EPA to consult with the Federal Aviation Administration on aircraft emission standards. EPA cannot change the aircraft engine emission standards if such a change would significantly increase noise and adversely affect safety. The Clean Air act also requires that local and state standards for aircraft emissions be identical to federal standards.

PORT OF PORTLAND
Possibility. In every direction.®

Alternatives to Lead in Aviation Gasoline

In some countries, methyl tertiary butyl ether (MTBE) is used as an AvGas additive instead of lead. However, MTBE causes other significant environmental problems.

Seventeen states in the United States have banned the use of MTBE in highway vehicle gasoline entirely.

The vast majority of leaded AvGas that is produced and available is called 100 Octane Low Lead (100LL); it can contain up to 2.12 grams of lead per gallon of fuel.

Piston-engine aircraft that use AvGas account for about one half of the national inventory of lead emitted to the air.

The goal is to develop a drop-in replacement for leaded AvGas, which would require no engine modifications.

The FAA is working with the EPA and key stakeholders to replace 100LL fuel by 2018.

The Port of Portland has no authority to restrict or prohibit the sale or usage of 100LL aviation fuels, nor the authority to limit or restrict general aviation aircraft from using this type of fuel at the airport.

Efforts to Remove Lead from AvGas

The Federal Aviation Administration established the Fuels Program Office to help meet the agency's goal of making an unleaded fuel available for the general aviation fleet.

The FAA is working with the EPA and key stakeholders to replace 100 octane low-lead (100LL) fuel by 2018.

Ambient Air Quality Regulations

Lead is one of six Criteria Pollutants for which the EPA sets enforceable standards to limit the concentration in ambient air. These standards are designed to be protective of human health and the environment. EPAs current National Ambient Air Quality Standard (NAAQS) for lead is 0.15 micrograms per cubic meter.

Of the existing 111 counties the EPA monitors in the U.S., only 18 violate the NAAQS for lead. None of the violating counties are in Oregon, Washington or California.

As part of the Portland Air Toxics Solutions (PATS) program, Oregon Department of Environmental Quality established acceptable concentration values for 52 pollutants present in the air. The benchmarks were set at levels that provide public health protection. For lead, DEQ adopted 0.15 micrograms per cubic meter, the same as the NAAQS.

Based on dispersion modeling performed for the program, DEQ's final PATS Report and Recommendations show that the area around Hillsboro Airport meets EPA standards for public health and safety with regard to lead.

Additional Information:

EPA webpage on aircraft emissions:
www.epa.gov/oms/aviation.htm

EPA document on the use of leaded fuel in aircraft:
www.epa.gov/oms/regs/nonroad/aviation/420f10013.pdf

DEQ Oregon: Portland Air Toxics Solutions Program
www.deq.state.or.us/aq/toxics/pats.htm

FAA Alternative to AvGas Efforts:
www.faa.gov/about/initiatives/avgas/

Airport Lead Monitoring:
www.epa.gov/otaq/regs/nonroad/aviation/420f13032.pdf

Contacts:

Brooke Berglund | Community Relations | 503.415.6532
Kama Simonds | Public Affairs | 503.415.6151

REV. 9.13

From: Miki Barnes <miki@psg.com>
Sent: Monday, November 18, 2013 12:48 PM
To: Berglund, Brooke
Cc: james Lubischer
Subject: HARE 11/19/13 Leaded Fuel Subcommittee Meeting

Dear Brooke,

Please distribute Senator Waxman's 10/23/12 letter to the HARE leaded fuel subcommittee for consideration at their 11/19/13 meeting. It is available at the following link: http://waxman.house.gov/sites/waxman.house.gov/files/documents/UploadedFiles/Letter%20to%20FAA%20on%20Leaded%20AvGas%2010-23-12.pdf

In a 10/23/12 letter from Senator Waxman to the FAA, Senator Waxman urged the FAA to "accelerate efforts to reduce lead emissions from general aviation":

> The devastating health effects of lead are well documented. Lead is a potent neurotoxin that has especially debilitating effects on children, damaging the brain and nervous system and impairing development. According to the Centers for Disease Control, there is no identified level of lead exposure without harmful effects and the effects appear to be irreversible. Lead emissions from general aviation are a particular concern at airports located in close proximity to residential areas...Frequent touch-and-go flights by piston aircraft can also result in pollution concentrations in areas surrounding an airport.

He further explains that:

> The FAA's plans with regard to addressing the use of leaded fuel for general aviation are described in the Unleaded Avgas Transition Aviation Rulemaking Committee report released in February 2012. This report outlines steps to identify, test, and certify an unleaded "drop-in" replacement fuel by 2018, but it does not identify any efforts to reduce the use of leaded fuel before such a replacement fuel becomes available, even though, according to the report, it may be 11 years or more before the new fuel will be phased in. This extended time-frame is simply too long, given the certain and serious harms to human health from lead exposure and the availability of alternatives to leaded fuels.

Thank you.

Miki Barnes

Miki Barnes
miki@psg.com

From: James Lubischer <annejim1@clear.net>
Sent: Sunday, November 17, 2013 6:44 PM
To: Berglund, Brooke
Subject: Submissions to Chairman of the HARE Subcommittee on Lead from Lubischer
Attachments: Nigg 2010 low low Pb ADD (hilites) .pdf; Schneider 2003 STUDY highlighted.pdf; Social Policy Report - with Nigg commentary copy hilites.pdf; CDC LeadPoisoning-10 hignlites copy.pdf; Integrated Science Assessment for Lead.pdf; Airports 17 Pb monitoring 2013 - hilited.pdf

11-17-13

Ms. Berglund,

Please forward this email with the attached materials to the chairman of the HARE subcommittee on lead for consideration in the subcommittee's review of the lead issue.

Thanks,

Jim Lubischer
503-828-7406

The Nigg 2010 research shows that very, very low levels of lead in a child's blood contribute to ADHD in children.

The Schneider 2002 research shows that lead at very low concentrations damages brain cell growth.

In the Social Policy Report 2010: "The researchers found that lead levels as low as 2.5μg/ dL were associated with significantly greater amounts of parent- and self-reported criminal activity and higher rates of police intervention." (p10) "Results indicated that increased lead levels were significantly associated with increases in the number of total arrests and violent crimes committed by the participants in adulthood." (p11) "Researchers have known since the early 1900s that lead is harmful to children's development. When the CDC set the current BLL to 10μg/dL in 1991, reports were already beginning to appear that even lower levels of lead are detrimental to children's health. For the past 10 years, study after study has indicated that children are being exposed to unacceptable levels of lead in their daily lives, and that even a low level of lead exposure harms children. The U.S. is negligent in its testing, reporting, prevention, and treatment practices for lead exposure. Lead exposure in

children is fully preventable, yet the U.S. government has failed to commit fully to the resolution of the problem. Cost-benefit analyses show that it is a relatively inexpensive problem to solve, and its resolution would lead to great economic returns. (p 15)

The CDC's 2005 "Preventing Lead Poisoning in Young Children" Statement is an exhaustive document which states that "The data demonstrating that no 'safe' threshold for blood lead levels (BLLs) in young children has been identified highlights the importance of preventing childhood exposures to lead. It confirms the need for a systematic and society wide effort to control or eliminate lead hazards in children's environments before they are exposed. This emphasis on primary prevention, although not entirely new, is highlighted here and is clearly the foremost action supported by the data presented in *A Review of Evidence of Adverse Health Effects Associated with Blood lead Levels <10 ug/dL in Children*."

EPA's 2013 *The Integrated Science Assessment for Lead*" provides a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the National Ambient Air Quality Standards." (p xliv) "Studies that have undergone scientific peer review and have been published or accepted for publication and reports that have undergone review are considered for inclusion in the ISA." (p. xlv) "The 2008 National Emissions Inventory reported ambient air Pb emissions of 950 tons...piston-engine aircraft emissions comprise the largest share (58%) of total atmospheric Pb emissions in the U.S." (p. 1-6) "The primary contribution of ambient air Pb to young children's blood Pb concentrations is generally due to ingestion of Pb following its deposition in soils and dusts rather than inhalation of ambient air." (p. lxxix) "...there is no evidence of a threshold below which there are no harmful effects on cognition from Pb exposure." (p. lxxxviii) "The 2006 Pb AQCD concluded that neurodevelopment effects in children and cardiovascular effect in adults were among the effects best substantiated as occurring at the lowest blood Pb levels, and that these categories of effect were clearly of the greatest public health concern. The evidence reviewed in the current assessment supports and builds upon this conclusion. Evidence in a few cohorts of children that indicated the supralinear concentration-response blood Pb-FSIQ relationships, did not identify a threshold for Pb-associated neurodevelopmental effects in the range of blood Pb levels examined." (p. 1-68) "With each successive Pb AQCD and supplement, the epidemiologic and toxicological study findings show that progressively lower blood Pb levels or Pb exposures are associated with cognitive deficits in children...No evidence of a threshold for the effects of Pb on neurodevelopmental effects has been reported across the range of blood Pb levels examined in epidemiologic studies. Compelling evidence for a larger decrement in cognitive function per unit increase in blood Pb among children with lower mean

blood Pb concentrations compared to children with higher mean blood Pb concentrations was presented in the 2006 Pb AQCD." (p. 1-73)

The EPA's Airport Lead Monitoring Update 6/13 shows that all 17 of the airports which were monitored have measurable ambient air lead.

Published in final edited form as:
J Child Psychol Psychiatry. 2010 January ; 51(1): 58–65. doi:10.1111/j.1469-7610.2009.02135.x.

Confirmation and Extension of Association of Blood Lead with Attention-Deficit/Hyperactivity Disorder (ADHD) and ADHD Symptom Domains at Population-Typical Exposure Levels

Joel T. Nigg, Ph.D.,
Oregon Health & Sciences University

Molly Nikolas, M.A.,
Michigan State University, Department of Psychology

G. Mark Knottnerus, B.S.,
Michigan Department of Community Health, Bureau of Laboratories

Kevin Cavanagh, Ph.D., and
Michigan Department of Community Health, Bureau of Laboratories

Karen Friderici, Ph.D.
Michigan State University, Department of Microbiology

Abstract

BACKGROUND—Recent studies have suggested that child ADHD and its symptom domains are related to blood lead level, even at background exposure levels typical in western countries. However, recent studies disagreed as to whether lead was related to inattention or hyperactivity-impulsivity within the ADHD domain. More definitive evaluation of these questions was sought.

METHODS—236 children aged 6–17 years participated (61 ADHD-Combined type, 47 ADHD Predominantly Inattentive type, 99 non-ADHD control, 29 unclassified borderline, situational, or NOS cases). Formal diagnosis was reliably established by a best estimate procedure based on a semi-structured clinical interview and parent and teacher ratings. Lead was assayed from whole blood using inductively coupled plasma mass spectrometry with a method detection limit of 0.3 μg/dL.

RESULTS—Blood lead levels were slightly below United States and Western Europe population exposure averages, with a mean of 0.73 and a maximum of 2.2 μg/dL. This is the lowest level of blood lead ever studied in relation to ADHD. After statistical control for covariates including IQ and prenatal smoking exposure, blood lead was associated with ADHD-combined type but not inattentive type. Parent and teacher report indicated association of blood lead with Conners cognitive problems, but only teacher report showed effects on DSM-IV inattention symptoms. Blood lead was associated with hyperactivity-impulsivity in parent report regardless of measurement method, whereas teacher report effects depended on child treatment history.

CONCLUSIONS—These findings confirm that in children with typical U.S. population lead exposure, careful identification of children with ADHD also identifies children with slightly elevated blood lead.

Corresponding Author Information: Joel Nigg, Department of Psychiatry, 3181 Sam Jackson Park Road, Mail Code OP02, Oregon Health & Science University, Portland OR 97239-3098, niggj@ohsu.edu; PH 517-203-3114.

Keywords

ADHD; hyperactivity; inattention; blood lead

Attention deficit hyperactivity disorder (ADHD) occurs in 3 to 7% of children, with etiology believed to be multifactorial. The DSM-IV (APA, 2000) specifies three clinical subtypes: predominantly hyperactive (ADHD-PH), predominantly inattentive (ADHD-PI), and combined (ADHD-C). The subtypes are arrived at through combinations of two primary symptom dimensions: inattention-disorganization, and hyperactivity-impulsivity. These symptom domains may have partially distinct etiological inputs (Nigg, 2006). Because they appear to be an extreme of a behavioral continuum, the symptom dimensions also serve as useful foci to study etiology. Indeed, a factor analytic tradition has arrived at related but slightly different item sets than DSM-IV to capture population variation in "cognitive problems" and hyperactivity/impulsivity (e.g., Conners et al., 2007).

Lead exposure via water, soil, and other sources remains a worldwide health concern (Centers for Disease Control, 2005). Blood lead above 10 μg/dL has been associated reliably with ADHD and related behaviors, with the only real dispute being the magnitude of the effect (Burns et al., 1999; Silva, Hughes, Williams, & Faed, 1988; Thomson et al. 1989). Regulation of commercial uses of lead has markedly reduced the incidence of frank lead poisoning in recent decades in the U.S. (CDC, 2005), Western Europe (e.g., Delschen, Machtolf, Sugiri, & Wilhelm, 2008), and Scandinavia (Stromberg, Lundh, & Skerfving, 2008). Perhaps as a result, lead exposure has not been highlighted as an ongoing concern related to ADHD.

This reassuring picture, however, is eroding. Even at lower blood levels (< 10 μg/dL) lead has been linked to reduced intellectual functioning (IQ; Lanphear et al., 2005). Recent findings point to an association with ADHD as well, even at low exposures. Three years ago, Braun, et al. (2006), in a US population survey, found that blood lead was related to parent report that their child was diagnosed or treated for ADHD. This effect held even at blood levels below 5 μg/dL (i.e., children with blood lead > 2 μg/dL were more like to have ADHD than children with blood lead <0.7 μg/dL). One year later, Chiodo et al. (2007) reported that blood lead was related to teacher rated symptoms of inattention and activity, but not impulsivity, using the Conners rating scales and other standard scales in a high-risk sample. The next year Nigg et al (2008) conducted the first low-level lead study of children formally diagnosed with ADHD. Blood lead was related to ADHD and to parent reported DSM-IV symptoms of hyperactivity but not inattention. Those results supported an association to ADHD but appeared partially to contradict Chiodo et al (2007) as to the affected symptom domain.

The present study sought more definitive evaluation in a larger, well-diagnosed sample. The aim was to scrutinize relations with both DSM-IV and Conners ratings, by both parent and teacher report, so as to confirm and extend prior findings as well as to clarify the apparent contradiction in the last two studies reported. Dozens of potential confounds have been ruled out in relation to lead exposure and ADHD (Chiodo et al. 2007; Silva, et al., 1988; Thomson et al. 1989), but mostly at higher lead exposure levels. Thus, an expanded set of confounders and covariates was also considered here, as outlined in Methods.

Confirmation of the association of ADHD with lead exposure even at very low blood lead levels would be of major importance to public health, because exposure levels in the range of 1–5 μg/dL remain very common. Yet, most public authorities continue to use 10 μg/dL as the criterion of concern. If the association of low levels of lead exposure with ADHD is

verified, it opens the potential for new insights into the etiology of ADHD, because lead can serve as a model insult affecting frontal-striatal circuitry in ways that are relatively well understood. It also could open potential new opportunities for study of susceptibility-insult or gene by experience models. It could also provide clues to prevention via dietary supplementation (Kordas et al., 2007), via renewed caution before introducing new toxins into children's environments, or via aggressive efforts to continue to eliminate all lead exposure.

METHODS

Participants

Recruitment and Evaluation—Participant recruitment and characterization followed the same procedures as Nigg et al. (2008), but this was an entirely new sample. In all, 236 children aged 6–17 completed the study. Because some of these children also participated in our sib-pair study of genetics of ADHD, the sample included 78 sibling pairs (n=156 siblings). All children were recruited via mailings to parents in regional school districts, public advertisements, and outreach to local clinics. Parents provided written informed consent and children provided written informed assent. All procedures were approved by the University Institutional Review Board and complied with NIH and APA guidelines for protection of human participants.

Families entered a multi-stage screening process to establish diagnostic groupings. To confirm ADHD and comorbid diagnoses, a semi structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia (*K-SADS-E*) was completed with a parent by a trained clinician. Interviewers had a master's degree in clinical psychology or social work. Each interviewer double coded 20 tapes with a criterion interviewer to ensure process fidelity and inter-interviewer reliability (all disorders $k > .80$ in this report). In addition, parents and teachers completed the *ADHD Rating Scale* (DuPaul et al., 1998) and the Conners et al (1997) *ADHD Rating Scale, Revised* (hereafter, Conners).

Exclusion criteria—Rule outs were long-acting psychotropic medication (e.g. antidepressants), history of seizure, neurological impairments, a prior diagnosis of mental retardation or autistic disorder, head injury with loss of consciousness, sensorimotor handicap, or other major medical conditions in the child, as reported by the parent. At the diagnostic interview youth were ruled out if they had substance addiction, bipolar disorder, history of psychosis, sleep disorder, medical or neurological condition discovered at the clinical screen, or IQ <75. Control children were also excluded for ADHD, learning disability, or conduct disorder.

Establishment of Final ADHD and Other Diagnoses—Using all available data, a best estimate diagnosis was arrived at independently by two experienced clinicians (a board certified child psychiatrist and a fully licensed child clinical psychologist) blind to study hypotheses and blood lead levels. Their agreement rates for ADHD, conduct disorder, and oppositional defiant disorder were acceptable (all $k > .80$). Disagreements were resolved by discussion. Consistent with DSM-IV ADHD criteria, the clinicians required that another disorder did not better account for symptoms, evidence of impairment, and evidence of cross-situational symptoms. When ADHD symptoms were situational (only noticeable at home or school) or were subthreshold (5 symptoms), a diagnosis of ADHD-NOS was assigned. Those youth were included in this report for purposes of regression analysis of symptom scores but not for between-group analyses.

Measures

Blood Lead—Over 90% of children approached agreed to the blood draw for the lead assay. Children had 2 ml whole blood drawn through venipuncture in the arm. The blood was drawn into a 2 ml purple-top Vacutainer tube (tubes were lot checked for lead by lab prior to use). Blood samples were labeled with a study number, frozen and stored at −20C prior to analysis. Samples were assayed using the process of inductively coupled plasma mass spectrometry (ICPMS). This method had a detection limit for lead of 0.3 μg/dL; inter-run precision was 5.8% (coefficient of variation) at a lead value of 2.9 μg/dL. The process began with whole blood samples brought to room temperature and vortexed so no particulate matter remained at the bottom of the sample. Samples were diluted 1:50 with a diluent composed of 1.0% tetramethylammonium hydroxide, internal standard (iridium), 1.0% isopropyl alcohol, 0.01% ammonium pyrrolidene dithiocarbamate (APDC), and 0.05% wetting solution (Triton X). Samples were then mixed by inverting 3–4 times. The analysis then entailed quantitating the sum of masses 206, 207, and 208 based on three replicates per sample on a Perkin Elmer Elan DRC Plus ICP-MS. Three children were below the limit of detection. Following Braun et al (2006; p. 1905), those levels were scored as 0.2 ($0.3/\sqrt{2}$). Following Burns et al. (1999), the blood lead score was $\log_{10}$ transformed to reduce influence of outliers.

IQ and achievement—To estimate full scale IQ, children completed a 3-subtest short form of the Wechsler (2003) Intelligence Scales for Children-4th Edition comprised of Vocabulary, Block Design, and Information,[1] with reliability of .93 and validity in relation to the full WISC-IV of r=.88 (Sattler, 2001, p. 771). All completed the word reading and spelling subtests of the Wechsler (2005) Individual Achievement Test-2nd edition to estimate academic achievement and enable evaluation of learning disability by the team.

Behavior Disorders and Symptoms—Total KSAD symptom counts were used for parent DSM-IV ADHD symptom dimensions. To reduce collinearity, oppositional and conduct symptom scores (r=.63) were summed into an "externalizing" total score. For teachers, ADHD symptoms were assessed on the *ADHD Rating Scale* (symptoms scored as absent if rated 0, 1 and as present if rated 2, 3) and summed. The Conners ratings served as additional dimensional measures. Age and sex adjusted T scores were computed for oppositional, hyperactive-impulsive, and cognitive problems/inattention for teachers and mothers.

Other Covariates and Confounders—Total gross annual income in the child's primary household was reported by parents. Maternal smoking during pregnancy has been of keen interest as a possible contributor to ADHD, yet also tends to be correlated with low income and thus with lead exposure (Braun et al., 2006). Maternal smoking during pregnancy was reported retrospectively by the mother and coded as "none" (0) or "any" (1). Although retrospective recall limits the ability to verify these reports, maternal recollection of smoking in pregnancy at child age of six years has agreed with post-partum report at 90% (Hensley-Alford, Lappin, Peterson, & Johnson, 2008). Due to recent interest in nutritional status, particularly the role of iron in the lead-ADHD relationship (Kordas et al., 2007), blood hemoglobin was assayed by standard methods to assess iron status. Normal hemoglobin values for children are 11–13 gm/dL, and in adolescents, 12–16 (women) or 14–18 (men). Values in the current sample ranged from 11.0–15.6. Child history of stimulant medication treatment was reported by mothers on the KSADS interview, and was coded as a 0 or 1 (no

[1]Children over the age of 16 completed the same 3 subtests on the WAIS-III; it has reliability=.95 and validity=.91; Sattler, 2001, p. 825.

history of stimulants, versus treatment history; 43 children had stimulant treatment). It was examined as a potential moderator of teacher reports.

Data Reduction and Analysis

Unless otherwise noted, analyses were conducted in MPLUS v5.1 (Muthen & Muthen, 1998–2008), with family as a clustering value and analysis set to "type=complex;" this procedure removes variance due to siblings being from the same family. Missing data were handled using full information maximum likelihood procedures in MPLUS. Missing data were minimal with the exception of income (7% missing). Three extreme outliers for the income variable were truncated. All effects were evaluated with the following covariates: household income, maternal smoking, and child age, sex, and blood hemoglobin level. Low IQ is a possible complication yet there is controversy as to whether it represents part of the ADHD syndrome. Results are therefore reported with and without covarying IQ. For regression models, standardized parameter estimates were computed. For continuous measures, these were standardized on X and Y variables. The resulting coefficient is interpreted as the amount of change in Y in standard deviation units for a one standard deviation change in X. For the categorical (0, 1) variables (sex and prenatal smoking), they were standardized on the Y variable--yielding amount of change in Y (in standard deviation units) for a change in the X variable from 0 to 1.

RESULTS

Descriptive Overview

The sample comprised four groups: non-ADHD, ADHD-PI, ADHD-C, and ADHD-NOS. "NOS" meant subthreshold, 5 symptoms, or situational. Note that ADHD primarily hyperactive type was rarely identified (n=2). Those two cases were assigned to the "NOS" group. Table 1 provides a descriptive and clinical overview of the sample groups. It supports the validity of the clinical groupings. Only the ADHD-PI and ADHD-C groups consistently exceeded clinical cutoffs on the Conners ADHD Index. The ADHD-NOS group was intermediate on several clinical measures between the control group and the ADHD groups. Groups differed in exactly the way suggested by the diagnostic assignments in teacher and parent ratings. Some suppression of symptoms in teacher ratings was expected, because some children were in treatment (Table 1).

The groups were similar on IQ, but they differed in age, gender ratio, and household income (leading to differences in rate of families estimated to reside in poverty). As shown in Table 1, the sample as a whole was relatively more well off economically than the U.S. national average. The ethnic breakdown of the sample was 75% Caucasian, 7% African American, 3% Latino, 1% Native American, and 14% mixed or other. Race was unrelated to blood lead and was not covaried or analyzed further.

Child blood lead ranged from less than 0.3 μg/dL (undetectable, n=3) to 2.20 μg/dL with a mean of 0.73 (SE=0.04). Table 2 shows that blood lead in the current sample was even lower than in Nigg et al (2008), and equal to or lower than recent averages in the U.S., Scandinavia, and Western Europe (Braun et al., 2006, used the NHANES sample shown in Table 2). Thus, the sample had typical background exposure. This blood lead level was the lowest ever evaluated in relation to ADHD to date.

As expected, and as in prior studies, blood lead was related to lower family income (B=−.15, p<.05), male sex (B= −43, p<.01), and younger age (B=−.23, p<.01). Before covariates, blood lead was correlated to KSAD inattention (B=.19, p<.01), hyperactivity/impulsivity, (B=.28, p<.01), the externalizing composite, (B=.21, p<.01) and to all Conners scales. Blood

lead in siblings was correlated at r=.47 (p<.001), supporting the supposition that it might be a shared environment effect and the importance of controlling sibling status.

Association of ADHD Diagnosis with Blood Lead Level

The three-group ANCOVA (omitting the "NOS" group; see Method) was conducted in SPSS v. 17. It yielded nearly a medium effect size for group assignment, F(2,200)=5.16, partial eta squared=.049, p=.007 (sibling status not controlled). Follow up simple comparisons were conducted using effect coding in MPLUS (controlling for sibling status; blood lead was the dependent variable and all covariates were included). The ADHD-C group had higher lead level than the control group (B=.141, p=.033; with IQ covaried, B=.057, p=.041). The ADHD-PI group did not differ from the control group (p=.27). Thus, group effects were confined to ADHD-C.

Regression Analysis of ADHD and Externalizing Symptom Dimensions

Parent Report—Regression models were conducted for symptom domains as dependent variables (n=236, see Method). Table 3 summarizes the results for parents for both DSM-IV symptoms (KSADS) and the Conners, with and without IQ as a covariate. As it shows, blood lead level was marginally associated with attention problems, but not after covarying IQ. Blood lead was reliably associated with hyperactivity/impulsivity regardless of covariates. On the Conners, both cognitive problems and hyperactivity/impulsivity were reliably related to blood lead.

The KSADS externalizing composite was also related to blood lead (B=.21, p<.01; with IQ covaried, B=.20, p<.05); the same held for oppositional behavior on the Conners (B=.22, p<.01, with IQ covaried, B=.21, p<.01). Specificity was examined for each model by making blood lead the outcome variable. To conserve power, IQ was omitted and other covariates removed in stepwise fashion (income, p>.50, and hemoglobin, p>.20, were thus removed in all models). In the DSM-IV model, hyperactive symptoms were specifically related to blood lead (B=.144, p=.043), whereas externalizing symptoms were shy of significant (B=.136, p=.121). The same held using the Conners: blood lead was related to hyperactivity (B=.18, p=.034) but not oppositional behaviors (B=.09, p=.34) or cognitive problems (p=ns).

Teacher Report—Table 4 shows the complete models for teacher reported DSM-IV symptoms and Conners ratings. On the ADHD Rating Scale, blood lead was unrelated to inattention or hyperactivity-impulsivity. On the *Conners Rating Scale*, results were similar to those reported for teachers by Chiodo et al (2007) and different from the ADHD Rating Scale results. As Table 4 shows, cognitive problems were related to blood lead level, whereas hyperactivity-impulsivity was related to blood lead prior to covarying IQ, but not after.

Conners oppositional behavior was also related, weakly, to blood lead (B=.13, p<.05), though not after IQ was covaried (B=.11, p=.07). The specificity model was computed just as with parent data. Cognitive problems were uniquely related to blood lead (B=.16, p=.031), whereas oppositional behavior (p=.76) and hyperactivity (p=.34) were not.

Interaction of Teacher Findings with Child Treatment Status—The interaction of child treatment history with blood lead was examined (all covariates included). For DSM-IV inattention, there was no interaction (p>.50), but for DSM-IV hyperactivity/impulsivity, there was (B=−.193, p=.009). For children never treated (including controls), there was a reliable relation of blood lead to hyperactivity (with all covariates; B=.151, p=.017). For the children who had been treated, the relation disappeared (B=−.177, p=.19). This result suggested that medication treatment masked the relation of lead to teacher-rated DSM-IV

hyperactive symptoms. For the Conners ratings, the interaction of treatment status with blood lead was shy of significance for hyperactivity (B=−.11, p=.064), but robust for cognitive problems (B=−.18, p=.002). Again, for children not in treatment, the effect of blood lead on cognitive problems was easily seen (with all covariates, B=.17, p=.004); but not in the treated children (B=−.13, p=.446). These interactions did not reproduce when checked in the smaller Nigg et al (2008) sample (all p> .20).

DISCUSSION

Whereas ADHD carries well-established genetic influences on susceptibility (Waldman & Gizer, 2006), environmental risk factors may interact with that susceptibility in complex ways (Purcell, 2002). Several studies have linked blood lead with ADHD, but usually in samples with lead levels much higher than current population averages in the U.S. or Western Europe. More recent studies have begun to show that even very low levels of lead exposure (< 5 μg/dL), blood lead is associated with ADHD. Nigg et al. (2008) was the first low-lead study to look at children formally diagnosed with ADHD by standardized methods and the first to use ICPMS technology to measure blood lead. That technology is important because it has detection limits 3–8 fold lower than other methods typically used clinically or in most prior studies of ADHD. ICPMS was used again in the current report in a new sample.

The present study provides a more definitive confirmation of Nigg et al (2008) in a larger sample, with additional covariates, with more examination of teacher ratings, and at the lowest levels of blood lead ever measured in relation to ADHD. It confirms that in a sample selected for ADHD, there are reliable relations of blood lead with lifetime symptoms of hyperactivity-impulsivity as assessed by structured clinical interview of the parent. Hyperactivity effects are either weak or are moderated by treatment history when based on teacher report. On the other hand, the association of blood lead with inattention (or cognitive problems) was observed in parent and teacher Conners ratings and in teacher but not parent DSM-IV ratings.

Thus, like Nigg et al (2008), we found that blood lead was reliably associated with hyperactivity but not inattention when using DSM-IV ratings. However, like Chiodo et al (2007), we also found that Conners ratings revealed a clearer association of blood lead with cognitive problems than with hyperactivity-impulsivity in teacher ratings. This apparent disagreement across methods and raters could be readily understood. The Conners scales have slightly different items than the DSM-IV and are selected to be sensitive to intervention effects (lead may be an intervention). The Conners scales also had somewhat better normal distribution properties (for inattention, Shapiro-Wilk > .90 for maternal and >. 80 for teacher ratings, versus weaker values for the respective DSM-IV scales). Furthermore, it is sensible to expect that teachers would have more opportunity to observe cognitive problems (relevant to classroom behavior), whereas parents and teachers might be equally good observers of hyperactive or impulsive behaviors.

With all that in mind, the pattern that emerges is still rather clear. Inattention/cognitive problems were related to blood lead when measured via the Conners but not when measured via DSM-IV symptoms. This finding, which explains the prior difference between Chiodo et al (2007) and Nigg et al (2008), is due to either the different item set or the better psychometric properties of the Conners T score. Further study to see which of those events is true will be of interest. In contrast, hyperactivity/impulsivity is related to blood lead when rated by parents, but based on these data we tentatively suggest that this effect may be suppressed in teacher ratings by child treatment history. Overall, the conclusion is that both ADHD symptom domains are related to blood lead, but that further consideration of the

measurement scale and treatment effects remains important in quantifying these associations.

Limitations of this study should be noted. Most important, it is unclear how well concurrent lead levels reflect risks that probably occurred earlier in development. Effects of lead on the brain may depend on age of exposure (Manton et al., 2000). The ages of exposure and the peak early exposure level of the children in this study are unknown. However, the exposure levels observed are consistent with U.S. national levels in children at this age. Those U.S. surveys indicate that even preschool children average less than 5 μg/dL of exposure (CDC, 2005). Second, it is possible that hyperactive children ingested more lead, rather than that lead influenced hyperactivity. However, the only study we are aware of to test that question (David et al., 1977) found that lead levels were not elevated in hyperactive children with a known organic etiology (e.g., head injury), but were elevated in other hyperactive children. Further, an extensive animal experimental literature suggests lead has causal effects on neurodevelopment that make it a plausible influence on ADHD (Cory-Slechta, 1995). Thus, the most parsimonious summary of the data is likely that lead influenced ADHD rather than the reverse.

Last, this was not a random population sample, so sampling biases cannot be ruled out (characteristics of refusers were unknown). The sample was economically somewhat more well off, less representative of minority groups, and less lead-exposed than the nation as a whole. This may have resulted in under-estimation of effect magnitudes in relation to lead exposure and ADHD, although effect sizes reported were similar to those reported by Chiodo et al (2007) in a lower income, African American sample. In short, this study confirms that ADHD, both as a diagnosis and as symptom dimension, is associated with blood lead level at low exposure levels, even below 2.5 μg/dL.

In conclusion, background-levels of lead exposure were associated with ADHD in a clinically characterized sample, at the lowest levels of blood lead ever studied in relation to ADHD, and in both parent and teacher reports. This evidence that ADHD and its symptom domains are associated with blood lead has rather significant implications, because exposures in the range studied here remain widespread by definition. Lead exposure is a plausible neurobiological candidate for involvement in ADHD because it disrupts midbrain dopamine and other neurotransmission circuitry (Cory-Slechta, 2005), systems that are also implicated in ADHD (Nigg, 2006). It contributes to what is now an emerging body of literature linking ADHD to lead exposure even at population typical exposures. Implications for prevention, practice, and policy warrant further discussion.

Key points

- Lead is a known neurotoxicant previously associated with ADHD at high exposure
- Recent studies suggested low, population typical exposures may also related to ADHD
- Current study obtained fresh confirmation in a sample with very low, population typical lead exposure
- Children with ADHD had higher lead level than children without ADHD
- Both parent and teacher reports confirm the association of blood lead with ADHD symptoms.
- Further review of actionable lead level exposure in children is indicated

Acknowledgments

Author Statement: Financial Support and Conflicts of Interest

This work was supported by NIMH R21-MH070542 (JTN), RO1-MH070004 (KHF and JTN), by the MSU Office of the Vice President for Research, and by the U.S. Centers for Disease Control via Public Health Preparedness and Response for Bioterrorism grant to the Michigan Department of Community Health, which partially supported the laboratory analysis. All authors report no biomedical financial interests or potential conflicts of interest.

ABBREVIATIONS

dL	deciliter=.1 (or 1/10th) liter
µg	microgram=.001 milligrams
B	standardized regression coefficients
ICPMS	inductively coupled plasma mass spectrometry
NOS	not otherwise specified
CDC	Centers for Disease Control

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. Washington, DC: American Psychiatric Association; 2000. text rev

Braun J, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. Environmental Health Perspective. 2006; 114:1904–1909.

Burns JM, Baghurst PA, Sawyer MG, McMichael AJ, Tong S. Lifetime low-level exposure to environmental lead and children's emotional and behavioral development at 11–13 years: The Port Pirie Cohort Study. American Journal of Epidemiology. 1999; 149:740–749. [PubMed: 10206624]

Centers for Disease Control. Third National Report on Human Exposure to Environmental Chemicals. Atlanta: National Center for Environmental Health; 2005. Publication No. 05-0570

Chiodo LM, Covington C, Sokol RJ, Hannigan JH, Jannise J, Ager J, Greenwald M, Delaney-Black V. Blood lead levels and specific attention effects in young children. Neurotoxicology and Teratology. 2007; 29:538–546. [PubMed: 17553667]

Conners, CK. Conners Rating Scales-Revised. Toronto: Multi-Health Systems; 1997.

Cory-Slechta DA. Relationships between lead-induced learning impairments and changes in dopaminergic, cholinergic and glutamatergic neurotransmitter system functions. Annual Review of Pharmacology and Toxicology. 1995; 35:391–415.

Cory-Slechta DA. Lead-induced impairments in complex cognitive function: offerings from experimental studies. Child Neuropsychology. 2003; 9:54–75. [PubMed: 12815522]

David OJ, Hoffman SP, Sverd J, Clark J. Lead and hyperactivity: lead levels among hyperactive children. Journal of Abnormal Child Psychology. 1977; 5:405–416. [PubMed: 604381]

Ranft U, Delschen T, Machtolf M, Sugiri D, Wilhelm M. Lead concentration in the blood of children and its association with lead in soil and ambient air--trends between 1983 and 2000 in Duisburg. Journal of the Toxicology and Environmental Health Alliance. 2008; 71:710–715.

DuPaul, GJ.; Power, TJ.; Anastopolous, AD.; Reid, R. ADHD Rating Scale—IV: Checklists, Norms, & Clinical Interpretation. New York: Guilford Press; 1998.

Fewtrell LJ, Prüss-Ustün A, Landrigan P, Ayuso-Mateos JL. Estimating the global burden of disease of mild mental retardation and cardiovascular diseases from environmental lead exposure. Environmental Research. 2004; 94:120–133. [PubMed: 14757375]

Hensley-Alford SM, Lappin RE, Peterson L, Johnson CC. Pregnancy associated smoking behavior and six year postpartum recall. Maternal Child Health Journal. 2009 in press, Epub ahead of print Sep 26, 2008.

Kordas K, Casavantes M, Mendoza C, Lopez P, Rongquillo D, Rosado JL, Vargas GG, Stoltzfus RJ. The association between lead and micronutrient status, and children's sleep, classroom behavior, and activity. Archives of Environmental & Occupational Health. 2007; 62:105–112. [PubMed: 18316268]

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environmental Health Perspectives. 2005; 113:894–899. [PubMed: 16002379]

Manton WI, Angle CR, Stanek KL, Reese YR, Kuehnemann TJ. Acquisition and retention of lead by young children. Environmental Research. 2000; 82:60–80. [PubMed: 10677147]

Muthen, LK.; Muthen, BO. MPLUS Users Guide. 5. Los Angeles, CA: Muthen & Muthen; 1998–2008.

Nigg, JT. What causes ADHD? Understanding what goes wrong and why. New York: The Guilford Press; 2006.

Nigg JT, Knottnerus GM, Martel MM, Nikolas M, Cavanagh K, Karmaus W, Rappley MD. Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. Biological Psychiatry. 2008; 63:325–331. [PubMed: 17868654]

Purcell S. Variance components models for gene-environment interactions in twin analysis. Twin Research. 2002; 5:554–571. [PubMed: 12573187]

Sattler, JM. Assessment of children: Cognitive applications. San Diego: Author; 2001.

Silva PA, Hughes P, Williams S, Faed JM. Blood lead, intelligence, reading attainment, and behaviour in eleven year old children in Dunedin, New Zealand. Journal of Child Psychology and Psychiatry. 1988; 29:43–52. [PubMed: 3350882]

Strömberg U, Lundh T, Skerfving S. Yearly measurements of blood lead in Swedish children since 1978: the declining trend continues in the petrol-lead-free period 1995–2007. Environmental Research. 2008; 107:332–335. [PubMed: 18466895]

Thomson GO, Raab GM, Hepburn WS, Hunter R, Fulton M, Laxen DP. Blood-lead levels and children's behavior results from the Edinburg Lead Study. Journal of Child Psychology and Psychiatry. 1989; 30:515–528. [PubMed: 2768355]

Waldman ID, Gizer IR. The genetics of attention deficit hyperactivity disorder. Clinical Psychology Review. 2006; 26:396–432. [PubMed: 16513236]

Wechsler, D. Wechsler Intelligence Scale for Children-Fourth Edition: Technical and interpretive manual. San Antonio: The Psychological Corporation; 2003.

Wechsler, D. Weschler Individual Achievement Test--Second Edition. Examiner's Manual. San Antonio: Psychological Corporation; 2005.

Table 1

Sample Summary Statistics (Mean and Standard Deviation)

	Control	"NOS"	ADHD-PI	ADHD-C	p
N	99	29	47	61	
% male	43%[a]	48%[a]	68%[b]	74%[b]	<.05
% White	73%[a]	33%[b]	81%[a]	81%[a]	<.05
Child age (years)	11.8(2.5)[a]	11.8(2.4)[ab]	12.4 (2.5)[s]	10.6(2.6)[b]	.05
Annual home income ($k)	87.1(41)[a]	67.4(27)[ab]	81.4(42)[ab]	63.9(42)[b]	.05
% under poverty line ($21,200)	4.0%[a]	3.1%[a]	4.2%[a]	21.1%[b]	<.01
Child Full Scale IQ	107.9(12)	104.9(13)	102.2(15)	103.4(15)	ns
KSADS Inattention Lifetime	0.6(1.1)[a]	4.5(2.7)[b]	7.6(1.1)[c]	7.8(1.5)[c]	<.01
KSADS Hyperactive Lifetime	0.4(0.8)[a]	2.8(2.9)[b]	2.1(2.1)[b]	6.9(1.7)[c]	<.01
KSADS Inattention Current	0.6(1.1)[a]	4.3(2.7)[b]	7.4(1.1)[c]	7.8(1.5)[c]	<.01
KSADS Hyperactive Current	0.4(0.8)a	2.7(2.8)[b]	1.7(1.8)[b]	6.6(1.8)[c]	<.01
Teacher ADHD RS Inatt Sx	0.33(1.1)a	1.4(2.6)[a]	3.1(3.3)[b]	4.3(3.4)[b]	<.01
Teacher ADHD RS Hyp Sx	0.2(0.8)a	1.1(2.4)[b]	0.7(1.9)[b]	3.2(3.4)[c]	<.01
% Conduct Disorder (Life)	0%a	9.4%[b]	7.4%[b]	13%[c]	<.01
% ODD (Lifetime)	2%	19%[b]	15%[b]	38%[c]	<.01
P-Conners Cognitive	46.5(6)[a]	61.9(11)[b]	71.6(9)[c]	71.4(11)[c]	<.01
P-Conners Hyperactivity	46.7 (4)[a]	59.1(14)[b]	58.2(12)b	72.7(12)[c]	<.01
P-Conners Oppositional	45.7(7)[a]	55.7(13)[b]	58.7 (14)[b]	64.3(15)[c]	<.01
P-Conners ADHD Index	46.4(6)[a]	61.5(10)[a]	70.2(10)[b]	72.7(10)[b]	<.01
T-Conners Cognitive	48.2(7)[a]	55.3(10)[b]	57.4(9)[b]	60.2(10)[b]	<.01
T-Conners Hyperactive	49.5(9)[a]	53.8(11)[ab]	54.2(11)[b]	61.7(13)[c]	<.01
T-Conners Oppositional	47.1(4)[a]	52.8(12)[b]	51.3(9)[b]	57.7(12)[c]	<.01
T-Conners ADHD Index	49.1(9)[a]	57.3(13)[b]	60.4(10)[b]	66.3(11)[c]	<.01
% treated stimulants (lifetime)	0%	7%	25%	48%	<.01
% pregnancy smoke		13.8%	10.6%	13.1%	ns
Child unadjusted blood lead	0.2(.30)[a]	0.78(.24)[ab]	.72(.35)[ab]	.88(.44)[b]	<.01

Notes to Table 1: KSADS symptom scores and diagnoses are lifetime unless otherwise marked. For dimensional scores, post-hoc Tukey tests were conducted if variances were homogenous; or the Dunnet T3 post hoc if variances were not homogenous. Different superscripts indicate pair-wise differences on post-hoc tests at $p<.05$. For example, "a" under control Conners' Cognitive indicates a significant difference from "b" for ADHD-PI for the same variable; because ADHD-C also has a "b" it differs from controls also, but not from ADHD-PI. "ab" indicates does not differ from the group with the "a" or "b" superscript. ADHD-PI =Inattentive type; ADHD-C=combined type. Poverty is defined as < 50% of the median household income of $50,233 in the U.S. in 2007 (16% of national population below that cutoff), in keeping with one type of convention for defining poverty. The comparisons in this table do not control for sibling non-independence.

J Child Psychol Psychiatry. Author manuscript; available in PMC 2011 January 1.

Table 2

Median Blood Lead Level of Current Replication Sample, Nigg et al (2008), U.S. National Sample, and Selected European Data By Two Age Groups

Sample	Years Surveyed	%Male	Age in years	Mean/median blood lead μg/dL
Adolescents				
U.S.A. (CDC[1] NHANES)	1999, 2002	50%	12–19	0.94–1.10
Western Europe[2]	1996–2000	50%	0–18	3.5
Nigg et al 2007 (n=115)	2005–2006	64%	12–17	1.03 (SE=.05)
Current sample (n=96)	2006–2008	53%	12–17	0.68 (SE=.03)
Children				
U.S.A. (CDC NHANES)	1999, 2002	50%	6–11	1.25–1.51
Sweden[3]	2005, 2007	50%	7–11	1.31–1.32
Chiodo et al (2007)	1996–1997	51%	6–7	5.0
Nigg et al 2007 (n=35)	2005–2006	63%	8–11	1.04 (SE=.09)
Current sample (n=140)	2006–2008	63%	6–11	0.77(SE=.03)

[1] CDC=Centers for Disease Control; the U.S. national (from the CDC NHANES sample) reflect surveys at two points in time, one in 1999 and one in 2002. The lower value represents the 2002 value, and the higher value represents the 1999 value.

[2] Western Europe represents a meta-analytic average computed by Fewtrell et al (2004) from studies in Denmark, Sweden, Germany, France, Israel, and Greece in the late 1990's.

[3] Stromberg et al. 2007. The recent data represent two cities measured two years apart.

Table 3

Regression Analyses of Lead association with Parent–Reported ADHD Symptoms, Standardized Results Showing Parameter (standard error)

	KSADS Lifetime		Conners	
	Inattention	**Hyp-Imp**	**Cognitive**	**Hyp-Imp**
Without IQ covaried				
Age	.06(.07)	−.09(.07)	.13(.07)$^{+}$	.07(.08)
Sex	−.43(.15)**	−.30(.14)*	−.01(.15)	−.04(.14)
Income	−.14(.06)*	−.19(.07)**	−.09(.06)	−.18(.07)**
Hemoglobin	−.02(.07)	.02(.07)	−.11(.08)	−.07(.08)
Smoking	.29(.20)	.03(.23)	.27(.22)	−.19(.19)
Blood lead	.12(.07)$^{+}$	.19(.06)***	.21(.07)**	.26(.07)***
With IQ Covaried				
Age	.05(.07)	−.10(.07)	.12(.07)	.06(.08)
Sex	−.44(.14)**	−.30(.14)*	−.02(.15)	−.05(.14)
Income	−.10(.06)	−.17(.07)*	−.05(.06)	−.17(.08)*
Smoking	.24(.21)	.01(.23)	.22(.22)	−.20(.19)
Hemoglobin	.01(.06)	.04(.07)	−.09(.08)	−.06(.08)
IQ	−.12(.07)$^{+}$	−.09(.06)	−.12(.07)$^{+}$	−.05(.07)
Blood Lead	.11(.07)	.18(.06)***	.20(.07)**	.25(.07)***

Parameter estimates are standardized as explained in Method. Sex is coded 1=male, 2=female.

$^{+}$ p<.10;

* p<.05,

** p≤.01,

*** p≤.001.

Table 4

Regression Results for Association of Child Blood Lead with Teacher Behavior Ratings, Showing Standardized Parameter Estimates (standard error)

	ADHD Rating Scale		Conners	
	Inattention	**Hyp-Imp**	**Cognitive**	**Hyp-Imp**
Without IQ covaried				
Age	−.08(.07)	−.25(.07)***	.10(.08)	.08(.08)
Sex	−.60(.12)***	−.43(.10)***	−.02(.13)	.32(.13)*
Income	−.16(.07)*	−.07(.07)	−.33(.07)***	−.20(.07)**
Hemoglobin	−.05(.07)	−.05(.06)	.01(.08)	.02(.09)
Smoking	−.03(.24)	−.07(.20)	.12(.27)	−.42(.17)*
Blood lead	.09(.06)	.11(.06)+	.19(.07)**	.14(.06)*
With IQ Covaried				
Age	−.10(.07)	−.26(.06)***	.02(.02)	.06(.08)
Sex	−.62(.12)***	−.44(.10)	−.03(.06)	.30(.13)*
Income	−.12(.06)	−.04(.07)	−.23(.06)***	−.12(.07)+
Smoking	−.11(.24)	−.14(.21)	−.02(.26)	−.53(.15)**
Hemogl	−.02(.06)	−.03(.06)	.05(.07)	.05(.08)
IQ	−.19(.08)*	−.15(.07)*	−.35(.06)***	−.30(.07)***
Blood Lead	.06(.06)	.09(.06)	.15(.06)*	.11(.06)+

Parameter estimates are standardized as explained in Method. Sex is coded 1=male, 2=female.

+ p<.10;

* p<.05,

** p≤.01,

*** p≤.001.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neurotoxicology and Teratology 25 (2003) 555–559
NEUROTOXICOLOGY AND TERATOLOGY
www.elsevier.com/locate/neutera

Effects of low-level lead exposure on cell survival and neurite length in primary mesencephalic cultures

J.S. Schneider*, F.N. Huang, M.C. Vemuri

Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, 1020 Locust Street, 521, JAH, Philadelphia, PA 19107, USA

Received 18 November 2002; received in revised form 4 February 2003; accepted 10 February 2003

Abstract

The effects of low-level lead exposure on survival and neurite length of rat E15 primary ventral mesencephalic dopaminergic neurons were studied. Lead acetate (0.001–10 μM) added to primary cultures for 48 h (in serum-free defined media [DM]) caused a loss of tyrosine hydroxylase (TH)-positive neurons only at the highest concentrations (1 and 10 μM). In contrast, significant effects on neurite length were observed at concentrations as low as 0.001 μM. Lead-induced decrease in neurite length became more apparent at concentrations of 0.01 μM (mean 37.9% decrease) and 0.10 μM lead acetate (mean 43.9% decrease). These data show that very low concentrations of lead, well below the level necessary to adversely affect neuronal survival, can have dramatic effects on neurite growth. These results support recent clinical findings of detrimental effects of low-level lead exposure on brain development.

Keywords: Lead; Neurons; Ventral mesencephalon; Development

1. Introduction

The general toxic effects of lead have been known for centuries, yet lead is still a major environmental poison affecting primarily pediatric populations in the United States as well as in other countries worldwide. Although the level of concern for pediatric lead poisoning, as set by the Centers for Disease Control in 1991, is 10 μg/dl [6], studies performed over the last decade indicate that, indeed, a safe level of lead in the blood of children has not yet been identified. Evidence for detrimental effects on behavior and cognitive development have been reported with blood lead levels below 10 μg/dl [17,25].

Although neuropsychological studies of lead's effects in children may differ in basic characteristics of the study groups and in the choice of tests administered, the description of deficits in certain functional domains, such as attention and fine motor skills, has been remarkably consistent (see Ref. [19] for review). In fact, a number of cognitive deficits associated with lead poisoning, such as attention and executive function problems, may be due at least in part to lead's effects on dopamine systems. Animals with dopamine-depleting lesions of the cortex or striatum have a number of cognitive and behavioral deficits including impairments in attention, impulsivity, short-term memory, cognitive flexibility (and other executive functions), as well as behavioral abnormalities including apathy, low frustration tolerance, and aggressiveness [4,5,23,24]. In addition to the well-documented learning and memory problems in lead-exposed animals, attentional problems have also been described [3]. Attention and executive functioning problems are a known consequence of lead poisoning in children [10,30] and are present with dopamine dysfunction, as in Parkinson's disease [16].

The effects of lead on dopaminergic cells in culture have been described previously [27]. Short-term exposure of cultures to high concentrations of lead (3–50 μM) killed neurons and glia at the highest concentrations, whereas concentrations at the lower end (3 μM) significantly inhibited [^{3}H]dopamine uptake [27]. Lead exposure has also been reported to alter the concentration of dopamine and decrease the activity of the dopamine-synthesizing enzyme tyrosine hydroxylase (TH) in midbrain and diencephalic regions [21] as well as in rat [29] and primate retina [15]. In consideration of the clinical and experimental data described above

* Corresponding author. Tel.: +1-215-503-0370; fax: +1-215-923-3808.
E-mail address: jay.schneider@mail.tju.edu (J.S. Schneider).

0892-0362/$ – see front matter © 2003 Elsevier Science Inc. All rights reserved.
doi:10.1016/S0892-0362(03)00018-7

on lead effects on the dopamine system, the present study was conducted to examine effects of low concentrations of lead (0.001–0.1 μM, equivalent to 0.024 and 2.40 μg/dl, respectively) on survival and growth (e.g., elaboration of neurites) of fetal dopaminergic neurons in culture.

2. Methods

2.1. Primary cultures of ventral mesencephalic neurons

Timed-pregnant Sprague–Dawley rats were euthanized with carbon dioxide. Embryos (E-15) were removed and the ventral mesencephalon was dissected out and placed in Dulbecco's phosphate-buffered saline, (DPBS; pH 7.4) on ice. The tissue was minced and incubated in a trypsin solution (0.01% in Ca^{2+}/Mg^{2+} free Hank's balanced salt solution) with 0.05% DNAse for 20 min at 37 °C with gentle agitation. The supernatant was removed and replaced with Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum, glucose (6 mg/ml), glutamine (204 μg/ml) and penicillin/streptomycin (100 U/ml) and the cells were dissociated by passage through a fire-polished Pasteur pipette. Dissociated cells were then passed through a nylon-filter cell strainer (70 μM). The number of viable cells were counted for trypan blue exclusion using a hemocytometer and plated at a density of 1.5×10^5 cells per well on poly-D-ornithine (PO; 0.01% in borate buffer; pH 8.4) coated Lab-Tek eight-well slides. After 1 h of stabilization at 37 °C in an atmosphere containing 5% CO_2, the media was changed to serum-free defined medium (DM) containing DME/F12, 1% ITS supplement, glucose (6 mg/ml), glutamine (204 μg/ml) and penicillin/streptomycin (100 U/ml). The cultures were grown at 37 °C in 5% CO_2 for 3 days before commencing experimental manipulations.

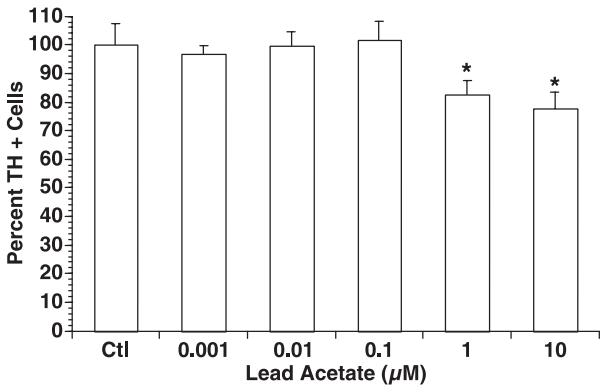


Fig. 1. Effects of lead exposure on the number of TH-positive cells in primary ventral mesencephalic cultures. Addition of lead acetate (0.001–10 μM, in serum-free DM) for 48 h caused a significant loss of TH+ cells at lead acetate concentrations of 1 and 10 μM. Bars show mean cell counts ± S.E.M. Ctl = control cultures (no lead); $*P < .01$ vs. control. Data were derived from quadruplicate samples for each experimental condition, repeated with four independent cultures.

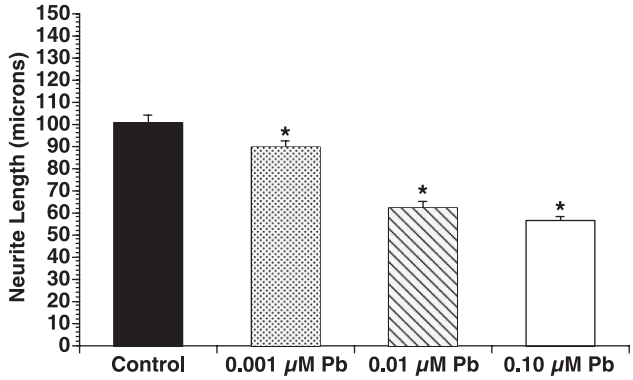


Fig. 2. Effects of lead exposure on length of primary neurites of E-15 dopaminergic neurons in culture. The lowest concentration of lead acetate used (0.001 μM) caused a significant decrease in neurite length, that was exacerbated by incubation in higher concentrations of lead (0.01 and 0.10 μM). These effects were observed at lead concentrations below those that caused a decrease in cell survival. Bars show mean length of primary neurites ± S.E.M. $*P < .01$ vs. control. Data were derived from quadruplicate samples for each experimental condition, repeated with four independent cultures.

2.2. Lead exposure studies

To investigate the effect of lead on cell survival and neurite length, lead acetate was added to media (DM) at different concentrations (0.001, 0.01, 0.1, 1.0 and 10 μM) for 48 h.

2.3. TH immunohistochemistry and cell counts

At the end of the lead exposure period, cultures were fixed in 4% paraformaldehyde and stained for the presence of TH using a polyclonal TH antibody (1:2000, 4 °C for 24 h, Pel-Freeze, Rogers, AR), biotinylated goat anti-rabbit IgG (1:1000, 1 h at room temperature, Pel-Freeze, Rogers, AR, Jackson Immunoresearch Laboratories, Inc., West Grove, PA). TH-positive cells were visualized after incubation in ABC substrate (Vector Laboratories, Burlingame, CA) and metal-enhanced diaminobenzidine (Pierce, Rockford, IL). Immunopositive cells were counted in consecutive fields across the largest diameter of the cell bed using an eye piece reticule at 10× magnification.

2.4. Neurite length measurement

Neurite length measurements were taken of the longest neurite present on 150 TH-positive cells from control cultures and each lead-exposed culture, using a neurite length measurement macro (provided online by V.I. Pikov) and NIH Image software (v. 1.68). Fields were sampled randomly and the person performing the measurements was blind to treatment condition. Briefly, the images of TH-positive cells were captured at 20× magnification and contrast was adjusted until neurites appeared as contiguous as possible with low background. The longest neurite on each cell in the

field was drawn using the pencil tool from the Image program. The length of the outlined neurite was then computed by the macro from a thresholded image.

2.5. Statistical analysis

All experiments were run in quadruplicate and repeated on four separate occasions. Cell number and neurite length measurement data were analyzed by one-way ANOVA followed by pairwise post hoc comparisons (Newman–Keuls *t* test). Data from four replicate studies were combined for analysis. Frequency histograms of neurite lengths were also constructed, using GB Stat v.6.5.6 software. Comparisons of frequency histograms were made using a Kruskal–Wallis one-way ANOVA.

3. Results

3.1. Lead effects on cell survival

No lead precipitation was observed in any of the media used in these studies. In addition, measurement of lead levels (PPM, performed by ESA Laboratories, Chelmsford, MA) in filtered and unfiltered media samples showed linear increases in measured lead levels after addition of 1, 10 or 100 μM lead acetate.

In primary mesencephalic cultures, a 48-h exposure to lead acetate caused a significant decrease in the number of TH-positive cells only in cultures exposed to high concentrations of lead acetate (e.g., 1.0 and 10 μM, $P<.05$ vs. control) (Fig. 1). TH-positive cell number was completely unaffected by lower levels of lead.

3.2. Lead effects on neurite length

A dose-dependent effect of lead on neurite length of TH-positive neurons was observed ($F=80.08$, $P<.001$, Figs. 2, 3 and 4). The mean length of primary neurites of TH-positive neurons was decreased by an average of 10.9% after 48 h exposure to as little as 0.001 μM lead acetate ($P<.01$ vs. control). This detrimental effect on neurite length was exacerbated after exposure to 0.01 μM (mean 37.9% decrease, $P<.01$ vs. control) and 0.10 μM lead acetate (mean 43.9% decrease, $P<.01$ vs. control) (Fig. 4). There was no significant difference between

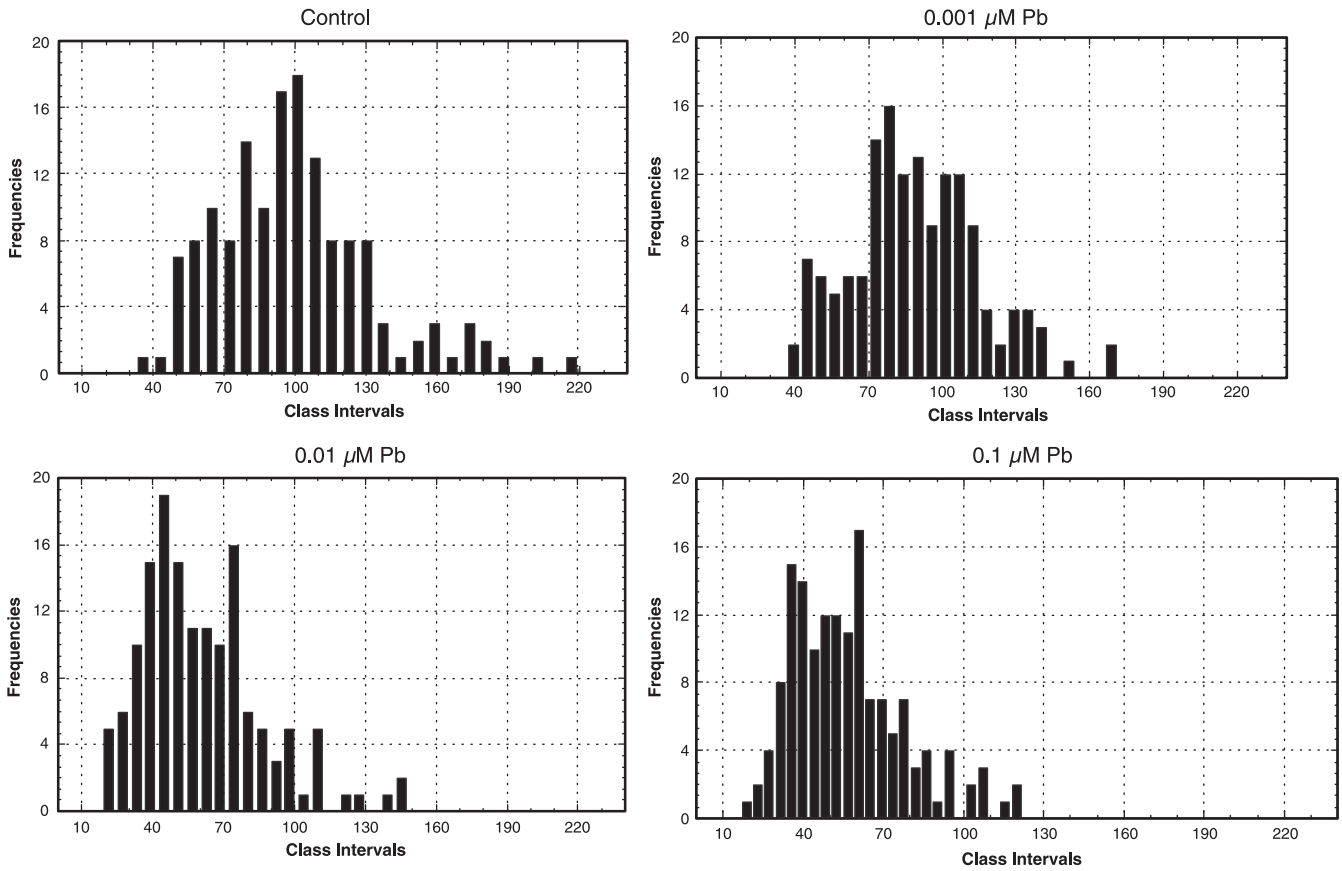


Fig. 3. Histograms showing the distributions of primary neurite lengths in control and lead-treated cultures. After 48 h incubation in 0.001 μM lead acetate, the longest neurites were lost but the overall shape of the distribution was not different from that seen in control cultures. In contrast, after 48 h incubation in 0.01 or 0.10 μM lead acetate, there was a clear shift to the left in the distribution histograms. Data were derived from quadruplicate samples for each experimental condition, repeated with four independent cultures.

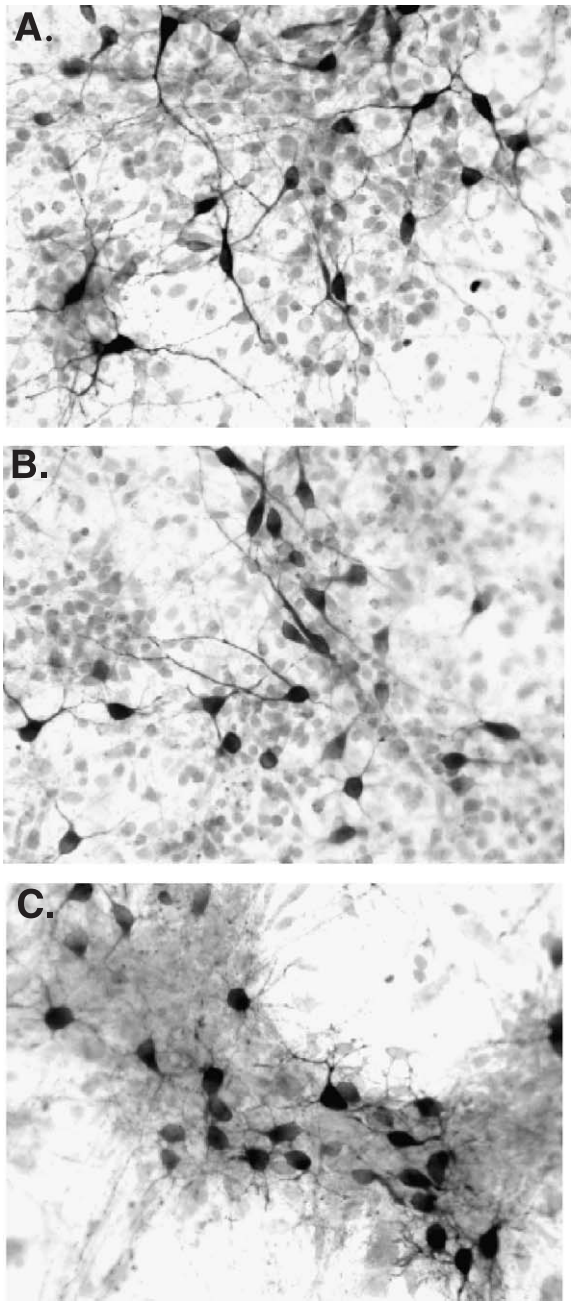


Fig. 4. Photomicrographs of TH-positive neurons in control cultures (A) and in cultures exposed to (B) 0.001 and (C) 0.01 μM lead acetate for 48 h. Note the progressive decrease in neurite length with exposure to increasing concentrations of lead.

neurite lengths measured in cultures exposed to 0.01 or 0.10 μM lead. The distribution of neurite lengths was plotted for each culture condition (Fig. 3). After 48-h incubation with 0.001 μM lead acetate, the longest neurites were lost, although the rest of the distribution of neurite lengths remained essentially the same as in control cultures. However, in cultures exposed to 0.01 and 0.10 μM lead acetate, there was a clear shift to the left ($P < .05$) in the distributions of neurite lengths.

4. Discussion

The present results indicate that exposure of fetal dopaminergic neurons to very low levels of lead (0.001–0.1 μM, analogous to 0.024–2.4 μg/dl of lead, using the convention for measuring blood lead levels) for a brief period of time (e.g., 48 h) causes significant disruption of neurite elaboration without any appreciable effect on dopamine neuron survival. Although the reasons for this effect are not clear at this time, lead effects on calcium homeostasis may have played an important role. Intracellular and nuclear transport of calcium are involved in elaboration of axons and dendrites. Calcium release from intracellular stores stabilizes dendrites during the period of synapse formation [20]. Local calcium release is a mechanism by which afferent activity (e.g., neurotransmission evoked calcium release) can regulate dendritic structure and arborizations that are critical to attaining a normal pattern of adult synaptic connections [20]. Since lead suppresses activity associated with calcium-dependent release of neurotransmitters [9,18], affects presynaptic calcium channels involved in transmitter release [22] and essentially substitutes for calcium in a multitude of physiological functions [2], it is not surprising that lead would also affect calcium-dependent arborization of neurites. What was surprising was the low level of lead (0.001, 0.01 μM) needed to adversely affect neurites. However, lead is known to affect physiological processes at levels below that required by endogenous activators. For example, lead at picomolar concentrations activates protein kinase C, an action normally induced by nanomolar concentrations of calcium [1].

Lead may also have affected neurite morphology by directly interacting with cytoskeletal proteins. Previously, lead exposure, in the absence of serum, altered cytoskeletal protein expression (tau, MAP-2b, MAP-2c, and GAP-43) after only a 3-h exposure to 3 or 6 μM lead [26]. Prolonged lead exposure in vivo (through age 15 months) also modified astrocyte cytoskeletal proteins (e.g., GFAP, vimentin) [28]. Slow axonal transport of neurofilament proteins and tubulins was impaired in animals exposed to lead in their drinking water for 13 weeks [32].

Previous studies have described a significant inhibitory effect of high (1 mM) and low (1 nM) concentrations (but not at intermediate concentrations) of lead on neurite initiation in fetal (E-18) hippocampal and cortical neurons grown in culture [14]. Effects of lead on axon length, number of dendrites/cell and number of branches/axon were complex and dependent upon the concentration of serum in the media [14]. Lead's inhibitory effects on neurite development in cultured hippocampal neurons were attributed at least in part to an inappropriate stimulation by lead of protein phosphorylation by calcium/calmodulin-dependent protein kinase or cyclic AMP-dependent protein kinase [13]. Other studies have reported impairment of growth of retinal axons (e.g., reduced area and branchtip number of retinal ganglion cell axon arborizations in the optic tectum) with a

6-week in vivo exposure to nanomolar concentrations of lead [7]. In contrast to the inhibitory effects of lead on neurite growth in vivo or in primary cells in culture, various concentrations of lead (e.g., 0.025–0.05 μM in one study [8]; 0.1–100 μM in another study [31]) were shown to promote neurite outgrowth from PC12 cells in the presence or in the absence of NGF, while higher lead concentrations (1–10 mM) were less effective. At low concentrations, lead did not cause neurite outgrowth in NGF-treated PC12 cells but enhanced NGF-induced neurite outgrowth and promoted the formation of multiple neurites per cell [31]. These latter results, however, are difficult to compare with the present findings due to differences in the type of cells (e.g., primary neurons vs. tumor cell line) and culture conditions utilized.

The finding that neurite morphology is significantly altered at lead concentrations 1/1000th to 1/100th of that necessary to stimulate overt cell death may have significant implications for fetal brain development and the hard wiring of the brain under conditions of lead exposure. Mobilization of maternal bone lead stores is a major source of fetal lead exposure [11] with a strong correlation between maternal and umbilical cord blood lead levels. Emphasizing the danger of transfer of lead from mother to fetus [12], a recent prospective study found increased levels of lead in maternal bone and umbilical cord blood (mean 6.7 μg/dl) that were associated with lower Mental Development Index scores on the Bayley Scales of Infant Development at 24 months of age [11]. These findings, together with the current results, underscore the potential danger of even very low levels of lead on fetal neuronal development.

References

[1] J. Bressler, K.A. Kim, T. Chakraborti, G. Goldstein, Molecular mechanisms of lead neurotoxicity, Neurochem. Res. 24 (1999) 595–600.
[2] J.P. Bressler, G.W. Goldstein, Mechanisms of lead neurotoxicity, Biochem. Pharmacol. 41 (1991) 479–484.
[3] B.J. Brockel, D.A. Cory-Slechta, Lead, attention and impulsive behavior: changes in a fixed ratio waiting-for-reward paradigm, Pharmacol. Biochem. Behav. 60 (1998) 545–552.
[4] L.L. Brown, J.S. Schneider, T.I. Lidsky, Sensory and cognitive functions of the basal ganglia, Curr. Opin. Neurobiol. 7 (1997) 157–163.
[5] T. Brozoski, R.M. Brown, H.E. Rosvold, P.S. Goldman, Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey, Science 2015 (1979) 929–931.
[6] Centers for Disease Control and Prevention, Preventing Lead Poisoning in Young Children: A Statement by the US Centers for Disease Control—October 1991, U.S. Department of Health and Human Services, Atlanta, GA, 1991.
[7] H.T. Cline, S. Witte, K.W. Jones, Low lead levels stunt neuronal growth in a reversible manner, Proc. Natl. Acad. Sci. 93 (1996) 9915–9920.
[8] T. Crumpton, D.S. Atkins, N.H. Zawia, S. Barone Jr., Lead exposure in pheochromocytoma (PC12) cells alters neural differentiation and Sp1 DNA-binding, Neurotoxicology 22 (2001) 49–62.
[9] P. Devoto, G. Flore, A. Ibba, W. Fratta, L. Pani, Lead intoxication during intrauterine life and lactation but not during adulthood reduces nucleus accumbens dopamine release as studied by brain microdialysis, Toxicol. Lett. 121 (2001) 199–206.
[10] D. Faust, J. Brown, Moderately elevated blood lead levels: effects on neuropsychologic functioning in children, Pediatrics 80 (1987) 623–629.
[11] C. Gardella, Lead exposure in pregnancy: a review of the literature and argument for routine prenatal screening, Obstet. Gynecol. Surv. 56 (2001) 231–238.
[12] A. Gomaa, H. Hu, D. Bellinger, J. Schwartz, S.W. Tsaih, T. Gonzalez-Cossio, L. Schnaas, K. Peterson, A. Aro, M. Hernandez-Avila, Maternal bone lead as an independent risk factor for fetal neurotoxicity: a prospective study, Pediatrics 110 (2002) 110–118.
[13] M. Kern, G. Audesirk, Inorganic lead may inhibit neurite development in cultured rat hippocampal neurons through hyperphosphorylation, Toxicol. Appl. Pharmacol. 134 (1995) 111–123.
[14] M. Kern, T. Audesirk, G. Audesirk, Effects of inorganic lead on the differentiation and growth of cortical neurons in culture, Neurotoxicology 14 (1993) 319–328.
[15] K. Kohler, H. Lilienthal, E. Guenther, G. Winneke, E. Zrenner, Persistent decrease of the dopamine-synthesizing enzyme tyrosine hydroxylase in the rhesus monkey retina after chronic lead exposure, Neurotoxicology 18 (1997) 623–632.
[16] K.W. Lange, T.W. Robbins, C.D. Marsden, M. James, A.M. Owen, G.M. Paul, L-Dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction, Psychopharmacology 107 (1992) 394–404.
[17] B.P. Lanphear, K. Dietrich, P. Auinger, C. Cox, Cognitive deficits associated with blood lead concentrations <10 μg/dl in US children and adolescents, Public Health Rep. 115 (2000) 521–529.
[18] S.M. Lasley, M.C. Green, M.E. Gilbert, Influence of exposure period on in vivo hippocampal glutamate and GABA release in rats chronically exposed to lead, Neurotoxicology 20 (1999) 619–630.
[19] T.I. Lidsky, J.S. Schneider, Lead neurotoxicity in children: basic mechanisms and clinical correlates, Brain 126 (2003) 5–19.
[20] C. Lohmann, K.L. Myhr, R.O. Wong, Transmitter-evoked local calcium release stabilizes developing neurites, Nature 418 (2002) 177–181.
[21] M.J. McIntosh, P.A. Meredith, M.A. Petty, J.L. Reid, Influence of lead exposure on catecholamine metabolism in discrete rat brain nuclei, Comp. Biochem. Physiol. 89 (1988) 211–213.
[22] D.A. Nachsen, Selectivity of the Ca binding site in the synaptosome Ca channels. Inhibition of Ca influx by multivalent metal cations, J. Gen. Physiol. 83 (1984) 941–967.
[23] A. Nieoullon, Dopamine in the regulation of cognition and attention, Prog. Neurobiol. 67 (2002) 53–83.
[24] J.S. Schneider, C.J. Kovelowski, Chronic exposure to low doses of MPTP: I. Cognitive deficits in motor asymptomatic monkeys, Brain Res. 519 (1990) 122–128.
[25] J. Schwartz, Low-level lead exposure and children's IQ: a meta analysis and search for a threshold, Environ. Res. 65 (1994) 42–55.
[26] M. Scortegagna, E. Chikhale, I. Hanbauer, Effect of lead on cytoskeletal proteins expressed in E14 mesencephalic primary cultures, Neurochem. Int. 32 (1998) 353–359.
[27] M. Scortegagna, I. Hanbauer, The effect of lead exposure and serum deprivation on mesencephalic primary cultures, Neurotoxicology 18 (1997) 331–340.
[28] A. Selvin-Testa, C.F. Loidl, E.M. Lopez, F. Capani, J.J. Lopez-Costa, J. Pecci-Saavedra, Prolonged lead exposure modifies astrocyte cytoskeletal proteins in the rat brain, Neurotoxicology 16 (1995) 389–401.
[29] L.M. Shulman, S.V. Kala, A.L. Jadhav, D.A. Fox, Alterations in the regulation of retinal dopamine content and release following lead exposure during development, Toxicologist 30 (1996) 26.
[30] L. Stokes, R. Letz, F. Gerr, M. Kolczak, F.E. McNeil, D.R. Chettle, W.E. Kaye, Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience, Occup. Environ. Med. 55 (1998) 507–516.
[31] T.M. Williams, A.M. Ndifor, J.T. Neary, R.R. Reams-Brown, Lead enhances NGF-Induced neurite outgrowth in PC12 cells by potentiating ERK/MAPK activation, Neurotoxicology 21 (2000) 1081–1090.
[32] K. Yokoyama, S. Araki, Assessment of slow axonal transport in lead-exposed rats, Environ. Res. 59 (1992) 440–446.

sharing child and youth development knowledge
volume 24, number 1
2010

Social Policy Report

Protecting Children from Exposure to Lead
Old Problem, New Data, and New Policy Needs

Claire Cole & Adam Winsler
George Mason University

Abstract

The detrimental effects of lead exposure in children have been known for over 100 years. Although a few initial measures implemented about 30 years ago were effective in somewhat reducing levels of lead exposure in children, relatively little has been done recently from a policy perspective to protect children from lead. We now know from recent research that much more work is needed. Recent events highlighted in the media show that several urban communities still have unacceptable levels of lead in water systems. Early research identified high levels of lead as being particularly detrimental to children's intellectual and behavioral development. However, new studies have discovered that lower levels of lead, levels once thought safe, also cause considerable damage to children's developmental outcomes. This social policy report summarizes new data on the intellectual, academic, and behavioral deficits seen in children exposed to both low and high levels of lead, discusses the biological and neurological mechanisms of lead poisoning, explores sources of environmental lead exposure and lead abatement practices, shows that current federal and state-level child screening and lead level reporting practices are inadequate, and makes policy recommendations centered on increasing education, intensifying abatement efforts, strengthening and regulating mandatory screening practices, and reducing the federal threshold of allowable levels of lead.

Social Policy Report
Volume 24, Number 1 | 2010
ISSN 1075-7031
www.srcd.org/spr.html

Social Policy Report
is published four times a year by the
Society for Research in
Child Development.

From the Editor

With Volume 24, Issue 1, a team from Frank Porter Graham Child Development Institute at The University of North Carolina at Chapel Hill will begin the editorship of the SRCD *Social Policy Report* (*SPR*). Reiterating our statement in the last issue, we appreciate the great expertise and leadership that Lonnie Sherrod and Jeanne Brooks-Gunn provided for SPR. We hope to extend and elaborate on the momentum they created for the quarterly report. *SPR* stands as the preeminent policy publication addressing developmental science topics for policymakers and broader consumer audiences. The report's translational function is complemented with concise and attractive *SPR Briefs* produced by Marty Zaslow, Sarah Hutcheon, and Sarah Mandell in the SRCD Office for Policy and Communications, and Anne Bridgman, the *Brief* science writer. SRCD strives to inform policy through scientific evidence, and we will continue to make the *SPR* the premier report for lawmakers, policy experts, and researchers involved in developmental science issues.

This issue also inaugurates some important changes. The *SPR* has a new look and feel but maintains the essential informational elements of the old format. This new format will be disseminated only electronically but conforms to the word length requirements of the previous print issues. However, if you print out the issue, it will take more pages because of the changes in design, which we hope will enhance readability. Also, the electronic format includes links to available citations and abstracts, allowing our readers to go directly to the information source. In the future, we hope to use other forms of technology to add convenience and convey the most essential information covered in the *SPRs*. We invite readers to share their observations or comments about the new format. Please send any questions or comments to Anne Hainsworth at anne.hainsworth@unc.edu.

When we sat down to discuss topics for the first report of 2010, we debated the merits of focusing on the ongoing issue of childhood lead exposure. The topic did not seem to be very cutting edge. Did we as a society not address this problem years ago, and is not the situation better now? Cole and Winsler's review of newer (as well as older) data on the detrimental effects of low-level lead exposure made us sit up and pay attention. Nigg highlights in his commentary the research linking lead to ADHD and raises the question about other future potential neurotoxins. Lanphear's commentary reminds us of the world's long struggle to reduce lead levels in children and recommends increased efforts to eliminate lead from consumer products. A separate commentary by Gould and Hertel-Fernandez, though, raises the important issue of considering cost-benefit ratios of various lead reduction strategies before recommending or implementing policies. Although some progress has been made over the past 20 years, it is very clear that more can be done to reduce and prevent lead exposure among our nation's children. We hope this issue of *SPR* brings renewed interest in this old, but nevertheless dangerous, problem.

— Sam Odom (Lead editor)
Donna Bryant (Issue editor)
Kelly Maxwell, Anne Hainsworth
FPG Child Development Institute, The University of North Carolina at Chapel Hill.

Protecting Children from Exposure to Lead
Old Problem, New Data, and New Policy Needs

In 2000, the District of Columbia Water and Sewer Authority (WASA) instituted a new method of water disinfection, changing from the use of free chlorine to chloramines. The addition of chloramines to the water system had several unintended side effects, primarily increased corrosion of the city's water pipes, many containing lead. Such corrosion led to dangerous increases in lead levels in the city's drinking water (Edwards, Triantafyllidou, & Best, 2009; Environmental Protection Agency [EPA], 2007; Guidotti, Moses, Goldsmith, & Ragain, 2008). The current allowable amount of lead in drinking water is set by the EPA at 15µg/L (EPA, 2004a; EPA, 2006). A water lead level above this amount exposes the public to unsafe amounts of lead. By late 2001, tests of the D.C. drinking water showed lead water level readings in excess of the allowable level set forth by the EPA. In 2004, a *Washington Post* article exposed the elevated water lead levels, instigating widespread concern among community members worried about the effects of elevated levels of lead. WASA serves over 500,000 D.C. residents, and many parents were appropriately concerned with the effect of lead on their children. Many parents and community members searched for information on the effects of increases in lead exposure that remained below the federal threshold, but earlier reports were not conclusive as to the effects of low levels of lead on children.

D.C. is not alone in its trouble with lead-contaminated drinking water. Articles in the *Seattle Post* (Bach, 2004) and *Seattle Times* (Bhatt, 2005) reported that in 2004, tests of Seattle's public schools indicated that 70 of 88 schools had at least one water fountain test above the EPA recommended lead level. Nineteen of the schools tested had over half of their drinking fountains exceed the limit. One fountain tested at 1,600µg/L, an amount more than 80 times greater than the EPA's allowable lead level. Tests conducted back in 1990 and 1992 also indicated elevated lead levels within the Seattle school system, indicating an ongoing problem.

In a follow-up to the initial D.C. article, Leonning, Becker, and Nakamura (2004) of the *Washington Post* examined past records of lead water level tests. Their results indicated that large municipalities including Boston, Philadelphia, and New York had avoided testing homes that were likely to show high water lead levels, and had dismissed tests that indicated unsafe levels of lead within their water systems. Additionally, some states chose not to report federally required water lead level violations to the EPA, as federally required, providing even more uncertainty about the safety of our nation's water. These reports indicate that high lead levels in drinking water may be more common than generally thought and that we have not done enough yet to prevent the exposure of children to lead. In addition, water is just one of many potential sources of lead exposure, which include lead-based paints, house dust, soil, and consumer products. Thus, it is critical for us to understand the effect of lead on child outcomes.

It is critical for us to understand the effect of lead on child outcomes.

In 1994, the Society for Research in Child Development (SRCD) published a *Social Policy Report* describing the most recent research concerning the effects of lead on children, and suggested possible ways of protecting children from exposure (Tesman & Hills, 1994). In 1991, the EPA safety threshold for Blood Lead Level (BLL) was set at 10µg/dL, and any BLL greater than this was considered unsafe. The prior *SPR* detailed the effects of large amounts of lead on children's development (BLL > 10µg/dL), and only hinted at possible effects of low-level exposure (BLL < 10µg/dL). In the last 15 years, many new studies have focused on the effects of lead on children's development when exposure is well below the current 10µg/dL threshold. The results of these studies are quite disturbing. The goal of the present report is to review and update our knowledge base on the negative developmental effects of even low levels of lead exposure on children and to make an urgent call for policy action to reduce and eliminate the harmful

effects from this fully preventable risk factor for negative child outcomes.

This report is divided into three main sections. First, we will discuss the research on the effects of lead exposure in children after providing a brief history of research conducted in this area. The biological mechanisms of human lead exposure will also be discussed, as will children's particular neurodevelopmental sensitivity to lead. The second section will describe environmental sources of lead and ways in which children's exposure to lead can be reduced via parent education, lead abatement, and child screening practices. The report will conclude by showing the inadequacies of the current reporting and screening systems and suggesting policy recommendations aimed at the long-term reduction of lead exposure in children.

History of Childhood Lead Research

Concerns about potential negative effects of lead on children began to emerge in the 1890s, with reports from Australia documenting various unusual illnesses. Children were found to have symptoms such as headache, nausea, and motor problems, and in 1904, these symptoms were traced to high lead levels in both home water tanks and paint dust (Gibson, 1904; Needleman, 2004; Tesman & Hills, 1994). Initially, there was widespread skepticism as to the negative effects of lead on children, but in the 1930s and 1940s, societal views began to change. Several outbreaks of acute lead poisoning in the United States gave researchers an opportunity to observe the effects of large levels of lead exposure firsthand. In 1943, a study of 20 children who had suffered acute lead poisoning found that 19 of them had long-term deficits in behavior, learning, and school performance (Byers & Lord, 1943, as cited in Needleman, 2004). These early studies promoted the general understanding that toxic lead poisoning causes long-term developmental deficits in children.

Prior to the mid-1970s, the Centers for Disease Control and Prevention (CDC) had mandated that a BLL above 60µg/dL be deemed toxic to children (CDC, 1991). In the early 1970s, the federal government enacted guidelines for lead screening in children (Tesman & Hills, 1994). Data from these screenings provided new information indicating that children who had high (>10µg/dL) but not toxic (>60µg/dL) BLLs also showed deficits in behavior, learning, and intelligence. Based on this research, the CDC revised its standards for blood levels in children and reduced the acceptable amount to 30µg/dL. Research conducted in the mid-1970s and 1980s focused on the effects of high BLLs on children. In response to this research, the CDC again reduced acceptable BLLs in children to 25µg/dL and eventually to 10µg/dL. Researchers wondered, however, if even lower levels of lead negatively affected children (CDC, 1991; Tesman & Hills, 1994).

Mechanisms of Lead Neurotoxicity

Although researchers have long known that lead negatively affects child outcomes, it is only recently that the biological mechanisms of lead exposure have been discovered. Although there are many different mechanisms by which lead affects development, there seem to be several broad categories of function. First, lead seems to promote abnormal cell apoptosis (programmed cell death); second, it seems to perturb normal protein function within the brain; and third, it seems to alter neurochemical functioning within the brain. Many of lead's varying mechanisms of action are driven by its ability to bind to calcium receptors within the body. Lead passes through the body's blood-brain barrier in part because of its ability to "substitute" for calcium. In a normal brain, neurons employ calcium channel pumps to regulate their electrical gradient, allowing for the production of action potentials and electrical impulses. These electrical impulses serve as one of the main modes of communication within the brain. Lead has the ability to be taken in by calcium channel pumps and enter neurons in this manner (Kerper & Hinkle, 1997). Once lead enters the neuron, it disrupts normal cell functioning which causes apoptosis. The intake of lead into the neuron disrupts the calcium gradient within the cell, damaging neuronal mitochondria which often results in cell death. In addition, when present in large amounts, lead is absorbed by the mitochondria, damaging the organelle and preventing proper neuronal energy production. Mitochondrial damage prevents normal cell functioning and results in abnormal neuronal signal transmission (Lidsky & Schneider, 2003). Mitochondrial apoptosis has been observed in

Once lead enters the neuron, it disrupts normal cell functioning which causes apoptosis.

cultures and in the retina at levels of 10nm to 1um (He, Poblenz, Medrano, & Fox, 2000).

Lead also affects neuronal development by disrupting normal protein function. In rats, lead has been found to alter lipid peroxidation, which causes damage to neuronal cell membranes. Lead also affects Protein Kinase C (PKC), which plays an important role in neuronal potentiation. In a normal cell, PKC is regulated by nanomolar concentrations of calcium, but when large amounts of lead are present, PKC expression is reduced. Reduced levels of PKC affect neuronal potentiation and differentiation, which may have long-term effects on the development of learning and memory (Nihei, McGlothan, Toscano, & Guilarte, 2001). Studies using rat models have shown that small concentrations of lead can perturb normal PKC function (Markovac & Goldstein, 1988).

Lead also can affect neurotransmission through perturbation of neurochemical functioning. The presence of lead causes an abnormal inhibition of delta aminolevulinic acid dehydratase. Inhibition of this enzyme results in increased levels of amniolevulinic acid (ALA) within the brain. ALA is a gamma-aminobutyric acid (GABA) agonist and therefore reduces GABA release through pre-synaptic inhibition. This perturbation in GABA release is thought to be responsible for many of the behavior changes associated with lead exposure (Needleman, 2004). Campagna, Huel, Girard, Sahuquillo, and Blot (1999) discovered that perturbation in delta aminolevulinic acid dehydratase functioning can be seen when BLLs are above 3.2µg/dL, but not below, suggesting a possible threshold effect. In addition, lead seems to target mesencephalic dopamine cells, causing apoptosis. This destruction of dopamine-specific cells results in abnormal changes in dopamine levels and transmission throughout the brain, and has been seen at lead concentrations as low as .3 um (Scortegagna & Hanbauer, 1997). Lead's effects on brain function are severe and wide reaching, because lead's ability to substitute for calcium presents many possible mechanisms of action within the brain. Additionally, observed effects of lead seem to occur at relatively low levels of exposure and affect not only the development of the overall structure of the brain, but also communication between neurons, as well as the internal working of the neurons themselves.

Children in low-income families are more likely to be exposed to lead.

Children's Sensitivity to Lead

Although lead exposure is not beneficial at any age, children are particularly sensitive to its negative effects, arising from both their early development stage as well as their biologically driven sensitivity to lead. Exposure can begin prenatally, since lead easily crosses the placental barrier, and research indicates that mother and placental lead levels are very similar. The presence of lead in the womb is extremely troublesome as it can disrupt normal developmental processes (Goyer, 1990). BLLs in children have generally been found to peak around the age of 2 and decline in the following years (Brody et al., 1994). This peak in lead levels around the age of 2 is due to children's crawling and walking behaviors coupled with their desire to mouth objects. Lead contaminated house dust is one of the most common sources of lead exposure and is often found on the floor and in windows of older homes. Young children are particularly vulnerable to lead dust, as their early crawling and walking behaviors position them near the floor. When young children come in contact with lead, they are likely to ingest it via hand/object-to-mouth exposure. In addition, the gastrointestinal tract absorbs lead more efficiently than the lungs or the skin, which can lead to increased lead intake for this young population (Leggett, 1993).

Another factor that makes children specifically vulnerable to lead is that children generally absorb lead more efficiently as it mimics calcium within the body. Young children's rapid growth, and their resulting need for calcium, often results in greater absorption of lead by the gastrointestinal tract than typically would be seen in adults. Increased lead absorption by the gastrointestinal tract results in larger lead levels in the blood, bone, and teeth of this age group, and therefore, larger lead-related effects (Cory-Schlecta & Schaumburg, 2000). In children, bone is constantly being built and re-absorbed by the body (Matkovic, 1991). This means that lead stored in bone can leach into children's blood over time, and thereby access the brain. In addition, children's blood-brain barriers are less efficient at filtering out lead, which means more is allowed into the brain. Increased lead levels in the brain result in further damage to brain function.

Children in low-income families are more likely to be exposed to lead (Brody et al., 1994; Lin-Fu, 1992; Rutter, 1983). Brody et al. (1994) found that as income

increased, lead levels tended to decrease in children. In this study, 16.3% of children categorized as low income were found to have elevated lead levels (>10µg/dL) as compared to 5.4% and 4.0% for children categorized as medium or high-income. In addition, children from low-income households appear to be more sensitive to the effects of lead and show deficits at lower BLLs than their high-income counterparts (Bellinger, Leviton, & Solman, 1990). This may be due to the fact that children in poverty are likely to have other risk factors, such as low birthweight, school absences, less education, more stress, more punitive parents, and lower levels of self-esteem (Aber, Bennett, Conley, & Li, 1997).

The half-life of lead is 35 days when located in the bloodstream, 2 years when located in the brain, and decades when located in the bone (Lidsky & Schneider, 2003). The inefficiency of children's blood-brain barrier, coupled with their rapid growth, makes it more likely that lead will be stored in their bone and brain tissue. This storage causes lead to persist longer in children than in adults, which in turn increases the duration of time that lead can perturb child functioning. Finally, due to the developing nature of the child's brain, children are more sensitive to the changes in protein and neurochemical regulation that lead produces. Lead exposure in children, therefore, has the potential for longer and more widespread effects on development and later performance than is seen in adult exposure (Lidsky & Schneider, 2003).

Methods of Lead Detection

The main ways of detecting lead in children are through tests of the blood, teeth, and bones, although urine, feces, nail, hair and saliva samples have been used in the past. We will briefly discuss each measurement technique. BLLs are detected through capillary or venous puncture samples and are generally reported in micrograms per deciliter (µg/dL). These samples reflect the amount of lead currently in a person's system, as blood does not store lead the way bones and teeth do. BLL may be assessed by looking at whole blood or blood plasma. Plasma lead level is thought to provide a more useful representation of exposure to lead. Tooth, or dentine, lead levels represent a person's lifetime exposure to lead, since lead is stored in the teeth as we grow. Different teeth emerge at different points during childhood, and different tissues of the teeth form and absorb lead at different time points. This allows for a history of lead exposure to be assessed. For dentine lead collection, families usually submit a baby tooth for examination. Dentine lead levels are typically reported in micrograms (µg/g) or parts per million (ppm). Studies that have compared dentine lead levels to BLLs indicate that these measures roughly relate in a 1:2 ratio, that is, finding a 1µg/g level of dentine lead generally relates to a finding of 2µg/dL of lead in that child's blood (Rabinowitz, 1995).

Bone lead levels also reflect a person's lifetime exposure to lead as it is also stored in the bones as we grow. Lead in bone can be detected through post mortem collection or through a type of low energy x-ray called an XRF (in vivo X-ray fluorescence). XRF tends to become unreliable as the amount of tissue covering the bone increases; therefore, this technique would be more accurate for certain bones. Additionally, different bones may absorb lead at different rates, depending on the amount of blood flow to that bone and the type of bone tissue. Therefore, appropriate bone samples must be carefully chosen for these types of analyses. Generally, blood or bone lead detection methods are preferred (Barbosa, Tanus-Santos, Gerlach, Parsons, 2005; Lanphear et al., 2008; Tesman & Hills, 1994).

Lead sampling from urine represents current lead levels and is the most useful in long-term lead tracking studies (mostly longitudinal occupational lead exposure studies) since single-sample measures have produced inconsistent results. Fecal samples tend to reflect current lead levels as undigested lead or lead that has been processed through endogenous fecal routes. Although this technique is generally non-invasive, differences in day-to-day biological processing result in variations in fecal lead levels that could be wrongfully attributed to changes in lead exposure. Nail sampling represents long-term lead exposure. Clippings are generally taken from the toes as they are less contaminated than fingernails by external lead exposure. A drawback of this method is that there is variation in lead levels between individual fingers and toes from the same subject. Hair sampling techniques are non-invasive, but lead absorption by the hair seems to differ based on age, gender, ethnicity, and hair color. Additionally, it is difficult to distinguish internal lead absorption from external environmental presence on top of the hair. Saliva samples are easily collected but lead measurements across time points are not consistent. Lead readings change depending on the time of day the sample is collected, whether it is collected before or after a meal, or whether the sample is stimulated or naturally occurring. Given that urine, fecal, nail, hair, and saliva samples often produce inconsistent results, they are rarely found within the scientific literature (Barbosa, Tanus-Santos, Gerlach, &

Parsons, 2005; Tesman & Hills, 1994).

Developmental Effects of Lead Exposure

The effects of lead exposure on children are seen in many domains of development, but most prominently in intelligence/cognitive functioning and behavior. We will briefly review findings concerning large levels of lead exposure on neurodevelopmental functioning (studies focusing on lead levels above 10µg/dL) and will then present new evidence concerning the effects of lower levels of lead exposure (studies focusing on lead levels below 10µg/dL) in these same areas.

Intelligence/Cognition

High lead levels. Several studies have documented the effects of high levels of lead on children's intelligence. In 1979, Needleman and colleagues studied children with dentine lead levels between 12 and 54µg/dL. Researchers split the children into high- (m=35.5µg/dL) and low- (m=23.8µg/dL) lead groups. Children's intelligence and school experiences were assessed at age 6-7, and again when they reached 5th grade. Additionally, 39 control variables that might account for IQ performance were recorded, such as parents' IQ, child and parent SES, parental occupation, home environment, and parenting practices. Results indicated that dentine lead levels significantly related to performance. Children with high levels of dentine lead scored about a third of a standard deviation lower (a non-trivial difference) on the Full WISC-R (Wechsler, 1974) than those with low lead levels. Children with high lead levels also showed worse verbal processing.

Several studies have documented the effects of high levels of lead on children's intelligence.

Another study tested primary-school-aged children of skilled manual workers living in London (Yule, Lansdowne, Millar, & Urbanowicz, 1981). Children had BLLs between 7 and 32µg/dL with mean BLL being 13.5µg/dL. Results indicated a relation between BLL and IQ and verbal skills, statistically significant even after controlling for children's SES. These two studies are representative of much research examining IQ and lead exposure. It is now well established that lead levels greater than 10µg/dL negatively affect IQ, particularly reading and verbal skills.

Low lead levels. Research focusing on the effects of low levels of lead exposure presents a more nuanced picture of the effect of lead on intelligence. Several methodologically rigorous, prospective longitudinal studies have examined the effects of lead on children's cognitive performance. Canfield and colleagues (2003) followed children with both low BLLs (<10µg/dL) and children with high BLLs (>10µg/dL) from age 6 months until age 60 months. Child intelligence was assessed using the Stanford-Binet Intelligence Scale-IV (Thorndike, Hagen, & Sattler, 1986). Several covariates were included in the analysis—child sex, birthweight, race, mother's IQ and years of education, tobacco use during pregnancy, and SES. Results indicated that BLL was significantly related to differences in IQ performance. Specifically, as BLL concentrations increased from 1 to 10µg/dL, IQ decreased an average of 7.4 points. This trend was seen in children with BLLs above 10µg/dL as well, but decreases in IQ score were less pronounced (a 2.5 point IQ drop when BLL rose from 10 to 30µg/dL).

Lanphear and colleagues (2005) prospectively followed children with a wide range of BLL until the age of 10. Information on children's sex, birth order, and their mother's age and marital status were included as covariates. Exposure to lead had a statistically significant effect on IQ as measured by the WISC-III. Specifically, 3.9 IQ points were lost when BLL rose from 2.4-10µg/dL while only a 1.9 point IQ drop was associated with a BLL rise from 10-20µg/dL, and a 1.1 point drop with a BLL rise from 20-30µg/dL. This study indicates that increases in BLL from 0-10µg/dL have a greater effect on IQ than increases in BLL above 10µg/dL, and that even at low levels of exposure, increasing lead level is related to decreases in intelligence and performance.

Several cross-sectional studies have also shown effects of low-level lead exposure on children's cognitive performance, confirming the results of the longitudinal research reported above. Lanphear, Dietrich, Auinger, and Cox (2000) examined data from the Third National Health and Nutrition Examination Survey (NHANES III). Children in the study had BLLs of between 2.5 and 10µg/dL. Researchers evaluated children's performance on assessments of arithmetic skills, reading skills, nonverbal reasoning skills, and short-term memory using the WISC-R (Wechsler, 1974) and the Wide Range Achievement Test

(Jastak, 1984). Covariates included gender, race/ethnicity, poverty, region of the country, parent educational level, marital status, the child's serum ferritin level (blood iron level), and the child's serum cotinine level (measure of exposure to smoking). For every 1µg/dL increase in BLL (up to 10µg/dL), there was a .7 point decrease in arithmetic score, a 1 point decrease in reading score, a .1 point decrease in non-verbal reasoning tasks, and a .5 decrease in short term memory. Given that the standard deviation on these measures is 15, and the point decreases reported have to do with just a 1µg/dl increase in BLL, the difference in cognition for children with, say, 10µg/dl compared to 2µg/dl is clinically important.

In a similar study, Kordas and colleagues (2006) examined children with BLLs between 0 and 45µg/dL. Children between the ages of 6 and 8 years old were assessed using 14 different measures of cognitive achievement. Covariates included in this study were age, gender, SES, maternal education, parental involvement in schooling, family structure, birth order, and arsenic level. Researchers found statistically significant decreases in cognitive functioning associated with lead exposure. Specifically, an increase in BLL from 0-14µg/dL was associated with greater cognitive losses than BLL increases above 14µg/dL.

In 2007, Surkan and colleagues (2007) conducted a study on the effects of low levels of lead on children's intelligence. Children ages 6 to 10 with BLLs between 1-2µg/dL, 3-4µg/dL, and 5-10µg/dL were compared on the WISC-III (Wechsler, 1991). Intelligence was significantly related to age, race, SES, birthweight, parent IQ, and marital status so the researchers adjusted scores to account for these covariates. IQ was found to be significantly different between the 1-2µg/dL and the 5-10µg/dL groups, but not between the 1-2µg/dL and the 3-4µg/dL groups. On average, children with BLLs between 3 and 4µg/dL scored .12 points lower on the WISC-III compared to children with BLLs of 1-2µg/dL. However, children with BLLs of 5-10µg/dL were found to score 5-6 points lower on the WISC-III compared to children with BLLs of 1-2µg/dL.

A recent study by Hornung, Lanphear, and Dietrich (2009) examined children between the ages of 2 and 6. Researchers were interested in determining both the effects of lead on intelligence, and the age when lead exposure has the greatest effect on IQ. Children's BLL was collected at ages 2 and 6. At age 6, children were assessed using the WISC-R (Wechsler, 1974). Researchers used a multiple regression model to determine the effect of children's past and current BLL on IQ. Researchers controlled for home environment, birthweight, maternal IQ, and maternal education. After accounting for lifetime lead exposure, results indicated that having a higher BLL at age 6 as compared with age 2 was associated with lower IQ scores at age 6. In fact, children who had greater BLL levels at age 6 had an estimated 5.3 point loss in IQ compared to children whose BLL had peaked at age 2. This regression model predicted even greater proportional losses in IQ when analysis was restricted to children with BLLs of ≤10µg/dL. This study indicates that current, rather than past, BLL is a better predictor of intellectual outcomes, which highlights the importance of reducing and treating lead exposure when found in later childhood. Importantly, these authors also show that the effect size for lead's influence on cognitive outcomes is similar in magnitude or greater than other well-known risk factors, such as poverty and maternal education.

… the effect size for lead's influence on cognitive outcomes is similar in magnitude or greater than other well-known risk factors, such as poverty and maternal education.

Although we have only highlighted a few recent studies, it is important to note that the evidence is quite robust, with many other investigations also finding negative effects of low levels of lead on children's cognitive skills (Al-Saleh et al., 2004; Bellinger et al.,1991; Bellinger, Stiles, & Needleman, 1992; Emory, Ansari, Pattillo, Archibold, & Chevalier, 2003; Jusko et al., 2008; Needleman & Gatsonis, 1990). Also worth noting is that these studies typically control for a whole host of other family and environmental factors known to correlate with intelligence. So the sizable effects observed here are net of other important factors associated with negative child outcomes showing that lead exposure, specifically, is indeed harmful to children's development.

Behavior

Similar to IQ, behavioral deficits have been seen in children exposed to both high and low levels of lead. Research on the behavioral effects of lead most often focuses on aggression, hyperactivity, and attention problems. As before, we will first discuss research focusing on high levels of lead exposure and will then discuss studies on low levels of lead exposure.

High lead levels. Many studies (Factor-Litvak, Wasserman, Kline, & Graziano, 1999; David, 1974; Ris, Dietrich, Succop, Berger, & Bornschien, 2004; Roy et al., 2009) have detailed the effects of high levels of lead on children's behavior. A study conducted in 1992 by Sciarillo, Alexander, and Farrell compared children with high BLLs (27.8µg/dL) to children with low BLLs (9.2µg/dL). Child behavior was measured using the *Child Behavior Checklist* (CBCL; Achenbach & Edelbrock, 1983). Researchers controlled for age of mother, maternal education and depression, parental employment, parental marriage status, and number of children currently in the household. Children with higher levels of lead were found to score higher on the Total Behavior Problem scale that includes both internalizing and externalizing behavior problems. Specifically, children in the high-lead group were 2.7 times more likely to score in the clinical range for behavior problems.

In 1994, Bellinger, Leviton, Allred, and Rabinowitz studied children with dentine lead levels between 0.1µg/g and 35µg/g. This study was specifically interested in how behavior changed as dentine lead level increased. Children's behavior was rated by their teachers using the Teacher Rating Scale of the *Child Behavior Profile* (Conners, 1969). Researchers controlled for SES and maternal characteristics. Results indicated that increases in tooth lead levels were associated with more internalizing and externalizing behavior problems. In addition, extreme behavior profiles were disproportionably identified in children with the highest tooth lead levels.

In a similar study (Needleman, Reiss, Tobin, Biesecker, & Greenhouse, 1996), the behavior of children with low (<15µg/dL) and high (>15µg/dL) bone and blood lead levels was examined. The researchers were interested in how behavior changed as bone lead level increased. Children's behavior was assessed at 7 and 11 years using the CBCL. In addition, every 6 months, children completed the *Self-Reported Delinquency Scale* (Elliott, Huizinga, & Ageton, 1985) and the *Self-Reported Antisocial Behavior Scale* (Loeber, 1989). The researchers accounted for the effects of maternal intelligence, SES, and quality of child rearing. Children in the high-lead group were more likely to be rated by their parents and teachers as aggressive, more delinquent, and to report more somatic complaints compared to their low-lead peers.

In yet another study conducted by Mendelsohn and colleagues (1998), the behavior of children with BLLs between 10 and 29µg/dL was examined using the Behavior Rating Scale of the *Bayley Scales of Infant Development* (Bayley, 1969). Researchers identified six variables that were related to behavior (child's age and gender, mother's age, verbal IQ, depression, and provision of cognitive stimulation) and included these variables in their regression models to account for their effects on child behavior. Results indicated that greater BLLs were associated with increased ratings of hyperactivity, distractibility, and frustration. The studies above indicate that high levels of lead are associated with increases in aggressive and destructive behavior and inattention, and that behavior problems increase as child lead levels increase.

Low levels of lead. Although it is well established that high levels of lead contribute to behavior problems in children, studies that include children with low levels of lead are less numerous. In a study of infants with a wide range of BLLs (between .52 and 25µg/dL), Plusquellec and colleagues (2007) examined infant behavior using the *Bayley Scales of Infant Development* and observer ratings of child behavior. Several factors were controlled for including parental education, maternal distress, maternal intelligence, home violence, SES, prenatal exposure to drugs, birth complications, and child characteristics (age, gender, etc.). Infants with BLLs as low as 4.5µg/dL showed a statistically significant increase in hyperactive behaviors and decreased attention spans. This study indicates that BLLs below 10µg/dL can affect child behavior.

Braun, Kahn, Froehlich, Auinger, and Lanphear (2006) used nationally representative data collected during the 1999-2002 National Health and Nutrition Examination Study (NHANES) to examine the relationship between BLL and ADHD diagnosis in children between the ages of 4 and 15. Researchers established ADHD status through parental report of child diagnosis and report of doctor prescription for ADHD medications. Researchers examined several covariates including child age, race, gender, SES, health insurance coverage, pre-school attendance, birth weight and complications, and blood iron levels. Logistic regression analysis indicated that BLL was a statistically significant indicator of ADHD diagnosis in children. This relationship was found even after researchers restricted

their analysis to children with BLLs of ≤5µg/dL. These researchers estimated that 21.1% of ADHD cases nationally, in children between the ages of 4 and 15, were attributable to having a BLL of >2µg/dL.

Chiodo, Jacobson, and Jacobson (2004) examined children with diagnoses of ADHD. After adjusting for 19 control variables (e.g., SES, age, parental marital status, parental education, gender, parenting quality, alcohol and drug use, and the home environment), higher lead levels were associated with greater ratings of ADHD behaviors, and significantly higher inattention scores on the *Barkley-DuPaul Attention Deficit Hyperactivity Scale* (Barkley, 1990). Children with higher BLLs were also rated by teachers as having poorer attention. Regression analysis in this study indicated that attention problems could be seen in children with BLLs greater than 3µg/dL, suggesting a possible threshold value for lead exposure.

Similarly, in 2008, Wang and colleagues studied children with BLLs between 5 and 10µg/dl. Researchers used a pair-match design to control for effects of age, gender, and SES. Results indicated that children with BLLs between 5-10µg/dL were found to be significantly more likely (3.5 to 7 times) to be diagnosed with ADHD than children with BLL less than 5µg/dL. This study complements research conducted by Nigg and colleagues (2008) where children already diagnosed with ADHD were assessed for levels of lead exposure. The sample had very low exposure levels (average BLL for ADHD-combined type = 1.26µg/dL), consistent with national averages, but results indicated that as lead levels increased from 0 to 3.4µg/dL, levels of hyperactivity and impulsivity in those with ADHD-combined type increased significantly. The results of this study have recently been replicated (Nigg, Nikolas, Knottnerus, Cavanagh, & Friderici, in press).

The levels of lead examined in these studies are commonly found in children in the U.S. and thus provide evidence of the possible effects of lead on a large proportion of American children. These studies provide further clear support that levels of lead below 10 µg/dL increase a child's risk for attention and behavioral problems. In addition, they provide evidence that lead exposure is related to increased risk of developing clinically significant attention and behavior problems.

Other Child Outcomes

We have seen that children exposed to both high and low levels of lead show cognitive deficits and disturbed behavior. Two long-term outcomes associated with these deficits can be seen in school performance and criminal behavior. Several studies have found that lead exposure has a negative impact on behavior and school performance, and in this section we will describe just a few.

In 1984, Bellinger, Needleman, Bromfield, and Mintz studied the school performance of 141 elementary school children who were classified as having either elevated (>20ppm), mid-range (10-19.9ppm), or low (<10ppm) dentine lead levels. Their study indicated that increases in dentine lead levels were associated with worse school performance. Additionally, students with higher dentine lead levels were more likely than their peers to repeat a grade. A longitudinal study of children exposed to lead was conducted by Needleman, Schell, Bellinger, Leviton, and Allred (1990). Children were assessed at 7 years of age and again at 18 years. Researchers considered maternal age and IQ, SES, family functioning, number of siblings, race, and past medical history as covariates. As BLL in children increased, so did their likelihood of not graduating from high school. This effect on drop-out was also seen in children with BLLs below 10µg/dL, but was more pronounced at higher levels of lead exposure.

Wang and colleagues (2002) found that elevated lead levels were negatively associated with student achievement. After controlling for possible confounds due to SES and maternal education level, children's academic performances in the areas of math, science, history, and language were all significantly negatively associated with BLL. In a final study, Fergusson, Horwood, and Lynskey (1997), collected dentine lead levels of children at 8 years of age and assessed their academic and intellectual performance at age 18. Measures of mother's education, responsiveness and punitiveness, and father's occupation/SES were collected and incorporated into the analysis. As dentine lead increased, so did the likelihood that children would fail to complete high school. The amount of dentine lead present in children was also negatively related to the number of educational certificates the students completed.

A second outcome often seen in children exposed to lead is criminal activity (Nevin, 2007; Stretesky & Lynch, 2004). In a 2001 study, Dietrich, Ris, Succop, Berger, and Bornschein examined the relationship between lead exposure and later criminal activity, analyzing data from the Cincinnati Lead Study. The researchers specifically assessed 30 possible covariates including SES, gender, maternal IQ, attendance in preschool, etc. The researchers found that lead levels as low as 2.5µg/dL were associated with significantly greater amounts of parent- and self-reported criminal activity and higher rates of police intervention.

Similarly, in 2008, Wright and colleagues measured the association between children's BLL from birth to 6 years of age and later criminal arrests. The subjects were contacted at 19-24 years of age, and past criminal activities were documented. Covariates included gender, birth weight, the quality of their early care giving, maternal drug use, maternal IQ, the total number of prior maternal arrests, and SES. Results indicated that increased lead levels were significantly associated with increases in the number of total arrests and violent crimes committed by the participants in adulthood. Specifically, every 5μg/dL increase in BLL during early childhood was associated with a 1.07 increase in the number of total crimes the subjects had committed, and a 1.3 increase in the number of violent crimes for which the subjects had been arrested.

Societal Costs

From the previous discussion, we have seen that lead negatively impacts children's intellectual and behavioral development and that the long-term consequences of this exposure result in lower school performance and greater instances of criminality in adulthood. Studies have indicated that the implications of lead exposure are not just intellectual, behavioral, or social, but monetary as well. The general medical treatment of a child with lead exposure is between $100 and $5,200 (CDC Cost of Illness Handbook, n.d.), but the long-term losses in relation to economic earning, tax contributions, and educational assistance can be much greater. In 1994, Schwartz conducted a cost analysis associated with children's lead exposure. He concluded that a reduction of 1μg/dL nationwide would result in a total benefit of $5.06 billion per year in earnings per annual birth cohort. In 1995, Schwartz reconsidered his estimates based on data from the National Longitudinal Study of Youth and recommended a 50% increase in his benefit estimates. This would bring the estimated economic benefit associated with a 1μg/dL drop in children's BLL to $7.56 billion per annual birth cohort. In an additional study, Landrigan, Schechter, Lipton, Fahs, and Schwartz (2002) explored the economic impact of lead exposure and showed that in 1997, children 5 years of age would lose $43.4 billion in future earnings due to IQ loss associated with lead exposure. Similarly, in 1991, the CDC estimated each 1μg/dL drop in a child's BLL was associated with an increase of $1,147 in later lifetime earnings (CDC, 1991).

Gould (2009) also demonstrated the economic costs associated with lead exposure and the economic benefits of lead reduction. Gould estimated that $11-53 billion are spent on health care costs associated with lead exposure treatment. Additionally, she estimated that the lowering of IQ due to lead exposure results in $190-268 billion in lost earnings and lost tax revenue. The costs associated with increases in special education needs and ADHD were estimated at an additional $297-413 million, and increased associated crimes cost society $1.7 billion. In sum, the overall cost of lead exposure can be estimated at $192-270 billion. Gould estimates that lead hazard control practices would likely cost under $11 billon. Therefore, for each dollar invested in lead hazard control, $17-221 would be returned through increased income and tax contributions, and health, crime, and special education savings.

The monetary benefit of reducing children's exposure to lead is greater than the monetary benefits seen for vaccinating children against common diseases ($5.30-16.50 saved for dollar spent on vaccinations). Vaccination programs are widespread and generally accepted as worthwhile by society. Based on this information, lead reductions should also be a socially promoted priority. Thus, lead exposure affects not only personal achievement, intelligence, and behavior, but impacts society as a whole. The personal and economic implications of exposure are great. It is for this reason that it is imperative that we increase efforts to reduce children's exposure to lead. We now turn our attention to the prevention of lead exposure in children. Sources of environmental lead will be identified and methods of lead abatement discussed.

Lead Abatement

Childhood exposure to lead remains a problem, but before we can address ways to prevent this exposure, we must understand the sources of lead in children's environment. Historically, one of the most recognized sources of childhood lead exposure is leaded gasoline. In 1973, the EPA began to reduce the amount of lead used in gasoline fuel, and by 1996, the sale of all leaded gasoline in the U.S. was banned. In 1999, Thomas, Socolow, Fanelli, and Spiro conducted a review of 19 studies describing the effects of leaded gasoline on lead exposure. The studies discovered that the elimination of lead in gasoline in the United States was associated with .8μg/dL drop in citizen BLLs per year. The elimination of lead in gasoline greatly reduced air-related lead exposure in children. Although lead in automobile gasoline has been banned, no such regulations exist for jet fuel. The presence of lead in jet fuel, and the presence of aerosolized lead from industrial sources are likely the reason why studies find that air-

related lead is still a significant source of lead contamination for children (Pirkle et al., 1998).

Children are particularly susceptible to contamination from lead-based paint and paint dust. In 1977, the U.S. Consumer Product Safety Commission banned the sale of leaded paint within the United States (Chisolm, 1986). This ban, however, did not affect houses built and/or painted before 1977. Lead dust and paint chips settle onto the floors of homes. Young children crawl on floors and mouth objects that have been on floors, activities that enable consumption of the lead (Lidsky & Schneider, 2003).

Children's exposure to lead through contact with contaminated soil is also a common occurrence. Lead levels in soil are highly correlated with lead levels found in air, dust, and paint. Air lead eventually settles on the ground and contaminates the soil. Similarly, lead-based paint chips and dust from the exteriors of older houses fall to the ground and mix with the soil. Unlike air-based or paint-based lead, soil lead is long lasting and can persist for months after the reduction of air levels or the removal of leaded paint (Weitzman et al., 1993).

Another important source of lead exposure in children comes from tap water. In 1986 and 1996, new amendments to the Safe Drinking Water Act required public water distribution systems to consistently check their drinking water for lead and to enact abatement services if lead levels were found in excess of the allowable action level (currently set at 15µg/L for public drinking water, and 20µg/L for water fountains in schools and childcare centers) (EPA Press Release, 1986, 1996, EPA 2004a, EPA 2006). Lead leeches into tap water through contact with lead-based piping or through the corrosion of pipes in water treatment systems and in household plumbing. PH imbalances in water may promote corrosion of pipes (CDC, 2002). This corrosion is particularly destructive as it can be hard to predict, and replacement of pipes can be costly.

An emerging area of concern is the presence of lead contaminated toys. The CDC identified leaded paint and leaded plastic as two potential sources of lead for children (CDC, 2009). Although lead paint was banned from houses, food containers, and children's products in 1978, it is still widely used in other countries. Therefore,imported toys may still contain amounts of lead. Additionally, lead is often used to soften plastics, making them more flexible and resistant to heat. When these plastics are exposed to sunlight, air, or detergents, the chemical bond between the lead and the plastic can break, creating leaded dust. In rare cases, lead may be used as part of a base for metallic toys. Exposure to lead from toys occurs when children mouth, chew, or swallow the toys.

Having identified the five main sources of lead exposure to children (air, paint/paint dust, soil, water, and toys), we will examine the ways that lead can be removed from children's environments. Since the elimination of lead from gasoline in 1997, the most prominent contributors to air lead levels are found in the industrial sector. The EPA estimates that 42.8% of lead in air comes from industrial processes (EPA, 2002). Many commercial enterprises, from food processors to plastics manufacturers, put off potentially harmful levels of lead during production. Three main procedures are recommended for the reduction of lead air levels from industrial sources. Most industrial lead abatement procedures can be accomplished through the use of dry systems, wet scrubbers, and electrostatic precipitators. Dry systems use gravity, filters, or centrifugal forces to trap lead in air, while wet scrubbers use water streams to increase the efficiency of lead collection. Electrostatic filters work by creating an electrostatic attraction that traps pollutants before they reach the atmosphere. The use of these three methods has been shown to significantly reduce the amount of lead released into the atmosphere (Hartman, Wheeler, & Singh, 1994).

42.8% of lead in air comes from industrial processes.

Lead abatement of contaminated paint and paint dust centers around removal, replacement, or encapsulation of the original lead paint. Paint removal is also paired with a concerted cleaning effort to reduce the amount of loose lead dust found in homes. Removal practices center around the complete removal of structures within the home that have been contaminated with lead paint. Replacement procedures seek to replace lead-contaminated materials with appropriate non-lead painted products, while encapsulation methods seek to seal lead paint behind a barrier (such as varnish) so that it can no longer chip or create lead paint dust (Virginia Department of Historic Resources, 1993). Studies indicate that traditional methods of removal and encapsulation do result in significant decreases in household lead, although

maintenance is needed to provide optimal reduction (Farfel, Chisolm, & Rhode, 1994). About 80% of houses built before 1950 are estimated to contain lead paint (Needleman, 2004). In 1991, abatement for paint in these houses (over a 30-year period) was estimated at $33.1 billion. While this seems expensive, the benefits from lead paint abatement were estimated conservatively at $61.7 billion (Needleman, 2004). Therefore, abatement of lead paint would provide an overall $28.6 billion in savings.

Cleaning procedures designed to remove lead dust from the home often include vacuuming and wet dusting of household surfaces, especially those that may be a source of lead contamination. In addition to cleaning these surfaces, residents are encouraged to wash their hands regularly. These are done in an attempt to reduce the amount of lead dust that settles from unabated structures and to prevent accidental ingestion of the lead dust. Studies have indicated that while dusting will remove lead-based paint in the short term, long-term BLL is dependent on permanent removal or encapsulation of the lead paint (Lanphear, Eberly, & Howard, 2000). Additionally, studies have found that while vacuuming reduces 95% of lead dust on hard floors, it is not an effective method for removing lead dust from carpets (Ewers, Clark, Menrath, Succop, & Bornschein, 1994).

Hand washing regimens are another method often implemented in an effort to reduce child lead intake within the home. Children and adults are encouraged to wash their hands before meals and after playing outside (if they have known soil contamination). A study conducted by Lanphear and Roghmann (1997) sought to determine the pathway of lead into children bodies. The researchers measured child lead levels and several factors that might contribute to elevations or reductions in child lead levels. Behaviors such as eating dirt, sucking thumbs, hand washing, mouthing, and vacuuming were investigated. Results indicated that hand washing before eating and hand washing after playing outside were not significantly related to child BLL, although these easy preventative steps (along with cleaning nails and frequent nail clipping) are still typically safely recommended for families as easily performed acts that might help.

Soil abatement practices include removal of contaminated soil and replacement with clean soil. Generally 15-20cm of topsoil is removed and replaced during the abatement process. Farrell, Brophy, Chisolm, Rohde, and Strauss (1998) found that soil replacement did not significantly lower children's lead levels. In a similar study, Aschengrau, Beiser, Bellinger, Copenhafer, and Weitzman (1994) found that soil abatement was effective but only for higher income persons who washed their hands before meals, had low initial lead levels, and who were away from home often. Children living in apartments where dust was present derived no benefit from the soil abatement. Studies seem to indicate that soil replacement is effective only if re-contamination of the soil does not occur. Soil replacement must be done in conjunction with exterior lead removal to ensure that soil is not re-contaminated (Weitzman et al., 1993).

Abatement of lead in water systems occurs mainly through the replacement of older pipes found to contain lead or treating the water so it is less corrosive. Additional methods of abatement include flushing of water systems before use, usually for 10 minutes. A study examining flushing practices in water systems of schools indicated that lead levels do reduce immediately after flushing but rapidly rebound, and seem to increase with frequent tap use (Murphy, 1993). If flushing is to be a useful way to reduce lead in water it must be done frequently throughout the day to prevent reestablishment of lead within the drinking water.

When considering removal of lead pipes as a method of abatement, it is important to remember that water service providers are only responsible for replacing pipes directly connected to their systems, so any internal piping within the home must be replaced by the homeowner. The D.C. water system has a program to replace lead pipes that are part of the public water system. WASA will replace lead pipes between the main line and homeowner's property line if the homeowner agrees to replace lead water lines on their private property (Quander-Collins, 2008). The District of Columbia replaces private lead pipes for the cost of $100 per foot (plus a $500 fee to extend the pipe into the home), and provides loans and grants to qualifying homeowners for the purpose of replacing their lead pipes (D.C. WASA, 2007; D.C. WASA, 2009). For homeowners who do not qualify for grants, or who live in a city without such a program, pipe replacement can be very costly, causing some homeowners to leave old water pipes in place even after the threat of lead is known (CDC, 2002).

Current State of Lead Control Policy

Two of the main agencies working to prevent the public's exposure to lead are the EPA and the CDC. The EPA's main goal is the creation and enforcement of environmental regulations and the protection of natural resources. The

EPA's role in lead exposure mainly concerns the promulgation and enforcement of regulations concerning lead levels in water, air, soil, paint, and drinking water (EPA, n.d.). The EPA sets action levels or levels of concern for lead in water, soil, and air. An action level is a threshold level, over which certain treatment requirements must be enacted. A level of concern relates to an amount of a substance that can cause harm to general populations. According to the Agency for Toxic Substances and Disease Registry (ATSDR, 2007), the current EPA action level for lead in drinking water is 15ppb. For soil, the EPA has set the level of concern (for federally funded projects) at 400ppm by weight in child play areas and 1200ppm by weight in non-play areas. The EPA's level of concern for ambient air is currently set at .15μg/m^3. In addition to setting the allowable environmental lead limits, the EPA also sets lead testing requirements for both public and private service providers. The CDC's primary goal is to develop and then apply disease prevention and control practices with the aim of improving public health (CDC, 2009a). As such, the CDC plays a major role in the establishment of allowable BLLs and in screening and reporting practices. Currently the CDC has set the allowable BLL limit at 10μg/dL (ATSDR, 2007).

Although both entities strive to prevent lead exposure, their regulations are not typically followed well. In a 2004 report, the EPA revealed that only 23% of water systems had reported their lead testing results as required (EPA, 2004b). Analysis of these water testing reports indicated that between 2000 and 2004, 29 states and D.C. had water systems test above the EPA allowable 15μg/L water lead level (EPA, 2005). Indeed, 4.2% of all water systems sampled had at least one test above the allowable lead water limit.

The CDC also is challenged in that they are not an enforcement entity and, therefore, have almost no way to require states to comply with their recommendations, however beneficial they might be. This leads to state and nationwide inconsistency in lead exposure practices. Currently, lead screening practices are created at the state level, with each state identifying and agreeing on its own lead screening guidelines (CDC, 2005). States vary widely in their approach to lead screening. Most states have a plan targeting children under the age of 6, but these plans vary greatly. Some state action plans are over fifty pages long while others are only three pages. Some states advocate universal screening (ex. Tennessee, Connecticut) while some advocate risk-based screening (ex. Illinois, Florida). Risk-based screening is usually accomplished through a parent questionnaire that identifies children who may be at higher risk for lead exposure and then only testing those at-risk. In addition, some states test children of certain SES designations, or who live in lower income areas or in older housing.

The CDC's 2006 national survey was answered by only 36 states and D.C. The map in Figure 1 shows data from this survey: each state's percentage of children screened for lead levels, the percentage of children tested found to exceed the minimum allowable lead level threshold, and the scope of the state's advocated screening approach (universal or risk targeted). Although states may create lead screening plans, they do not always follow their own guidelines. For example, Tennessee and Connecticut advocate universal lead testing, but had only tested 14% and 26% (respectively) of children less than 72 months of age. The average screening rate for states advocating universal testing was only 21.3% with Massachusetts (47%) testing the highest number of children and Kentucky (5%) the lowest. Among states that advocate risk-based testing, the numbers were even lower, with the average risk-based testing rate being 13.4%, with Minnesota as the highest test rate (22%) and Nebraska the lowest (.03%) (CDC, 2006).

Recommendations for Action

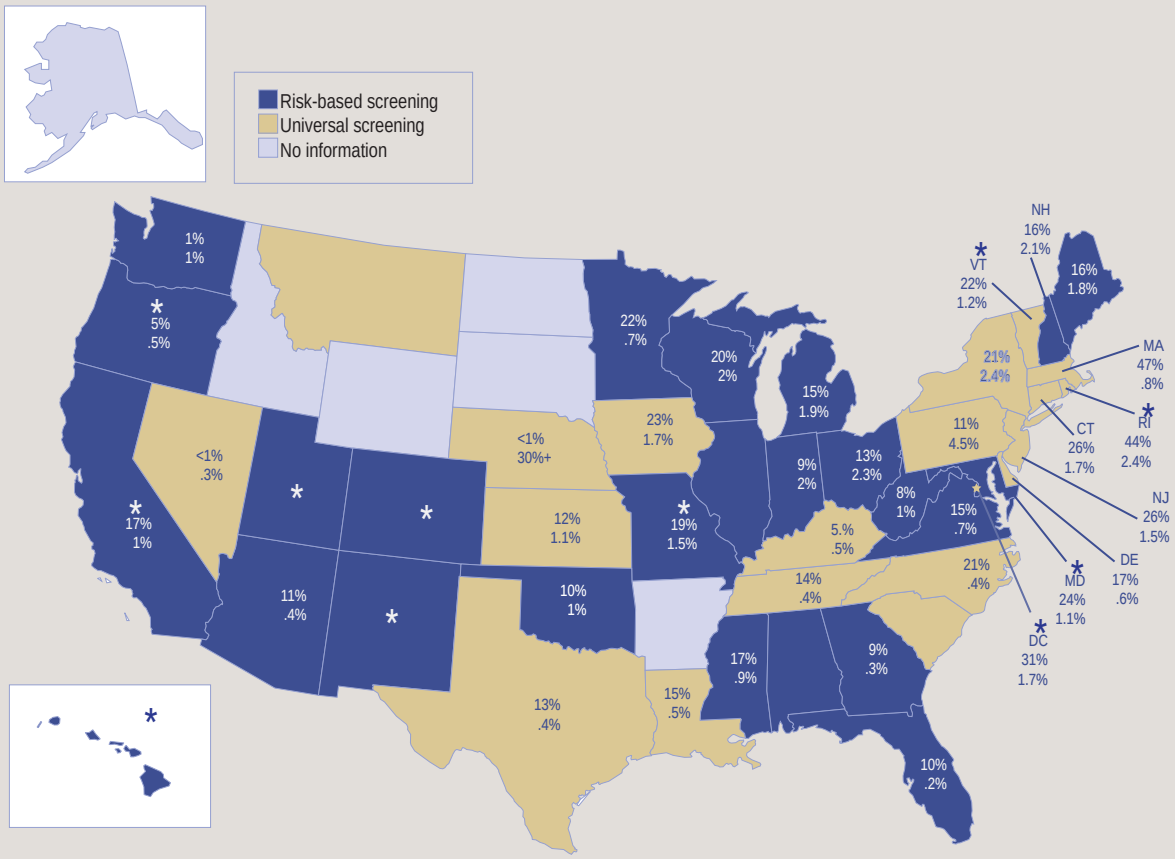
Researchers have known since the early 1900s that lead is harmful to children's development. When the CDC set the current BLL to 10μg/dL in 1991, reports were already beginning to appear that even lower levels of lead are detrimental to children's health. For the past 10 years, study after study has indicated that children are being exposed to unacceptable levels of lead in their daily lives, and that even a low level of lead exposure harms children. The U.S. is negligent in its testing, reporting, prevention, and treatment practices for lead exposure. Lead exposure in children is fully preventable, yet the U.S. government has failed to commit fully to the resolution of the problem. Cost-benefit analyses show that it is a relatively inexpensive problem to solve, and its resolution would lead to great economic returns. Research reported in this paper clearly shows that stricter regulations work and lead to less exposure. The new data summarized here suggest that new policy action is needed for this well-known problem. In order to prevent further exposure of children to lead, we suggest four main types of action be taken, specifically: 1) primary prevention in the form of regulations limiting lead exposure, 2) second-

ary prevention via increases in education, guidance, and screening practices, 3) tertiary follow-up support and treatment for children with known lead exposure, and 4) greater organizational cooperation (see Table 1).

Our first main recommendation is to prevent the exposure of children to lead through increases in environmental lead regulations, enforcement, and abatement practices. The detrimental effects of lead on children could be completely eliminated if children were not exposed to lead in the first place. In the previous sections, we mentioned several environmental sources of lead and the many ways that lead from environmental sources may be eliminated.

The most important recommendation may be simply to lower the acceptable BLL for children. Currently, the CDC sets the allowable BLL for children at 10µg/dL (CDC, 2005). In the past, when new research has shown that current lead levels are unsafe, the CDC has lowered its acceptable lead threshold (CDC, 1991). It is clear that levels of lead far below the 10µg/dL threshold have noticeable negative effects on children's intellectual and behavioral development (Lanphear, Dietrich et al., 2000; Surkan et al., 2007; Wasserman et al., 1998). Although current research indicates that there is no safe level of lead, we recommend setting the allowable limit of lead at least to 5µg/dL if not lower. Setting the threshold lower would allow assistance to be available for children with low-lead level contamination. Lowering the 'ac-

Figure 1. Lead Screening Plans and Statistics by State



Notes

- The top number for each state is the percentage of children less than 72 months old who were screened for lead.
- The bottom number for each state is the percentage of screened children less than 72 months old with lead levels >10ug/dL.
- Risk based screening varies from state to state, with some states basing screening on completion of a risk questionnaire, on the SES of the child, on the area where the child lives, or on the age of their domicile. Nationwide, all children receiving Medicare benefits are required to be screened for lead.
- Testing guidelines for states marked with an * were retrieved from the individual states Government and Department of Health webpages. All other guidelines were retrieved from the CDC (2009b). State and local testing programs. Retrieved on April 25, 2009, from http://www.cdc.gov/nceh/lead/programs.htm. Many states did not report.
- The percent of children screened for lead and the percent of children testing >10ug/dL were retrieved from the CDC (2006). 2006 Case and Screening Rate Maps by County for Selected States. Retrieved April 25, 2009 from http://www.cdc.gov/nceh/lead/data/national.htm.
- + The abnormally high figure for Nebraska may be due to the fact that incomplete data from this state were reported to the EPA and only a small % of children were tested.

Table 1. Recommendations for Action

1. Increase Abatement Practices
   - Lower the Lead Action Level
   - Lower the CDC's allowable lead level from 10ug/dL to 5ug/dL
   - Encourage the development and use of lead-free jet fuels
   - Provide stricter enforcement of industry pollution practices
   - Require companies to publicly disclose factory lead emission levels
   - Provide incentives and assistance to aid homeowners with replacement of lead pipes
   - Require homeowners to test their houses for lead paint before they rent or lease their property
   - Mandate abatement if lead is found in a home
   - Provide monetary assistance for testing and abatement in low-income populations
   - Increase federal regulation to insure that imported toys and child-related products are lead-free

2. Increase Education and Screening
   - Increase education concerning lead exposure for the general population
     - Pay increased attention to education of at-risk groups
       - Those in poverty
       - Those living in older or low-income housing
       - Pregnant women
       - Families with children under 6 years of age
   - Increase screening
     - Create federally-mandated screening guidelines
     - Require universal testing of children under age 6
       - Annual screening should occur at yearly well-child visits
     - Require lead screening for pregnant women
     - Establish a national testing compliance system to track state progress

3. Increase Follow-Up
   - Provide immediate lead abatement assistance when an elevated BLL is detected
   - Provide subsidized consultation and abatement services for low-income families
   - Provide immediate psycho-educational evaluation to lead-exposed children

4. Increase Collaboration between the EPA and the CDC
   - Encourage further use of the National Lead Information Center
     - Make the NLIC the central point for compiling information on lead from both the EPA and the CDC
     - Provide internet access to NLIC information
   - Encourage collaboration between the government agencies and the research community
   - Encourage partnerships between various disciplines interested in studying lead exposure

ceptable' level of lead is a critical first step to implementing the additional regulations proposed below to reduce exposure.

Although lead in automobile gasoline has been banned, no such regulations exist for jet fuel. Jet fuel may enter into the environment during the burning of the fuel, through evaporation during transportation, or through spills (Faroon, Mandell, & Navarro, 1995). We recommend the similar removal of lead from jet fuel and/or the development and use of alternative fuel compositions that don't include lead. The airline industry should encourage the development of these fuels and the use of them once they become available. Further, since industrial sources contribute 42.81% of the lead in the air (EPA, 2002), we recommend stricter regulations and better enforcement of industrial pollution practices. Currently it is extremely difficult to find information on lead output from factories. Lead measurements from individual facilities should be publicly disclosed so companies can be held accountable for their compliance (or lack thereof) with clean air practices.

The presence of lead in water is also an area where more could be done to eliminate exposure. States should subsidize programs that offer low-cost identification and replacement of lead piping. Cities that are in the process of replacing lead pipes located on public property should offer greater incentives and assistance to homeowners in replacing lead pipes on their private property. The replacement of lead piping can be costly, and many home-owners would benefit greatly from increased assistance in removing this health hazard. Removal of public lead pipes will not appreciably reduce lead

exposure unless lead-based pipes on private property are removed.

Lead paint and lead paint dust are a third main contributor to environmental lead. Currently owners of dwellings built before 1978 are required to provide a statement to renters or prospective buyers that lead may be a problem in a home. Additionally they are required to disclose any information they might have regarding the presence of lead paint in a home (U.S. Department of Housing and Urban Development, 2008). We recommend that all homeowners in possession of a dwelling built before 1978 be required to test their home for lead before that home is sold or rented. If lead is found in a home, that homeowner should be required to take appropriate abatement steps. Additionally, testing and abatement of lead in homes should be subsidized for those of low SES, especially given that these populations tend to live in poorer quality and older housing that is more likely to have lead problems (Evans & Kantrowitz, 2002).

We also recommend increased federal regulation to ensure that toys and other child-related products manufactured in other countries and imported to the U.S. are lead-free. The most basic way we can protect children from lead exposure is to remove lead from their environment. Encouraging detection and abatement of current air-, water- and paint-based lead sources will go a long way toward protecting our children.

Our second group of recommendations concerns increased education and screening practices. Among the general population, we must increase emphasis on the negative effects of lead exposure on children. Special attention should be paid to at-risk groups, such as pregnant women or low-income families with young children, groups who are more likely to live in older, inner-city, and/or low-quality housing with a greater risk of lead exposure. Outreach to both low SES groups and expectant mothers or mothers of small children could be accomplished in several ways. Pamphlets in the offices of pediatricians and obstetricians would assist with specifically targeting parents. Special consideration should be taken to target doctors serving lower income or Medicaid patients, and pamphlets should be written in a variety of languages to help target non-English speaking populations. Pamphlets should direct patients to additional resources, and it should be obvious who to call for screening, environmental testing, or help with abatement. Television, internet, and radio announcements would also be effective in reaching a large percentage of the population. Announcements could be performed in numerous languages on different stations based on the targeted population.

Screening practices at the state and national level should also be increased. Several states have no identifiable lead screening plan and are not reporting screening information to the CDC. Additionally, we know that many states only screen based on risk level and that no state (even those who advocate universal screening) tests all children. We therefore recommend creating federally-mandated screening practices for children under the age of 6 and for pregnant women. A federally-mandated screening requirement would allow for more uniform lead screening practices to take place. In addition to a federal mandate, a verification system should be put in place to ensure that states are complying with federal law. We should universally test children for lead. The first step in tackling this problem is obtaining good data on the magnitude of toxic lead exposure in our children and the amounts of lead present in our environment.

Screening of blood lead levels should begin prenatally. Lead passes through the placental barrier; therefore, pregnant women's exposure to lead can harm the fetus. If our goal is to protect children from lead exposure, then it is only natural that we begin with this group. After birth, children should be screened annually, with low-income children's testing being covered by Medicaid insurance. Annual screening will allow children's lead exposure to be tracked, and early detection will allow abatement procedures to remove the source of lead from the child's environment. Early screening will not only provide swift identification and intervention opportunities for children, but also save parents, schools, and society money in the long run.

Our third main recommendation involves follow-up practices for children found to have elevated BLLs. If a pregnant woman or child is found to have an elevated BLL during a pre-natal checkup or during annual screening, assistance with lead abatement should be immediately offered. The reduction of environmental lead is not effective unless the source of the lead is removed (Lanphear, Winter, Apetz, Eberly, & Weitzman, 1996); therefore, assistance should be offered in the identification and removal of sources of lead from the environment. Additionally, children who are found to have elevated levels of lead should be tested for learning and behavior problems. The effects of lead on cognition and behavior are well known (Lanphear, Dietrich et al., 2000; Surkan et al., 2007; Wasserman, Staghezza-Jaramillo, Shrout, Popovac, & Graziano, 1998). Early identification of these

problem areas in children could help reduce the long-term effect of lead exposure on their future achievement and functioning. The neurodevelopmental effects of lead are far reaching, and reduction of lead exposure will produce better outcomes for children in the long run. Better childhood outcomes will reduce the amount of future resources the state has to spend on special education and criminal justice programs.

One final recommendation is to promote better communication between the EPA, the CDC, researchers, and the public on the issue of lead exposure. Information concerning lead is scattered throughout several government agencies and websites. The information is often difficult to find and contradictory. The EPA and the CDC jointly contribute to the National Lead Information Center (NLIC) (http://www.epa.gov/lead/pubs/nlic.htm), a place where homeowners and interested persons can find information about lead on a variety of topics. The information may be requested over the phone or on the internet, and the information is either faxed or mailed to the requestor. Although this collaborative center is a valuable resource, we believe its utilization could be improved. This center could become a central location for the collection and publication of new information and rules and regulations concerning lead. Collecting and organizing information in one location would provide a better organized and inclusive view of the many facets of lead exposure. Information concerning environmental lead levels could be more easily coupled with blood screening information, resulting in a better understanding of the causes and effects of lead exposure. In addition, the multitude of information provided through this center could be uploaded to the NLIC website to allow for faster and easier access to its information.

In addition to cooperation between the EPA and the CDC, there should be more interaction between these government organizations and the research community. Researchers interested in studying the effects of lead come from many different disciplines, including persons from the fields of environmental science, toxicology, medicine, psychology, and education. Lead prevention activities and lead research could be greatly increased should communication between and within these groups and the government be encouraged. At present, it would appear there is little communication between these disciplines and the agencies that create and enforce lead policies and regulations. The CDC creates recommendations that guide acceptable exposure levels and testing practices for lead in humans, while the EPA creates policies, regulations, and testing practices concerning lead in the environment. But the link, for example, between how much lead is found in water systems and what that means for blood lead levels in children is not at all clear. The EPA, concerned with amounts of lead in the environment, needs to better communicate with the CDC, which is responsible for information concerning lead in children. These two agencies then need to address the scientific community and foster more cooperation between themselves and interested researchers.

> Our recommendation is to promote better communication between the EPA, the CDC, researchers, and the public on the issue of lead exposure.

Finally, applied developmental psychologists and interventionists working with children and families need to be cognizant of the possibility that lead exposure may be present for families and may be a significant contributor to the child behavior and cognitive problems observed. We know that lead affects children's behavior, intelligence, and attention. As such, lead exposure reduction needs to become a more central component of home-visiting, early education, and early intervention programs that are currently underway. Only with this combined cooperation can the issue of lead exposure in our children be fully addressed.

Although it is probably not possible to eliminate lead entirely from all children, a lowered lead exposure threshold would help reduce most of the negative effects seen at higher levels of exposure. Lead is detrimental to children's development, biologically, intellectually, and behaviorally. If we are to give our children the best opportunity to succeed, we must tackle the preventable and addressable problem of children's exposure to lead.

References

Aber, J., Bennett, N., Conley, D., & Li, J. (1997). The effects of poverty on child health and development. *Annual Review of Public Health, 18,* 463-483.

Achenbach, T., & Edelbrock, C. (1983). *Manual for the Child Behavior Checklist and the Revised Behavior Profile.* Burlington, VT: University Associates in Psychiatry.

Al-Saleh, I., Nester, M., DeVol, E., Shinwari, N., Munchari L., & Al-Shahria, S. (2004). Relationships between blood lead concentrations, intelligence, and academic achievement of Saudi Arabian schoolgirls. International *Journal of Hygene and Environmental Health, 204,* 165-174.

Aschengrau, A., Beiser, A., Bellinger, D., Copenhafer, D., & Weitzman, M. (1994). The impact of soil lead abatement on urban children's blood lead levels: Phase II results from the Boston Lead-In-Soil Demonstration Project. *Environmental Research, 67,* 125-148.

Agency for Toxic Substances and Disease Registry. (2007). *Lead toxicity: What are the U.S. standards for lead levels? Case Studies in Environmental Medicine.* Retrieved June 20, 2009 from http://www.atsdr.cdc.gov/csem/lead/pb_standards2.html

Bach, D. (2004, July, 2). Lead-tainted water in Seattle schools stuns parents. *Seattle Post.* Retrieved June 20, 2009 from http://www.seattlepi.com/local/180495_leadwater02.html

Barbosa, F., Tanus-Santos, J., Gerlach, R., & Parsons, P. (2005). A critical review of biomarkers used for monitoring human exposure to lead: Advantages, limitations and future needs. *Environmental Health Perspectives, 113,* 1669-1674.

Bayley, N. (1969). *Manual for the Bayley Scales of Infant Development.* New York: The Psychological Corporation.

Barkley, R. (1990). *Attention deficit hyperactivity disorder.* New York: Guilford.

Bellinger, D., Leviton, A., Allred, E., & Rabinowitz, M. (1994). Pre- and post-natal lead exposure and behavior problems in school-aged children. *Environmental Research, 66,* 12-30.

Bellinger, D., Leviton, A., & Sloman, J. (1990). Antecedents and correlates of improved cognitive performance in children exposed in-utero to low levels of lead. *Environmental Health Perspectives, 89,* 5-11.

Bellinger, D., Leviton, A., & Sloman, J., Rabinowitz, M. Needleman, H.,& Waternaux, C. (1991). Low level lead exposure and children cognitive function in the preschool years. *Pediatrics, 87,* 219-227.

Bellinger, D., Needleman, H., Bromfield, R., & Mintz, M. (1984). A follow-up study of the academic attainment and classroom behavior of children with elevated dentine lead levels. *Biological Trace Element Research, 6,* 207-224.

Bellinger, D., Stiles, K., & Needleman, H. (1992). Low level lead exposure, intelligence and academic achievement: A long term follow up study. *Pediatrics, 90,* 855-861.

Bhatt, S. (2005, March 25). Report says lead level in schools' water not dire. *The Seattle Times.* Retrieved June 20, 2009 from http://seattletimes.nwsource.com/html/localnews/2002219114_water25m.html

Braun, J., Kahn, R., Froehlich, T., Auinger, P., & Lanphear, B. (2006). Exposure to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environmental Health Perspectives, 114,* 1904-1909.

Brody, D., Pirkle, J., Kramer, R., Flegal, K., Matte, T., Gunter, E., et al. (1994). Blood levels in the U.S. population. Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991). *Journal of the American Medical Association, 272,* 277–283.

Campagna, D., Huel, G., Girard, F., Sahuquillo, J., & Blot, P. (1999). Environmental lead exposure and activity of d-aminolevulinic acid dehydratase (ALA-D) in maternal and cord blood. *Toxicology, 134,* 143-152.

Canfield, R., Henderson, C., Cory-Slechta, D., Cox, C., Jusko, T., & Lanphear, B. (2003). Intellectual impairment in children with blood lead concentrations below 10 µg per deciliter. *The New England Journal of Medicine, 348,* 1517-1526.

Centers for Disease Control and Prevention. (n.d). *Cost of illness handbook: Cost of reducing high lead levels in children.* Retrieved from http://www.epa.gov/oppt/coi/pubs/III_9.pdf

Centers for Disease Control and Prevention. (1991). *Preventing lead poisoning in young children—A statement by the Centers for Disease Control–Oct. 1991.* Atlanta: CDC, U.S. Department of Health and Human Services.

Centers for Disease Control and Prevention. (2002). *Managing elevated blood lead levels among young children: Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention.* Atlanta: CDC, U.S. Department of Health and Human Services. Retrieved June 25, 2009, from http://wwwtest.cdc.gov/nceh/lead/CaseManagement/caseManage_contents.htm

Centers for Disease Control and Prevention. (2005). *Preventing lead poisoning in young children.* Atlanta: CDC, U.S. Department of Health and Human Services.

Centers for Disease Control and Prevention. (2006). *CDC National Surveillance Data (1997-2006).* Atlanta: CDC, U.S. Department of Health and Human Services. Retrieved November 22, 2009, from http://www.cdc.gov/nceh/lead/data/national.htm

Centers for Disease Control and Prevention. (2009a). *About CDC.* Atlanta: CDC, U.S. Department of Health and Human Services. Retrieved June 22, 2009, from http://www.cdc.gov/about/

Centers for Disease Control and Prevention. (2009b). *State and local testing programs.* Atlanta: CDC, U.S. Department of Health and Human Services. Retrieved November 22, 2009, from http://www.cdc.gov/nceh/lead/programs.htm

Chisolm, J. (1986). Removal of lead paint from old housing: The need for a new approach. *American Journal of Public Health, 76,* 236-237.

Chiodo, L., Jacobson, S., & Jacobson, J. (2004). Neurodevelopmental effects of postnatal lead exposure at very low levels. *Neurotoxicology and Teratology, 26,* 359-371.

Conners, C. (1969). A teacher rating scale for use in drug studies with children. *American Journal of Psychiatry, 126,* 884-888.

Cory-Schlecta, D., & Schaumburg, H. (2000). Lead, inorganic. In P. Spencer, H. Schaumburg, & A. Ludolph (Eds.), *Experimental and clinical neurotoxicology* (2nd ed., pp. 708-720). New York: Oxford University Press.

David, O. (1974). Association between lower level lead concentrations and hyperactivity in children. *Environmental Health Perspectives, 7,* 17-25.

Dietrich, K., Ris, D., Succop, P., Berger, O., & Bornschein, R. (2001). Early exposure to lead and juvenile delinquency. *Neurotoxicology and Teratology, 23,* 511-518.

District of Columbia Water and Sewer Authority. (2007). *Lead service replacement—FAQs.* Retrieved June 22, 2009, from http://www.dcwasa.com/news/publications/DCWASAFAQ.pdf

District of Columbia Water and Sewer Authority. (2009). *Private side lead service line replacements: Financial assistance for private side replacements.* Retrieved June 22, 2009, from http://www.dcwasa.com/lead/replacements.cfm

Edwards, M., Triantafyllidou, S., & Best, D. (2009). Elevated blood lead in young children due to lead contaminated drinking water: Washington, DC, 2001-2004. *Environmental Science and Technology, 43,* 1618-1623.

Elliott, D., Huizinga, D., & Ageton, S. (1985). *Explaining delinquency and drug use.* Beverly Hills, CA: Sage.

Emory, E., Ansari, Z., Pattillo, R., Archibold, E., & Chevalier, J. (2003). Maternal blood lead effects on infant intelligence at 7 months of age. *Journal of Hepatology, 118,* S26-S32.

Environmental Protection Agency. (n.d.). *What we do.* U.S. Environmental Protection Agency. Retrieved June 22, 2009, from http://www.epa.gov/epahome/whatwedo.htm

Environmental Protection Agency. (1986). *Press release—President signs safe drinking water act amendments.* U.S. Environmental Protection Agency. Retrieved May 20, 2009, from http://www.epa.gov/history/topics/sdwa/04.htm

Environmental Protection Agency. (1996). *Press release—President Clinton signs legislation to ensure Americans safe drinking water.* U.S. Environmental Protection Agency. Retrieved May 20, 2009, from http://www.epa.gov/history/topics/sdwa/05.htm

Environmental Protection Agency. (2002). *National lead emissions by source sector.* U.S. Environmental Protection Agency. Retrieved June 25, 2009, from http://epa.gov/air/emissions/pb.htm#pbloc

Environmental Protection Agency. (2004a). *Lead and copper rule: A quick reference guide.* U.S. Environmental Protection Agency. Retrieved November 29, 2009, from http://www.epa.gov/safewater/lcrmr/pdfs/qrg_lcmr_2004.pdf

Environmental Protection Agency. (2004b). *90th percent lead level information for water systems serving more than 3,300 people - (Updated as of June 1, 2004): Full summary.* U.S. Environmental Protection Agency. Retrieved May 29, 2009, from http://www.epa.gov/OGWDW/lcrmr/lead_data.html

Environmental Protection Agency. (2005). *January 2005 data showing medium and large water systems exceeding the Action Level since January 2003: January 2005 summary of lead action level.* U.S. Environmental Protection Agency. Retrieved May 29, 2009, from http://www.epa.gov/OGWDW/lcrmr/lead_data.html

Environmental Protection Agency. (2006). *Preamble to the final rule of lead and copper.* Environmental Protection Agency. Retrieved November 29th 2009, from http://www.epa.gov/safewater/lead/excerptfrom58.htm

Environmental Protection Agency. (2007). *Elevated lead in DC drinking water – A study of potential causative events, final summary report.* Washington, DC: Office of Ground Water and Drinking Water.

Evans, G., & Kantrowitz, E. (2002). Socioeconomic status and health: The potential role of environmental risk exposure. *Annual Review of Public Health, 23,* 303-331.

Ewers, L., Clark, S., Menrath, W., Succop, P., & Bornschein, R. (1994). Clean up of lead in household carpet and floor dust. *American Industrial Hygiene Association Journal, 55,* 650-657.

Factor-Litvak, P., Wasserman, G., Kline, J., & Grazian, J. (1999) The Yugoslavia Prospective Study of environmental lead exposure. *Environmental Health Perspectives, 107,* 9-15.

Farfel, M., Chisolm, J., & Rohde, C. (1994). The longer-term effectiveness of residential lead paint abatement. *Environmental Research, 66,* 217-221.

Faroon, O., Mandell, D., & Navarro, H. (1995). *Toxicological profile for jet fuels JP-4 and JP-7.* Washington, DC: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

Farrell, K., Brophy, M., Chisolm, J., Rohde, C., & Strauss, W. (1998). Soil lead abatement and children's blood lead levels in an urban setting. *American Journal of Public Health, 88,* 1837-1839.

Fergusson, D., Horwood, L., & Lynskey, M. (1997). Early dentine lead levels and educational outcomes at 18 years. *Journal of Child Psychology and Psychiatry, 38,* 471-478.

Gibson, L. (1904). A plea for painted railings and painted walls of rooms as the source of lead poisoning amongst Queensland children. *Australian Medical Gazette, 23,* 149-153.

Gould, E. (2009). Childhood lead poisoning: Conservative estimates of the social and economic benefits of lead hazard control. *Environmental Health Perspectives, 117,* 1162-1167.

Goyer, R. (1990). Transplacental transport of lead. *Environmental Health Perspectives, 89,* 101-105.

Guidotti, T., Moses, M., Goldsmith, D., & Ragain, L. (2008). DC water and sewer authority and lead in drinking water: A case study in environmental health risk management. *Journal of Public Health Management and Practice, 14,* 33-41.

Hartman, R., Wheeler, D., & Singh, M. (1994). The cost of air pollution abatement. *Policy Research, 1,* 1-45.

He, L., Poblenz, A., Medrano, C., & Fox, D.(2000). Lead and calcium produce rod photoreceptor cell apoptosis by opening the mitochondrial permeability transition pore. *The Journal of Biological Chemistry, 275,* 12175-12184.

Hornung, R., Lanphear, B., Dietrich, K (2009). Age of greatest susceptibility to childhood lead exposure: A new statistical approach. *Environmental Health Perspectives, 117,* 1309-1312.

Jastak, S., & Wilkinson, G. S. (1984). *The Wide Range Achievement Test-Revised: Administration manual.* Wilmington, DE: Jastak Associates, Inc.

Jusko, T., Henderson, C., Lanphear, B., Cory-Slechta, D., Parsons, P., Canfield, R. (2008). Blood lead level concentrations ≤ 10μg/dL and child intelligence at 6 years of age. *Environmental Health Perspectives, 116,* 243-248.

Kerper, L., & Hinkle, P. (1997). Lead uptake in brain capillary endothelial cells: Activation by calcium store depletion. *Toxicological Applied Pharmacology, 146,* 127-133.

Kordas, K., Canfield, R., López, P., Rosado, J., Vargas, G., Cebrián, M., et al. (2006). Deficits in cognitive function and achievement in Mexican first-graders with low blood lead concentrations. *Environmental Research, 100,* 371-386.

Landrigan, P., Schechter, C., Lipton, J., Fahs, M., & Schwartz, J. (2002). Environmental pollutants and disease in American children: Estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environmental Health Perspectives, 110,* 721-728.

Lanphear, B., Dietrich, K., Auinger, P., & Cox, C. (2000). Cognitive deficits associated with blood lead concentrations <10 μg/dL in US children and adolescents. *Public Health Reports, 115,* 521-529.

Lanphear, B., Eberly, S., & Howard, C. (2000). Long-term effect of dust control on blood lead concentrations. *Pediatrics, 106,* 1-4.

Lanphear, B., Hornung, R., Khoury, J., Dietrich, K., Cory-Slechta, D., & Canfield, R. (2008). The conundrum of unmeasured confounding [Comment on *Can some of the detrimental neurodevelopmental effects attributed to lead be due to pesticides?* by Brian Gulson]. *Science of the Total Environment, 396,* 196-200.

Lanphear, B., Hornung, R., Khoury, J., Yolton, K., Baghurst, P., Bellinger, D., et al. (2005). Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. *Environmental Health Perspectives, 113,* 894-899.

Lanphear, B., & Roghmann, K. (1997). Pathways of lead exposure in urban children. *Environmental Research, 74,* 67-73.

Lanphear, B., Winter, N., Apetz, L., Eberly, S., & Weitzman, M. (1996). A randomized trial of the effect of dust control on children's blood lead levels. *Pediatrics, 98,* 35-40.

Leggett, R. (1993). An age-specific kinetic model of lead metabolism in humans. *Environmental Health Perspectives, 101,* 598–616.

Leonning, C., Becker, J., & Nakamura, D. (2004, October 5). Utilities manipulate or withhold test results to ward off regulators. *The Washington Post,* p. A01.

Lidsky, T., & Schneider, J. (2003). Lead neurotoxicity in children: Basic mechanisms and clinical correlates. *Brain, 126,* 5-19.

Lin-Fu, J. (1992). Modern history of lead poisoning: A century of discovery and rediscovery. In H. Needleman (Ed.), *Human lead exposure* (pp. 23–43). Boca Raton, FL: CRC Press.

Loeber, R. (1989). *Pittsburgh youth study.* Pittsburgh: University of Pittsburgh, Department of Psychiatry.

Markovac, J., & Goldstein, G. (1988). Picomolar concentrations of lead stimulate protein kinace C. *Nature, 334,* 71-73.

Matkovic, V. (1991). Calcium metabolism and calcium requirements during skeletal modeling and consolidation of bone mass. *American Journal of Clinical Nutrition, 54,* 245S-260S.

Mendelsohn, A., Dreyer, B., Fierman, A., Rosen, C., Legano, L., Kruger, H., et al. (1998). Low-level lead exposure and behavior in early childhood. *Pediatrics, 101,* 1-7.

Murphy, E. (1993). Effectiveness of flushing on reducing lead and copper levels in school drinking water. *Environmental Health Perspectives, 101,* 240-241.

Needleman, H. (2004). Lead poisoning. *Annual Review of Medicine, 55,* 209-222.

Needleman, H., & Gatsonis, C. (1990). Low level lead exposure and the IQ of children: A meta-analysis of modern studies. *Journal of the American Medical Association, 263,* 673-678.

Needleman, H., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., et al. (1979). Deficits in psychological and classroom performance of children with elevated dentine lead levels. *The New England Journal of Medicine, 300,* 689-695.

Needleman, H., Riess, J., Tobin, M., Biesecker, G., & Greenhouse, J. (1996). Bone lead levels and delinquent behavior. *Journal of the American Medical Association, 275,* 363-369.

Needleman, H., Schell, A., Bellinger, D., Leviton, A., & Allred, E. (1990). The long-term effects of exposure to low doses of lead in childhood. *New England Journal of Medicine, 322,* 83-88.

Nevin, R. (2006). Understanding international crime trends: The legacy of preschool lead exposure. *Environmental Research, 104,* 315-336.

New York Office of the State Comptroller. (1997). *Executive summary: Childhood lead poisoning.* New York: Author.

Nigg, J. T., Nikolas, M., Knottnerus, M., Cavanagh, K., & Friderici, K. (in press). Confirmation and extension of association of blood lead with attention deficit hyperactivity disorder (ADHD) and ADHD symptom dimensions at population typical exposure levels. *Journal of Psychology and Psychiatry.*

Nigg, J., Knottnerus, M., Martel, M., Nikolas, M., Cavanagh, K., Karmaus, W. et al. (2008). Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. *Biological Psychiatry, 63,* 325-331.

Nihei, M., McGlothan, J., Toscano, C., & Guilarte, T. (2001). Low level Pb2+ exposure affects hippocampal protein kinase Ca gene and protein expression in rats. *Neuroscience Letters, 298,* 212–216.

NY CLS Pub Health § 1370a. (2009)

Pirkle, J., Kaufmann, R., Brody, D., Hickman, T., Gunter, E., & Pachal, D. (1998). Exposure of the U.S. population to lead, 1991-1994. *Environmental Health Perspectives, 106,* 745-750.

Plusquellec, P., Muckle, G., Dewailly, E., Ayotte, P., Jacobson, S., & Jacobson, J. (2007). The relation of low-level prenatal lead exposure to behavioral indicators of attention in Inuit infants in Arctic Quebec. *Neurotoxicology and Teratology, 29,* 527-537.

Quander-Collins, M. (2008). DC water board revises lead service line removal. Retrieved June 22, 2009, from http://www.dcwasa.com/news/listings/press_release356.cfm

Rabinowitz, M. B. (1995). Relating tooth and blood lead levels in children. *Bulletin of environmental Contamination and Toxicology, 55,* 853-857.

Ris, M. D., Dietrich, K., Succop, P., Berger, O., & Bornschein, R. (2004). Early exposure to lead and neuropsychological outcome in adolescence. *Journal of the International Neuropsychological Society, 10,* 261-270.

Roy, A., Bellinger, D., Hu, H., Schwartz, J., Ettinger, A., & Wright, R., et al. (2009). Lead exposure and behavior among young children in Channai, India. *Environmental Health Perspectives, 117,* 1601-1611.

Rutter, M. (1983). Low level lead exposure: Sources effects and implications. In M. Rutter & R. Russell-Jones (Eds.), *Lead versus health* (pp. 333-370). Chichester, UK: Wiley.

Schwartz, J. (1994). Societal benefits of reducing lead exposure. *Environmental Research, 66,* 105-124.

Schwartz, J. (1995). Updated estimates of earning benefits from reduced exposure of children to environmental lead. *Environmental Research, 70,* 1-6.

Sciarillo, W., Alexander, G., & Farrell, P. (1992). Lead exposure and child behavior. *American Journal of Public Health, 82,* 1356-1360.

Scortegagna, M., & Hanbauer, I.(1997). The effect of lead exposure and serum deprivation on mesencephalic primary cultures. *Neurotoxicology, 18,* 331-339.

Stretesky, P., & Lynch, M. (2004). The relationship between lead and crime. *Journal of Health and Social Behavior, 45,* 214-229.

Surkan, P., Zhang, A., Trachtenberg, F., Daniel, D., McKinlay, S., & Bellinger, D. (2007). Neuropsychological function in children with blood lead levels <10 mg/dL. *Neurotoxicology, 28,* 1170-1177.

Tesman, J., & Hills, A. (1994). Developmental effects of lead exposure in children. *SRCD Social Policy Report, 8,* 1-19.

Thomas, V., Socolow, R., Fanelli, J., & Spiro, T. (1999). Effects of reducing lead in gasoline: An analysis of the international experience. *Environmental Science and Technology, 33,* 3942-3948.

Thorndike, R., Hagen, E., & Sattler, J. (1986). *The Stanford-Binet Intelligence Scale* (4th ed.). Chicago: Riverside.

United States Department of Housing and Urban Development. (2008). The lead disclosure rule. Retrieved from http://www.hud.gov/offices/lead/enforcement/disclosure.cfm

Virginia Department of Historic Resources. (1993). *Lead paint: Abatement and mitigation.* Retrieved April 20, 2009, from http://www.dhr.virginia.gov/pdf_files/LeadPaint1.pdf

Wang, H., Chen, X., Yang, B., Ma, F., Wang, S., Tang, M., et al. (2008). Case-control study of blood lead levels and attention deficit hyperactivity disorder in Chinese children. *Environmental Health Perspectives, 116,* 1401-1406.

Wang, C., Chuang, H., Ho, C., Yang, C., Tsai, J., Wu, T., et al. (2002). Relationship between blood lead concentrations and learning achievement among primary school children in Taiwan. *Environmental Research, 89,* 12-18.

Wasserman, G., Staghezza-Jaramillo, B., Shrout, P., Popovac, D., & Graziano, J. (1998). The effect of lead exposure on behavior problems in preschool children. *Journal of Public Health, 88,* 481-486.

Wechsler, D. (1974). *Manual for the Wechsler intelligence scale for children* (Rev. ed.). New York: The Psychological Corporation.

Wechsler, D. (1991). *Manual for the Wechsler intelligence scale for children* (3rd ed.). San Antonio: The Psychological Corporation.

Weitzman, M., Aschegrau, A., Bellinger, D., Jones, R., Hamlin, J., & Beiser, A. (1993). Lead-contaminated soil abatement and urban children's blood lead levels. *Journal of the American Medical Association, 269,* 1647-1654.

Wright, J., Dietrich, K., Ris, M., Hornung, R., Wessel, S., Lanphear, B., et al. (2008). Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Medicine, 5,* e101.

Yule, W., Lansdown, R., Millar, I., & Urbanowicz, M. (1981). The relationship between blood lead concentrations, intelligence and attainment in a school population: A pilot study. *Developmental Medicine and Child Neurology, 23,* 567-576.

Commentary

If Ever A Time for Precaution

Joel Nigg
Oregon Health & Science University

Cole and Winsler rightly refocus our attention on the once-forgotten story of lead exposure and child health. The story of lead provides an object lesson for policymakers. Decades after lead came into routine consumer and industrial use, scientists are still grappling with its subtle yet extraordinarily costly effects on children's development. It has been horrifying to discover that much of the deleterious effect of lead on cognition and behavior occurs at the beginning of exposure—equivalent to exposures still commonplace in America. The unusual consistency of findings showing that lead is correlated, even at levels still typical in the U.S. population, with lower IQ and attention-deficit/hyperactivity disorder (ADHD) is sobering for a field accustomed to conflicting and ambiguous scientific reports.

The increasingly well-documented effects on ADHD are important because ADHD develops very early and is a precursor to conduct disorder, delinquency, substance use disorders (Mannuzza et al., 2008; Martel et al., 2008), and other outcomes of major concern to society. Attention problems predict academic failure over and above externalizing problems (Breslau et al., 2009). In our data, decrements in attention problems due to lead exposure fully account for decrements in IQ, but not the reverse (Nigg et al., 2008), suggesting that lead damage to regulatory systems in the brain may also account for the well documented impacts on IQ. In short, the cascade of developmental effects beginning early in life that may be related to insults, like seemingly modest lead exposure, is of major concern to society.

Now policymakers, who many believed had dealt with lead a generation ago, have to grapple with two issues. The first is determining whether further reductions in societal lead burden are needed. The even more momentous issue is what to do about future potential neurotoxins. The regulatory policies of the past century have amounted in one sense to a colossal experiment on America's children, not only with lead but hundreds of other substances. What happens to children when exposed to lead? To the hundreds of new chemical compounds permitted in the past decade? To the dozens of new nanotechnologies now coming to market? Policymakers should learn from the lead experience that it may take decades for science to find the unfortunate answers, at enormous economic cost to society. Moreover, medical study of the health effects will never catch up with the pace of compounds being developed. Such an approach wastes scientific time and resources, diverting those efforts from finding cures to other serious disease.

These observations raise serious ethical and policy problems for domestic industry and government. Policymakers and industry need to grapple more honestly with applying a well-defined precautionary principle to potential neurotoxins—both chemical and nano—as is now required prior to the release of pharmaceuticals. Such an approach shifts the burden of proof for a potentially dangerous action from acting until proven dangerous, to waiting until proven safe. Extreme application of the principle can be rightly criticized, but reasonable and effective definitions, justifications, and applications are readily available (Fisher, Jones, & von Schomberg, 2006; Petrenko & McArthur, 2009) and have already been applied in international law and treaty (Fisher et al., 2006). Identifying the appropriate role of a precautionary principle in protecting children's health from potential neurotoxins is a policymaking discussion that is urgently overdue. This should be policymakers' take home realization from the present report.

References

Breslau, N., Breslau, J., Peterson, E., Miller, E., Lucia, V. C., Bohnert, K., & Nigg., J. (2009). Change in teachers' ratings of attention problems and subsequent change in academic achievement: A prospective analysis. *Psychological Medicine, 40*(1), 159-166.

Fisher, E., Jones, J., & von Schomberg, R. (2006). *Implementing the precautionary principle: Perspectives and prospects.* Northampton, MA: Edward Elgar.

Mannuzza, S., Klein, R. G., & Moulton, J. L. (2008). Lifetime criminality among boys with attention deficit hyperactivity disorder: A prospective follow-up study into adulthood using official arrest records. *Psychiatry Research, 160,* 237-246.

Martel, M. M., Pierce, L., Nigg, J. T., Jester, J.M., Adams, K., Puttler, L. I., et al. (2009). Temperament pathways to childhood disruptive behavior and adolescent substance abuse: Testing a cascade model. *Journal of Abnormal Child Psychology, 37*(3), 363-373.

Nigg, J. T., Knottnerus, G. M., Martel, M. M., Nikolas, M., Cavanagh, K., Karmaus, W., et al. (2008). Low blood lead levels associated with clinically diagnosed attention deficit hyperactivity disorder (ADHD) and mediated by weak cognitive control. *Biological Psychiatry, 63*(3), 325-331.

Petrenko, A., & McArthur, D. (2009). Between same-sex marriages and the large hadron collider: Making sense of the precautionary principle. *Science and Engineering Ethics,* Sep 12. [Epub ahead of print].

Commentary

Childhood Lead Poisoning: Designing Effective Public Policy

Elise Gould and Alexander Hertel-Fernandez
Economic Policy Institute

As Congress and the Obama administration debate an overhaul of our nation's health care system, the emphasis of the national discourse is predominately on medical care financing and insurance coverage. Discussions of public health, on the other hand, are notably absent. Although universal access to affordable medical care is necessary for a healthy nation, there is ample evidence that policymakers must look beyond the system of direct care to broader population-based initiatives. In no area is this more apparent than childhood lead poisoning, as Cole and Winsler describe in the present issue. Research has shown that at least 7 million children under the age of six (or about 25% of children that age) could have lead levels high enough to induce developmental damage. Cole and Winsler's piece provides an extensive review of the biological and neurological effects of lead poisoning on these children and analyzes possible interventions. The authors conclude by offering an extensive set of policy recommendations for reducing children's exposure to lead.

While we concur with many of the recommendations forwarded by Cole and Winsler, we would have liked to see more discussion of the costs of each measure relative to their risk reduction and net benefits. In a world of fixed government resources, policymakers must ultimately choose a limited set of actions. We thus encourage a more complete cost-benefit analysis of which recommendations would produce the largest gains in terms of population health. In particular we are wary of an increased focus on universal screening and medical intervention that could shift limited public health resources and medical attention away from at-risk populations (especially low-income and minority children) that are currently targeted for primary prevention.

Instead of increased laboratory screening for lead poisoning, some have called (see e.g. Brown and Meehan, 2004) for resources to be directed towards universal education for parents of lead hazards, better follow-up screening for infants that have elevated blood lead levels, improved coordination between state and federal governments, better risk factor screening, and household lead abatement (indeed, all suggestions

later offered by Cole and Winsler). Our own research has highlighted the cost-effectiveness of household lead abatement (Gould, 2009). This is especially true if household interventions are targeted towards historically at-risk neighborhoods and geographic areas. The emphasis of childhood lead policy thus ought to move towards more primary prevention of poisoning at their source.

Eliminating childhood lead poisoning is an economic and moral imperative, and ought to be pursued aggressively as part of a broader public health agenda. What form these policies should take, however, deserves careful attention to benefits (in the form of risk reduction) and costs, as well as unintended consequences for other at-risk populations.

References

Brown, M.J. & Meehan, P.J. (2004). Health Effects of Blood Lead Levels Lower than 10 MG/DL in Children. American Journal of Public Health. 94:8-9.

Gould, E. (2009). Childhood Lead Poisoning: Conservative Estimates of the Social and Economic Benefits of Lead Hazard Control. Environmental Health Perspectives. 117(7):1162-1167.

Lanphear, B.P., Dietrich, K., Auinger, P., & Cox, C. (2000). Cognitive deficits associated with blood lead concentrations <10 µg/dL in US children and adolescents. Public Health Reports. 111:521-529.

Commentary

The Saturnian Predicament

Bruce Lanphear
British Columbia Children's Hospital & Simon Fraser University

Lead is an ancient poison. Dioscorides, a Greek physician who lived in the first century A.D., wrote that lead makes the mind "give way" (Needleman, 2009). Lead poisoning, or Saturnism, was associated with Saturn by the alchemists because it was thought to be the most ancient of metals.

Saturn, the son of Earth (Tellus) and Sky (Caelus), was the supreme god or titan on earth. It was prophesized that he would be dethroned by one of his children. To retain his throne, Saturn devoured each of his children at birth. Saturn's predicament—losing his power or devouring his children—reflects our own predicament of losing a profitable poison or sacrificing our children to the toxic effects of lead.

Cole and Winsler have written a comprehensive review of toxicity and prevention of childhood lead exposure. There are a few points one might quibble about (e.g., it is unclear to what extent prenatal exposure elicits persistent effects on children). But more importantly, these two investigators have concluded what most objective scientists would if they took the time to study it; we have, for far too long, failed to

protect children from exposure to a substantial and preventable poison.

Their article is only the most recent in a series of pleas over the past century to prevent childhood lead poisoning. The first plea was published 100 years ago (Turner, 1908). After a decade of research and failed attempts to prevent lead poisoning by educating mothers, Turner concluded that "legislative interference" was necessary to protect children. In the 1920s, Alice Hamilton and Yandell Henderson argued—unsuccessfully—that the addition of tetra-ethyl lead to gasoline by the Ethyl Corporation would lead to cases of lead poisoning (Rosner & Markowitz, 1985; Rabin 1985). In the 1970s, research and legislation led to a reduction in allowable levels of lead in air, paint and water (Landrigan, Whitworth, Baloh, Staehling, Barthel, & Rosenblum, 1975; Needleman, Gunnoe, Leviton, Reed, Peresie, Maher, C., et al., 1979; Mahaffey, Annest, Roberts, & Murphy, 1882; Lanphear, Dietrich, & Berger, 2003). In the 1980s and 1990s, a series of studies implicating even lower levels of lead exposure with adverse effects on children's intellectual abilities were published (Lanphear, Dietrich, & Berger, 2003; Needleman, Schell, Bellinger, Leviton, & Allred, 1990; Burns, Baghurst, Sawyer, McMichael, & Tong, 1999; CDC, 1991). In the 1990s, the Centers for Disease Control (CDC) and the World Health Organization lowered the acceptable level of lead in blood to 10 µg/dL for children (CDC, 1991; Tong, von Schirnding, & Prapamontol, 2000). Finally, in the first decade of the 21st century, another wave of research implicated lead as a risk factor for cognitive deficits and psychopathology at blood levels considerably lower than 10 µg/dL, prompting calls for the global elimination of all non-essential uses of lead (Wright, Dietrick, Ris, Hornung, Wessel, Lanphear, et al., 2008; Lanphear, Hornung, Khoury, Yolton, Baghurst, Bellinger, et al., 2005; Froehlich, Lanphear, Auinger, Hornung, Epstein, Braun, et al., 2009; Nigg, Knottnerus, Martel, Nikolas, Cavanagh, Karmaus, et al. 2008).

At each wave of research or advocacy, a handful of physicians, policymakers, scientists or community leaders were utterly convinced that there was sufficient evidence to protect children against lead poisoning through legislation. Unfortunately, despite some success in banning or reducing lead in gasoline, paint, industrial emissions, solder used in food cans and other consumer products, we continued to use it (Lanphear, et al., 2003; Tong, et al., 2000). It was simply too profitable to ban lead and too easy to dismiss any long-term consequences on children's health.

Despite reductions in children's blood lead levels (Jones, Homa, Meyer, Brody, Caldwell, Pirkle, et al., 2009), too many children still have blood lead levels indicative of lead toxicity. Moreover, while there has been a dramatic decline in lead toxicity among children in developed countries, the prevalence of lead toxicity in many developing or industrializing countries is epidemic (Tong et al., 2000).

There is both renewed optimism and urgency about eliminating childhood lead exposure (Lanphear, 2007; Ramazzini Collegium, 2009). In many countries, childhood lead exposure is considerably lower today than at anytime in the past 50 years, and fewer than twenty countries continue to use leaded gasoline (OECD, 1999). It is feasible to eliminate lead from paint and many other consumer products worldwide. The elimination of lead won't be easy, but with concerted effort it could be the environmental equivalent of smallpox eradication. The myth of Saturn also offers some hope; Saturn's son, Jupiter, ultimately deposed his father after his mother, Rhea, kept him from being devoured.

References

Burns, J. M., Baghurst, P. A., Sawyer, M. G., McMichael, A. J., & Tong, S. L. (1999). Lifetime low-level exposure to environmental lead and children's emotional and behavioral development at ages 11-13 years. The Port Pirie Cohort Study. *American Journal of Epidemiology, 149,* 740-9.

Centers for Disease Control. (October 1991). *Preventing lead poisoning in young children: A statement by the Centers for Disease Control.* Atlanta: US Department of Health and Human Services.

Froehlich, T., Lanphear, B. P., Auinger, P., Hornung, R., Epstein, J. N., Braun J., et al. (2009). The association of tobacco and lead exposure with attention-deficit/hyperactivity disorder in a national sample of US children. *Pediatrics 124,* e1054-1063.

Jones, R. L., Homa, D. M., Meyer, P. A., Brody, D. J., Caldwell, K. L., Pirkle, J. L., et al. (2009). Trends in blood lead levels and blood lead testing among US children aged 1 to 5 years, 1988-2004. *Pediatrics, 123,* e376-e385.

Landrigan, P. J., Whitworth, R. H., Baloh R. W., Staehling, N. W., Barthel, W. F., & Rosenblum, B. F. (1975). Neuropsychological dysfunction in children with chronic low-level lead absorption. *Lancet, 7909,* 708-712.

Lanphear, B.P. (2007). The conquest of lead poisoning: A Pyrrhic victory. *Environmental Health Perspectives, 115,* A484-A485.

Lanphear, B. P., Dietrich, K. N., & Berger O. (2003). Prevention of lead toxicity in US children. *Ambulatory Pediatrics, 3,* 27-36.

Lanphear, B. P., Hornung, R., Khoury, J., Yolton, K., Baghurst P., Bellinger D. C., et al. (2005). Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. *Environmental Health Perspecitves, 113,* 894-899.

Mahaffey, K. R., Annest, J. L., Roberts, J., & Murphy, R. S. (1982). National estimates of blood lead levels: United States, 1976-1980. Association with selected demographic and socioeconomic factors. *New England Journal of Medicine, 307,*573-579.

Needleman, H. (2009). Low level lead exposure: history and discovery. *Annals of Epidemiology, 19,* 235-238.

Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H. Maher, C., et al. (1979). Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *New England Journal of Medicine, 300,* 689-95.

Needleman, H. L., Schell, A., Bellinger, D., Leviton, A., & Allred, E. N. (1990). The long-term effects of exposure to low doses of lead in childhood: An 11-year follow-up report. *New England Journal of Medicine,* 322, 83-88.

Nigg, J. T., Knottnerus, G. M., Martel, M. M., Nikolas, M., Cavanagh, K., Karmaus, W., et al. (2008). Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. *Biological Psychiatry, 63*(3), 325-31.

OECD. (1999). *Phasing lead out of gasoline: An examination of policy approaches in different countries.* Paris: Organisation for Economic Co-operation and Development. Retrieved November 24, 2009 from http://www.unep.fr/energy/transport/documents/pdf/phasingLead.pdf

Rabin, R. (1985). Warnings unheeded: A history of childhood lead poisoning. *American Journal of Public Health,* 79, 1668-1674.

Ramazzini Collegium. (2008). *Call for a worldwide ban on exposure to lead.* Capri, Italy: Author.

Rosner, D., & Markowitz G. (1985). A 'gift of God'?: The public health controversy over leaded gasoline during the 1920s. *American Journal of Public Health, 75,* 344-352.

Tong, S., von Schirnding, Y. E., & Prapamontol, T. (2000). Environmental lead exposure: A public health problem of global dimensions. *Bull World Health Organ, 78,* 1068-1077. Turner, A. J. (1908). Lead poisoning in childhood. *Australasian Med Congress (Melbourne) 1908,* 2-9.

Wright, J. P., Dietrich, K. N., Ris, M. D., Hornung, R. W., Wessel, S. D., Lanphear, B. P., et al. (2008). Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. PLoS Med 5, e101.

About the Authors

Claire Cole is a doctoral candidate in the Applied Developmental Psychology graduate program at George Mason University. Her current research examines social and emotional development in children. In addition to children's exposure to lead and a variety of other applied topics, she is particularly interested in the role of temperament and attention in the development of anxiety during childhood.

Adam Winsler, Ph.D., is Professor of Applied Developmental Psychology at George Mason University. He has published numerous articles and books exploring the role of private speech (self-talk) and parent-child interaction in the development of children's behavioral self-regulation, within typically developing children as well as children with behavior problems, ADHD, or autism. His current research is centered on school readiness, the transition to school, and early childcare experiences for ethnically diverse children in poverty. He is also interested in bilingual language development and the early education of language-minority children. Dr. Winsler is a fellow of the American Psychological Association and the American Educational Research Association, and is the current editor-in-chief of the *Early Childhood Research Quarterly.*

Alexander Hertel-Fernandez, B.A., is a research assistant at the Economic Policy Institute in Washington, D.C., where he works on issues of health policy and social insurance. Prior to joining EPI, Hertel-Fernandez served as a Senior Fellow for Social Insurance with the Roosevelt Institution and was the recipient of a Fulbright Fellowship. He has published research on public health and the political economy of social insurance in *Social Policy & Administration,* the *Bulletin of the World Health Organization,* and *Health Affairs.*

Elise Gould, Ph.D.,is Director of Health Policy Research at the Economic Policy Institute in Washington, D.C. Her research areas include employer-sponsored health insurance, the employer tax exclusion, the burden of health costs, income inequality and health, and retiree coverage. She has authored a chapter on health in *The State of Working America 2008/09,* co-authored a book on health insurance coverage in retirement, published in venues such as *The Chronicle of Higher Education, Challenge Magazine,* and *Tax Notes,* and academic journals including *Health Economics, Journal of Aging and Social Policy, Risk Management & Insurance Review,* and *International Journal of Health Services.*

Bruce Lanphear, M.D., M.P.H., is a Senior Scientist at the Child & Family Research Institute, BC Children's Hospital and Professor in the Faculty of Health Sciences at Simon Fraser University in Vancouver, British Columbia. The goal of his research is to prevent common diseases and disabilities in children, such as asthma and ADHD. To quantify the contribution of risk factors, he tests various ways to measure children's exposures to environmental toxicants using novel biomarkers measured during pregnancy and early childhood. Dr. Lanphear also designs experimental trials to test the efficacy of reducing children's exposures to environmental hazards on asthma symptoms and behavioral problems.

Joel Nigg, Ph.D., is Professor of Psychiatry and Behavioral Neuroscience at Oregon Health & Science University in Portland. His primary research focus is on causes of ADHD and determinants of altered neural development in children. He conducts experimental studies of cognitive and neuropsychological functioning in ADHD and learning disabilities, as well as studies of genetic and environmental correlates of ADHD in population and clinical samples. He has authored a recent scholarly book on causal mechanisms in ADHD (What Causes ADHD; Guilford Press, 2006) as well as over 100 peer reviewed scientific papers on clinical and causal correlates of ADHD and developmental psychopathology. His empirical research has been funded by the National Institute of Mental Health for the past 12 years.

Social Policy Report is a quarterly publication of the Society for Research in Child Development. The *SPR* provides a forum for scholarly reviews and discussions of development research and its implications for the policies affecting children. Copyright of the articles published in the *SPR* is maintained by SRCD. Statements appearing in the *SPR* are the views of the author(s) and do not imply endorsement by the Editors or by SRCD.

Purpose

Social Policy Report (ISSN 1075-7031) is published four times a year by the Society for Research in Child Development. Its purpose is twofold: (1) to provide policymakers with objective reviews of research findings on topics of current national interest, and (2) to inform the SRCD membership about current policy issues relating to children and about the state of relevant research.

Content

The *Report* provides a forum for scholarly reviews and discussions of developmental research and its implications for policies affecting children. The Society recognizes that few policy issues are noncontroversial, that authors may well have a "point of view," but the *SPR* is not intended to be a vehicle for authors to advocate particular positions on issues. Presentations should be balanced, accurate, and inclusive. The publication nonetheless includes the disclaimer that the views expressed do not necessarily reflect those of the Society or the editors.

Procedures for Submission and Manuscript Preparation

Articles originate from a variety of sources. Some are solicited, but authors interested in submitting a manuscript are urged to propose timely topics to the lead editor (slodom@unc.edu). Manuscripts vary in length ranging from 20 to 30 pages of double-spaced text (approximately 8,000 to 14,000 words) plus references. Authors are asked to submit manuscripts electronically, if possible, but hard copy may be submitted with disk. Manuscripts should adhere to APA style and include text, references, and a brief biographical statement limited to the author's current position and special activities related to the topic.

Reviews are typically obtained from academic or policy specialists with relevant expertise and different perspectives. Authors then make revisions based on these reviews and the editors' queries, working closely with the editors to arrive at the final form for publication.

The Committee on Policy and Communications, which founded the *Social Policy Report,* serves as an advisory body to all activities related to its publication.

Preventing Lead Poisoning in Young Children

A STATEMENT BY THE
CENTERS FOR DISEASE CONTROL AND PREVENTION
AUGUST 2005

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention

Preventing Lead Poisoning in Young Children

A Statement by the Centers for Disease Control and Prevention
August 2005

Centers for Disease Control and Prevention
Julie L. Gerberding, MD, MPH, Director

National Center for Environmental Health
Tom Sinks, PhD, Acting Director

Division of Emergency and Environmental Health Services
Jim Rabb, Acting Director

Lead Poisoning Prevention Branch
Mary Jean Brown, ScD, RN, Chief

U.S. Department of Health
and Human Services, Public Health Service

Suggested reference:
Centers for Disease Control and Prevention. Preventing Lead Poisoning in Young Children. Atlanta: CDC; 2005.

Table of Contents

Advisory Committee on Childhood Lead Poisoning Prevention Members, Ex-Officio and Liaison Representatives

CHAIR
Carla Campbell, MD, MS
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

EXECUTIVE SECRETARY
Mary Jean Brown, ScD, RN
Chief, Lead Poisoning Prevention Branch
National Center for Environmental Health
Centers for Disease Control and Prevention
Atlanta, Georgia

MEMBERS
William Banner, Jr. MD, PhD
The Children's Hospital at Saint Francis
Tulsa, Oklahoma

Helen J. Binns, MD, MPH*
Children's Memorial Hospital
Chicago, Illinois

Walter S. Handy, Jr., PhD
Cincinnati Health Department
Cincinnati, Ohio

Ing Kang Ho, PhD
University of Mississippi Medical Center
Jackson, Mississippi

Jessica Leighton, PhD, MPH
New York City Department of Health & Mental Hygiene
New York, New York

Valarie Johnson
Urban Parent to Parent
Rochester, New York

Tracey Lynn, DVM, MPH†
Alaska Department of Health and Social Services
Anchorage, Alaska

Sally Odle
SafeHomes, Inc.
Waterbury, Connecticut

George G. Rhoads, MD, MPH
University of Medicine and Dentistry of New Jersey
Piscataway, New Jersey

Catherine M. Slota-Varma, MD
Pediatrician
Milwaukee, Wisconsin

Wayne R. Snodgrass, PhD, MD
University of Texas Medical Branch
Galveston, Texas

Kevin U. Stephens, Sr., MD, JD
New Orleans Department of Health
New Orleans, LA

Kimberly M. Thompson, ScD
Harvard School of Public Health
Boston, Massachusetts

*ACCLPP member until May 2004
†ACCLPP member until October 2004

EX-OFFICIO
Centers for Disease Control and Prevention
Robert J. Roscoe, MS

Centers for Medicare and Medicaid Services
Jerry Zelinger, MD

National Institute for Occupational Safety and Health Sciences
Walter Rogan, MD

U.S. Agency for International Development
John Borrazzo, PhD

U.S. Consumer Product Safety Commission
Lori Saltzman

U.S. Department of Housing and Urban Development
David E. Jacobs, Ph.D., CIH

U.S. Environmental Protection Agency
Jacqueline E. Mosby, MPH

U.S. Food and Drug Administration
Michael P. Bolger, PhD

LIAISON REPRESENTATIVES
Alliance for Healthy Homes
Anne M. Guthrie, MPH

American Academy of Nurse Practitioners
Jan Towers, PhD

American Academy of Pediatrics
J. Routt Reigart, II, MD (1997-2004)

American Association of Poison Control Centers
George C. Rodgers, Jr., MD, PhD

American Industrial Hygiene Association
Steve M. Hays, CIH, PE

American Public Health Association
Ben Gitterman, MD

Association of Public Health Laboratories
Henry Bradford, Jr., PhD

Council of State and Territorial Epidemiologists
Ezatollah Keyvan-Larijani, MD, DrPH

National Center for Healthy Housing
Pat McLaine, RN, MPH

REVIEW OF EVIDENCE FOR EFFECTS AT BLLS <10 µg/dL WORK GROUP

Michael L. Weitzman, MD
Work Group Chair
Center for Child Health Research
University of Rochester

Tom Matte, MD, MPH
National Center for Environmental Health
Centers for Disease Control and Prevention

David Homa, PhD
National Center for Environmental Health
Centers for Disease Control and Prevention
Jessica Sanford, PhD
Battelle Memorial Institute

Alan Pate
Battelle Memorial Institute

Joel Schwartz, Ph.D.
Department of Environmental Health
Harvard School of Public Health

David Bellinger, PhD,
Neuroepidemiology Unit Children's Hospital
Harvard Medical School

David A. Savitz, PhD
Department of Epidemiology
University of North Carolina School of Public Health

Carla Campbell, MD, MS
Division of General Pediatrics
The Children's Hospital of Philadelphia

Patrick J. Parsons, PhD
Wadsworth Center for Laboratories and Research
New York State Department of Health

Betsy Lozoff, MD
Center for Human Growth and Development
University of Michigan

Kimberly Thompson, ScD
Department of Health Policy and Management
Harvard School of Public Health

Birt Harvey, MD
Pediatrician
Palo Alto, California

Preface

This is the fifth revision of *Preventing Lead Poisoning in Young Children* by the Centers for Disease Control and Prevention (CDC). As with the previous statements, the recommendations presented here are based on scientific evidence and practical considerations. This revision accompanies a companion document, *A Review of Evidence of Adverse Health Effects Associated with Blood Lead Levels <10 µg/dL in Children*, developed by Advisory Committee on Lead Poisoning Prevention which reviews the scientific evidence for adverse effects in children at blood lead levels below 10 µg/dL.

The data demonstrating that no "safe" threshold for blood lead levels (BLLs) in young children has been identified highlights the importance of preventing childhood exposures to lead. It confirms the need for a systematic and society wide effort to control or eliminate lead hazards in children's environments before they are exposed. This emphasis on primary prevention, although not entirely new, is highlighted here and is clearly the foremost action supported by the data presented in *A Review of Evidence of Adverse Health Effects Associated with Blood Lead Levels <10 µg/dL in Children.*

Although there is evidence of adverse health effects in children with blood lead levels below 10 µg/dL, CDC has not changed its level of concern, which remains at levels ≥10 µg/dL. We believe it critical to focus available resources where the potential adverse effects remain the greatest. If no threshold level exists for adverse health effects, setting a new BLL of concern somewhere below 10 µg/dL would be based on an arbitrary decision. In addition, the feasibility and effectiveness of individual interventions to further reduce BLLs below 10 µg/dL has not been demonstrated.

CDC is conducting several activities to focus efforts on preventing lead exposures to children. First, beginning in 2003, CDC required state and local health departments receiving funding for lead poisoning prevention activities to develop and implement strategic childhood lead poisoning elimination plans. Second, CDC and its federal partners, the Department of Housing and Urban Development and the Environmental Protection Agency, launched new initiatives to control lead-based paint hazards in the highest risk housing, addressing where successive cases of lead poisoning have been identified. Third, CDC and other federal agencies are developing a systematic and coordinated response to identify and eliminate non-paint sources of exposure (e.g., lead jewelry, food and traditional medicines, and cosmetics).

CDC continues to monitor progress toward the Healthy People 2010 objective of eliminating elevated BLLs in children at the national level through the National Health and Nutritional Examination Survey and at the state and local levels through the blood lead surveillance system. These complementary data provide

essential information for the rational distribution of resources to communities with the highest risk for lead exposure.

I wish to thank both current and former members of the Advisory Committee on Childhood Lead Poisoning Prevention and consultants who developed the documents in this statement and acknowledge their contribution to the health of the nation's children. The Committee considered a number of controversial issues, examined the existing data and reviewed the report of the work group. This 2005 statement represents agreement of 12 of the 13 Advisory Committee members serving on the committee as of October 19-20, 2004.

Thomas Sinks, Ph.D.
Acting Director
National Center for Environmental Health/Agency for Toxic Substances and Disease Registry

INTRODUCTION

The U.S. Department of Health and Human Services has established an ambitious goal of eliminating elevated blood lead levels (BLLs) in children by 2010, a qualitatively different goal from earlier goals that focused on reducing the BLL considered toxic by various target amounts.[1] Recent research on lead's health effects at low levels, which suggests societal benefits from preventing even low level lead exposure in childhood, underscores the importance of this public health goal.

This revised statement describes the public health implications of research findings regarding adverse health effects at low BLLs summarized in the accompanying review, and focuses on the Centers for Disease Control and Prevention's blood lead "level of concern." This statement aims to guide public health practice and policy development and review necessary steps to ensure progress toward meeting the 2010 goal.

PREVENTING CHILDHOOD LEAD POISONING IN THE UNITED STATES

The reduction of BLLs in the United States during 1970-1999, primarily because of implementation of federal and state regulations to control lead exposure, was one of the most significant public health successes of the last half of the 20th century.[2] Nonetheless, some populations and geographic areas remain at disproportionately high risk for lead exposure.[3-5] Specific strategies that target screening to high-risk children are essential to identify children with BLLs $\geq$10 µg/dL. Once identified, children with elevated BLLs should receive follow-up services as recommended in *Managing Elevated Blood Lead Levels Among Young Children*.[6]

However, *preventing* elevated BLLs is the preferred course of action. A compelling body of evidence points to the limited effectiveness of waiting until children's BLLs are elevated before intervening with medical treatments, environmental remediation, or parental education.[7-12] Data indicate that in many cases it takes years to reduce children's BLLs once levels are elevated whether the initial blood lead elevation is very high or moderate.[13-15] The most common high-dose sources of lead exposure for U. S. children are lead-based paint and lead-contaminated house dust and soil. Recent studies have identified methods to reduce common household lead hazards safely.[16] Thus, a multitiered approach that includes secondary prevention through case identification and management of elevated BLLs is needed to eliminate childhood lead poisoning. However, because no level of lead in a child's blood can be specified as safe, primary prevention must serve as the foundation of the effort.

CDC'S BLOOD LEAD LEVEL OF CONCERN

The adverse health effects associated with elevated BLLs have been widely studied and documented. Previously, CDC responded to the accumulated evidence of adverse effects associated with lead exposures by lowering the BLL of concern. Between 1960 and 1990 the blood lead level for individual intervention in children was lowered from 60 µg/dL to 25 µg/dL. In 1991 the CDC recommended lowering the level for individual intervention to 15 µg/dL and implementing community-wide primary lead poisoning prevention activities in areas where many children have BLLs ≥10 µg/dL.[17] Some activities, such as taking an environmental history, educating parents about lead, and conducting follow-up blood lead monitoring were suggested for children with BLLs of ≥10 µg/dL.[7] However, this level, which was originally intended to trigger communitywide prevention activities, has been misinterpreted frequently as a definitive toxicologic threshold.

As the accompanying review of recent studies indicates, additional evidence exits of adverse health effects in children at BLLs <10 µg/dL. The available data are based on a sample of fewer than 200 children whose BLLs were never above 10 µg/dL and questions remain about the size of the effect.

At this time there are valid reasons not to lower the level of concern established in 1991 including the following:

- No effective clinical or public health interventions have been identified that reliably and consistently lower BLLs that already are <10 µg/dL. Nonetheless, the sources of lead exposure and the population-based interventions that can be expected to reduce lead exposure are similar in children with BLLs <10 µg/dL and ≥10 µg/dL,[18] so preventive lead hazard control measures need not be deferred pending further research findings or consensus.

- No one threshold for adverse effects has been demonstrated. Thus the process for establishing a lower level of concern would be arbitrary and no particular BLL cutoff can be defended on the basis of the existing data. In addition, establishing a lower level of concern may provide a false sense of safety about the well being of children whose BLLs are below the threshold.

- The adverse health effects associated with elevated BLLs are subtle. Individual variation in response to exposure and other influences on developmental status, make isolating the effect of lead or predicting the overall magnitude of potential adverse health effects exceedingly difficult.

- Establishing a level of concern substantially <10 µg/dL probably would be accompanied by a sharp increase in misclassification of children as having an elevated BLL. The uncertainty associated with laboratory testing is too great to ensure that a single blood lead test reliably classifies individual children at

levels <10 µg/dL. This misclassification could confuse both parents and clinicians and expenditure of resources on testing that does not aid decision making.

- Efforts to identify and provide services to children with BLLs <10 µg/dL may deflect needed resources from children with higher BLLs who are likely to benefit most from individualized interventions.

- Efforts to eliminate lead exposures through primary prevention have the greatest potential for success. Reducing exposures will benefit all children, regardless of their current BLL.

RESPONDING TO DATA ON ADVERSE HEALTH EFFECTS AT BLOOD LEAD LEVELS <10 µg/dL FROM A PUBLIC HEALTH PERSPECTIVE

Since 1991, CDC has emphasized the need to make primary prevention of lead poisoning, through interventions that control or eliminate lead hazards before children are exposed**,** a high priority for health, housing, and environmental agencies at the state, local, and federal levels.[18-20] Federal and state policies and programs, largely as the result of Title X of the 1992 Housing and Community Development Act (Public Law 102-550), increasingly have focused on the need for primary prevention using strategies known to effectively reduce residential lead hazards.[21] Research findings also indicate that primary prevention would be expected to benefit all children at high risk because communities with the largest percentages of children with BLLs ≥20 µg/dL also have the largest percentage of children with BLLs that are lower but still above the national average of approximately 2 µg/dL.[18] These data underscore the importance of targeting efforts to communities where risk for exposure is highest and provide a strong rationale for primary prevention efforts. The strategies described below will effectively direct efforts to achieve the Healthy People 2010 objective to eliminate lead poisoning in young children and can be expected to reduce lead exposure for all children.[1]

Primary Prevention

CDC's Advisory Committee on Childhood Lead Poisoning Prevention recently issued updated recommendations calling for the nation to focus on primary prevention of childhood lead poisoning.[22] Because the 2010 health objective of eliminating childhood lead poisoning can be achieved only through primary prevention,[22] this document provides important guidance to state and local agencies regarding the implementation of primary prevention activities. Given that the most important measure of a successful primary prevention strategy is elimination of lead exposure sources for young children, we focus here on the two main exposure sources for children in the United States: lead in housing and non-essential uses of lead in other products.

Lead in Housing-Because lead-based paint is the most important source of lead exposure for young children, the first essential element of primary prevention is implementation of strategies to control lead paint-contaminated house dust and soil and poorly maintained lead paint in housing.[23-25] After 10 or more years of widespread blood lead testing and data collection by CDC-supported state and local agencies, the specific addresses of housing units at which children repeatedly have been identified with elevated BLLs are known to local officials. Two examples are:

- In Detroit, 657 addresses accounted for nearly 1,500 children with BLLs ≥20 µg/dL during the last 10 years because the sources of lead were never controlled completely when the initial case occurred. These housing units also probably were the source of lead exposure for several thousand Detroit children with BLLs ≥10 µg/dL.[26]

- In Louisville, Kentucky, 35% of children identified with elevated BLLs during the last 5 years resided in 79 housing units; these units represent <0.3% of all housing units in the community.[27]

These experiences are repeated in high-risk communities across the country. The infrastructure needed to identify high-risk housing and to prevent and control lead hazards in such housing is largely in place. Established firms certified in lead hazard evaluation and control now exist in most communities, as do other skilled trades people trained in lead-safe work practices necessary during routine maintenance and painting. Systematic identification and reduction of residential lead sources, particularly in old, poorly maintained housing where children with elevated BLLs are known to have lived, combined with periodic monitoring of housing conditions to detect new deterioration and resultant lead hazards will prevent lead exposure to children in the future and break the cycle of repeated cases of elevated BLLs.

Other steps critical to success in controlling lead hazards in housing and preventing lead exposure in the future are 1) enforcement of lead safety and housing code requirements to ensure good property maintenance; 2) widespread adoption of lead-safe work practices to control, contain, and clean up lead dust during painting and remodeling projects; and 3) periodic monitoring of housing conditions to detect new deterioration and resultant lead hazard.

Nonessential Uses of Lead-Because areas of the United States report that as many as 35% of children identified with elevated BLLs have been exposed to items decorated or made with lead, in some cases resulting in life-threatening BLLs,[28] the second crucial element of a primary prevention strategy is identification and restriction or elimination of nonessential uses of lead, particularly in both imported and domestically manufactured toys, eating and drinking utensils, cosmetics, and traditional medicines. This effort requires identifying communities where cultural practices and traditional medicines may put children at risk and incorporating

lead poisoning prevention activities into health and community services that reach families at high risk for lead exposure from nonpaint sources.[7] The 2010 health objective cannot be achieved without a more systematic approach that, at a minimum, allows identification of lead-contaminated items and prohibits their sale before children are exposed. Ultimately, all nonessential uses of lead should be eliminated.

RECOMMENDATIONS

Changes in the Focus of CDC-Funded Programs

To achieve these goals, CDC is focusing on eliminating childhood lead poisoning by preferentially funding programs to provide lead-related services for communities and populations with large numbers of children at high risk for lead exposure. The cooperative agreements with 42 state and local health departments funded for 2003-2006 emphasize the importance of primary prevention and require funded state and local programs to work aggressively to develop and implement the necessary partnerships, programs and activities. CDC requires its state and local partners to undertake a strategic planning process, which includes gathering input from housing professionals, pediatric health-care providers, advocacy groups, parents of children with elevated BLLs, and others interested in preventing lead poisoning in children. These strategic plans, developed by local partners to respond to local conditions, drive primary prevention activities for the 3-year grant cycle.

Progress toward eliminating childhood lead poisoning can be measured only by ongoing surveillance of BLLs in childhood populations where the risk for exposure is high, as well as continued monitoring of population-based BLLs through the National Health and Nutrition Examination Survey.[29] CDC's role in supporting state and local efforts and providing technical assistance to improve data management and reporting is essential to these activities.

Recommendations to Federal, State, and Local Government Agencies

Achieving the Healthy People 2010 objective to eliminate childhood lead poisoning requires collaboration by many different federal, state and local agencies. Many of the roles and responsibilities for federal partners in the elimination effort are detailed in the report of the President's Task Force on Environmental Health Risks and Safety Risks in Children.[29] However, all levels of government share responsibility for primary prevention of childhood lead poisoning. Government agencies have the ability, through legislative and enforcement actions to spearhead prevention efforts and articulate clear public health goals and strategic priorities at the federal, state, and local government levels.

Federal agencies should:

1. Support and disseminate information about, and adequately fund, programs and interventions that will lead to full implementation of primary prevention.

2. Expand financial resources for permanent measures to control or eliminate residential lead hazards.

3. Monitor and enforce regulations controlling lead content of various environmental media, including air, water, and soil.

4. Identify populations in which the risk for exposure to nonpaint sources of lead is high, and develop strategies to minimize the risk.

5. Develop and implement regulatory and voluntary strategies to control nonessential uses of lead, particularly in items that are easily accessible to young children, such as toys, jewelry, eating and drinking utensils, traditional remedies, and cosmetics.

6. Evaluate the effectiveness of primary prevention activities in reducing lead exposure and eliminating childhood lead poisoning, particularly in areas where the risk for lead poisoning is substantially higher than for the general U. S. childhood population.

7. Develop new mathematical models of lead exposure or modify existing models, e.g., the Integrated Exposure Uptake and BioKinetic (IEUBK) Model for lead in children, currently used to establish thresholds for lead exposure in consumer products and areas with pervasive lead contamination. The exposure modeling should predict the magnitude of the increase in BLLs in a child as a result of exposure to a specific lead source rather than the probability of a BLLs $\geq$10 µg/dL.

State and local agencies should:

1. Update or establish and enforce regulatory requirements for lead safe housing that link lead safety to the housing and/or sanitary code.

2 Require that properties that have undergone lead paint abatement or substantial renovation to lead painted surfaces meet the EPA dust clearance testing prior to re-occupancy. Require dust testing in all cases where public health agencies have ordered paint repair, particularly in the homes of children already identified with elevated BLLs.

3 Promote broad use of lead-safe work practices for routine painting and maintenance projects in older homes, and make training in such practices widely available at low or no cost to painters, remodelers, landlords, and maintenance workers.

4. Establish formal agreements among health, social services, housing, and legal agencies to increase the sharing of data, educational information, violations, and success stories.

5. Provide information to caregivers about temporary measures that can reduce lead exposure as described in *Managing Elevated Blood Lead Levels Among Young Children,*[6] as well as information and referral for permanent abatement services.

Recommendations to Health-Care Providers and Community-Based Health and Social Service Agencies

CDC recommends that health care providers continue their traditional role of providing anticipatory guidance as part of routine well-child care, assessing risk for exposure to lead, conducting blood lead screening in children, and treating children identified with elevated BLLs. In addition health-care and social service providers are urged to expand their roles. They should keep abreast of research data that clarify the relationship between lead exposure and neurocognitive development in children. They also can strongly advocate for children and foster lead exposure prevention by helping facilitate implementation of the specific strategic plans to eliminate childhood lead poisoning in their local and state communities. Health-care and social service providers are highly effective child advocates, and their active participation in the process provides the expertise and leadership needed to reach this goal. Health-care and social service providers should:

1. Provide culturally appropriate education to all pregnant women and to families with young children about the principal sources of lead and ways to reduce exposure.

2. Target outreach, education, and screening programs to populations with the greatest risk for lead exposure.

3. Become aware of, and actively support, lead poisoning elimination efforts in the community.

4. Express concern to federal, state, and local policy and decision makers that children live in a lead safe environment and actively support legislation and regulatory initiatives. Advocate for lead-safe, affordable housing by supporting appropriate legislation.

5. Become aware of and comply with lead screening policies issued by Medicaid or state and local health departments.

6. Ensure training of staff members engaged in housing renovation or rehabilitation in lead-safe work practices.

CONCLUSION

The Healthy People 2010 objective to eliminate BLLs >10 µg/dL in children is within our grasp. Research to further characterize and isolate the harmful effects of lead associated with various BLLs will help answer remaining questions and further refine the public health response. However, the approach needed is clear: identify and address existing lead hazards before children are exposed, otherwise hundreds of thousands of children will be placed at risk needlessly. The overall reduction of lead in the environment will benefit all children.

REFERENCES

[1]US Department of Health and Human Services. Healthy People 2010: Understanding and improving health. Washington, DC: US Department of Health and Human Services; 2000. Available at http://www.healthypeople.gov. Accessed 2005 Mar 5.

[2]Meyer PA, Pivetz T, Dignam TA, Homa DM, Schoonover J, Brody D. Surveillance for elevated blood lead levels among children—United States, 1997–2001. MMWR Surveill Summ 2003;52:1–21.

[3]Brown MJ, Shenassa E, Tips N. Small area analysis of risk for childhood lead poisoning. Washington, DC: Alliance to End Childhood Lead Poisoning; 2001.

[4]CDC. Blood lead levels in young children—United States and selected states, 1996–1999. MMWR 2000;49;1133–7.

[5]Kaufmann RB, Clouse TL, Olson DR, Matte TD. Elevated BLLs and blood lead screening among US children aged one to five years: 1988–1994. Pediatrics 2000;106:1–7.

[6]CDC. Managing elevated blood lead levels among young children: Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention. Atlanta: US Department of Health and Human Services; 2002. Available at http://www.cdc.gov/nceh/lead/CaseManagement/caseManage_main.htm. Accessed 2005 Mar 7.

[7]Rogan WJ, Dietrich KM, Ware JH, Dockery DW, Salganik M, Radcliffe J, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med 2001;344:1421–26.

[8]Rhoads GG, Ettinger AS, Weisel CP, Buckley TJ, Goldman KD, Adgate J, et al. The effect of dust lead control on blood lead in toddlers: A randomized trial. Pediatrics 1999;103:551–5.

[9]Tohn ER, Dixon SL, Wilson JW, Galke WA, Clark CS. An evaluation of one-time professional cleaning in homes with lead-based paint hazards. Appl Occup Environ Hyg 2003;18:138–43.

[10]Weitzman M, Aschengrau A, Bellinger D, Jones R, Hamlin JS, Beiser A. Lead-contaminated soil abatement and urban children's blood lead levels. JAMA. 1993;269:1647–54.

[11]Dietrich KN, Ware JH, Salganik M, Radcliffe J, Rogan WJ, Rhoads GG, et al. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics 2004;114:19–26.

[12]Brown MJ, McLaine P, Dixon S, Simon P. A randomized community-based trial of home visiting to reduce blood lead levels in children. Pediatrics. In press 2005.

[13] Moel DI, Sachs HK, Drayton MA. Slow and natural reduction in blood lead level after chelation therapy for lead poisoning in childhood. Am J Dis Child 1986;140:905–8.

[14] Roberts JR, Reigart JR, Ebeling M, Hulsey TC. Time required for blood lead levels to decline in nonchelated children. Clin Toxicol 2001;39:153–60.

[15] Manton WI, Angle CR, Stanek KL, Reese YR, Kuehnemann TJ. Acquisition and retention of lead by young children. Environ Res Sect A 2000;82:60–80.

[16] Clark S, Grote JA, Wilson J, Succop P, Chen M, Galke W, et al. Occurrence and determinants of increases in blood lead levels in children shortly after lead hazard control activities. Environ Res 2004;96:196–205.

[17]CDC. Preventing lead poisoning in young children. Atlanta: US Department of Health and Human Services; 1991.

[18]Bernard SM, McGeehin MA. Prevalence of blood lead levels ≥5 µg/dL among US children 1 to 5 years of age and socioeconomic and demographic factors associated with blood lead levels 5 to 10 µg/dL, Third National Health and Nutrition Examination Survey, 1988–1994. Pediatrics 2003;112:1308–13.

[19] CDC. Strategic plan for the elimination of childhood lead poisoning. Atlanta: US Department of Health and Human Services; 1991.

[20] Grosse S, Matte T, Schwartz J, Jackson R. Economic gains resulting from the reduction in children's exposure to lead in the United States. Environ Health Perspect 2002;110:563–9.

[21] Housing and Community Development Act. 1992. Title X Residential Lead-based Paint Hazard Eduction Act. Pub. L. 102-550, 42 U.S. 4822.

[22] CDC. Preventing lead exposure in young children: A housing-based approach to primary prevention of lead poisoning. Atlanta: US Department of Health and Human Services; 2004.

[23] Bornschein RL, Succop PA, Krafft KM, Clark CS, Peace B, Hammond PB. Exterior surface dust lead, interior house dust lead and childhood lead exposure in an urban environment. In: Trace Substances in Environmental Health; Proceedings of the University of Missouri's annual Conference on Trace Substances in Environmental Health. St. Louis: University of Missouri; 1987;20:322–32.

[24] Lanphear BP, Matte TD, Rogers J, Clickner RP, Dietz B, Bornschein RL, et al. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels. A pooled analysis of 12 epidemiologic studies. Environ Res 1998;79:51–68.

[25] Manton WI, Angle CR, Stanek KL, Reese YR, Kuehnemann TJ. Acquisition and retention of lead by young children. Environ Res 2000;82:60–80.

[26] Wendland-Bowyer W. Worst Michigan Neighborhoods: Lead-poisoned blocks pinpointed. Detroit Free Press 2003 July 29;1.

[27]Meyer PA, Staley F, Staley P, Curtis J, Blanton C, Brown MJ. Improving strategies to prevent childhood lead poisoning using local data. Int J Hyg Environ Health In Press 2005.

[28]CDC. Brief report: Lead poisoning from ingestion of a toy necklace—Oregon, 2003. MMWR 2004;53:509–11.

[29]President's Task Force on Environmental Health Risks and Safety Risks to Children. Eliminating childhood lead poisoning: A federal strategy targeting lead paint hazards. Washington, DC: President's Task Force on Environmental Health Risks and Safety Risks to Children; 2004.

APPENDIX

A REVIEW OF EVIDENCE OF ADVERSE HEALTH EFFECTS ASSOCIATED WITH BLOOD LEAD LEVELS <10 µg/dL IN CHILDREN

Reported by

Work Group of the Advisory Committee on
Childhood Lead Poisoning Prevention

to

CENTERS FOR DISEASE CONTROL AND PREVENTION
National Center for Environmental Health

AUGUST 2005

Appendix Table of Contents

List of Figures

List of Tables

EXECUTIVE SUMMARY

In March 2002, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) established a work group (WG) to review the available evidence of possible health effects of blood lead levels (BLLs) of below 10 micrograms per deciliter (µg/dL), the level of concern currently established by CDC. The WG was charged with designing and following a rigorous protocol to review studies of the health effects of lead exposure at very low BLLs. The workgroup intended to focus on studies of the effects of peak BLLs at <10 µg/dL in children never known to have a BLL exceeding 10 µg/dL. However, there are relatively few such studies and the workgroup decided to review the larger number of studies that could indirectly support or refute the existence of a threshold near 10 µg/dL. Although the workgroup members were the primary authors of this report, the ACCLPP reviewed the document and it was revised based on their comments. The majority of ACCLPP members accepted the findings of the report, with two members dissenting.

Methods

The following criteria were used for selecting relevant studies to review:

- BLLs were measured using graphite furnace atomic absorption spectrometry (GFAAS) or anodic stripping voltammetry (ASV);
- the study was published in English;
- for studies in which IQ or General Cognitive Index (GCI) was a measured outcome, an assessment of the association between BLLs in children and IQ or GCI was included; and
- for studies in which IQ or GCI was not a measured outcome, an assessment of the association between BLLs in children and a specified health outcome was included.

For each relevant study, a structured abstraction was performed that captured the following:

- study location and sample size;
- age at which BLL and cognitive or health outcome was measured;
- the distribution of BLLs (mean or other measure of central tendency and variance) and percentage of participants with BLL <10 µg/dL;

- crude and adjusted regression coefficients relating BLLs to outcome;
- other measures of association (e.g., correlation coefficients); and
- model type and covariates included in adjusted models.

When reviewing the evidence, including indirect evidence from IQ studies, the workgroup considered both alternate explanations for study findings and potential effect of residual confounding.

Conclusions

The main conclusions reached by the WG are summarized as follows.

1. **Does available evidence support a negative association between measured BLLs <10 µg/dL and children's health?**
    - The overall weight of available evidence supports an inverse (negative) association between BLLs <10 µg/dL and the cognitive function of children.
    - A steeper slope in the dose-response curve was observed at lower rather than higher BLLs.
    - The available evidence has important limitations, including the small number of directly relevant cohort studies and the inherent limitations of cross-sectional studies (i.e., the lack of data regarding both BLLs earlier in life and key covariates).
    - For health endpoints other than cognitive function (i.e., other neurologic functions, stature, sexual maturation, and dental caries), consistent associations exist between BLLs <10 µg/dL and poorer health indicators.

2. **Are the observed associations likely to represent causal effects of lead on health?**
    - Though not definitive, the available evidence supports the conclusion that the observed associations between BLLs <10 µg/dL and cognitive function are caused, at least in part, by lead toxicity.
    - The strength and shape of the causal relationship are uncertain because of limitations of the available evidence.

- The health effects of lead are uncertain in individual children who have BLLs measured at a single point in time. Thus, scientific evidence does not provide a basis for classifying individual children with BLLs <10 µg/dL as "lead poisoned," as the term is used in the clinical setting.

- The greatest source of uncertainty in evidence concerning the relationship between BLLs <10 µg/dL and children's cognitive function is the potential for residual confounding, especially by socioeconomic factors.

- The available data for health endpoints other than cognitive function, taken mostly from cross-sectional studies, are limited; therefore, firm conclusions concerning causation can not be made.

Future Research Needs

The WG identified the following research needs to address gaps in the existing base of evidence and to allow for more definite conclusions about the strength and shape of the causal relationship.

- Prospective observational studies designed to minimize the chance of residual confounding.

- Randomized trials to test interventions designed to reduce BLLs <10 µg/dL and assess the impact on children's cognitive development.

- Animal and in vitro studies to identify mechanisms of lead toxicity at low BLLs that could explain the observed steeper slope at lower compared with higher BLLs.

A Review of Evidence of Adverse Health Effects Associated with Blood Lead Levels <10 µg/dL in Children

Reported by

A Work Group of the CDC Advisory Committee on Childhood Lead Poisoning Prevention on Health Effects of Blood Lead Levels <10 µg/dL in Children

Work Group Members

Michael Weitzman, MD
Work Group Chair
Center for Child Health Research
University of Rochester

Joel Schwartz, PhD
Department of Environmental Health
Harvard School of Public Health

David Bellinger, PhD
Neuroepidemiology Unit
Children's Hospital
Harvard Medical School

David A. Savitz, PhD
Department of Epidemiology
University of North Carolina School of Public Health

Carla Campbell, MD
Division of General Pediatrics
The Children's Hospital of Philadelphia

Patrick J. Parsons, PhD
Wadsworth Center for Laboratories and Research
New York State Department of Health

Betsy Lozoff, MD
Center for Human Growth and Development
University of Michigan

Kimberly M. Thompson, ScD
Department of Health Policy and Management
Harvard School of Public Health

Birt Harvey, MD
Pediatrician
Palo Alto, California

This review was prepared for the work group by the following:

Thomas D. Matte, MD, MPH
David Homa, PhD
National Center for Environmental Health
Centers for Disease Control and Prevention
and
Jessica Sanford, PhD
Alan Pate
Battelle Memorial Institute

Abbreviations and Acronyms

AAS	atomic absorption spectrometry
ACCLPP	Advisory Committee on Childhood Lead Poisoning Prevention
ALAD	amino levulinic acid dehydratase
ALAU	urinary amino levulinic acid
ASV	anodic stripping voltammetry
ATSDR	Agency for Toxic Substances and Disease Registry
BLL	blood lead level
EBLL	elevated blood lead level
EP	erythrocyte protoporphyrin
EPA	Environmental Protection Agency
ETAAS	electrothermal atomization techniques based on the graphite furnace
ETS	environmental tobacco smoke
FEP	free erythrocyte protoporphyrin
GCI	General Cognitive Index

GFAAS	graphite furnace atomic absorption spectrophotometry
HOME	Home Observation for Measurement Environment
ICP-MS	inductively coupled plasma mass spectrometry
ID-MS	isotope dilution mass spectrometry
MCV	mean corpuscular volume
MDI	Mental Developmental Index of the Bayley Scales of Infant Development for children
MeHg	methylmercury
MSCA	McCarthy Scales of Children's Ability
NCCLS	National Committee for Clinical Laboratory Standards
NCEH	National Center for Environmental Health
NHANES	National Health and Nutrition Examination Survey
NMDA	N-methyl-D-aspartate
PbB	Blood lead
PCAACN	Practice Committee of the American Academy of Clinical Neuropsychology
PKC	protein kinase C, a calcium dependent enzyme

QA/QC	quality assurance/quality control
SES	socioeconomic status
U-RBP	urinary retinal binding protein
WG	work group
WISC-R	Wechsler Intelligence Scale for Children—Revised
WISC-III	Wechsler Intelligence Scale for Children—Third Edition
WRAT	Wide Ranging Achievement test arithmetic and reading scores
ZPP	zinc protoporphyrin

Background

Charge to the Work Group

In March 2002, the Advisory Committee on Childhood Lead Poisoning Prevention agreed to establish a work group (WG) to review evidence of possible health effects of lead at blood lead levels less than 10 micrograms per deciliter (µg/dL), currently the threshold for defining an elevated blood lead level according to CDC guidelines (CDC 1991). The work group was charged as follows:

> "In October 1991, the Centers for Disease Control and Prevention issued Preventing Lead Poisoning in Young Children. This document heralded a change in the definition of the level for intervention for children with elevated blood lead levels (EBLLs) from a lead level of 25 µg/dL to 10 µg/dL. The report explained that this change was due to new data that indicated significant adverse effects of lead exposure in children at levels once thought to be unassociated with adverse effects. The 1991 document identified a goal to reduce children's blood lead levels below 10 µg/dL. Interventions for individual children were recommended at levels of 15 µg/dL and above.
>
> Research findings published and disseminated since October 1991 suggest that adverse effects from lead exposure and toxicity occur at blood lead levels below 10 µg/dL. Some studies suggest that some effects may be greater at blood lead levels (BLLs) below 10 µg/dL than at higher BLLs. Such research findings raise concerns about the inability to control lead exposure with conventional methods and lend credence to the importance of primary prevention measures to prevent lead exposure to children.
>
> The work group will be convened by the Advisory Committee on Childhood Lead Poisoning Prevention to review the existing evidence for adverse effects of lead exposure and toxicity on children at very low blood lead levels and to focus on effects at levels of 10 µg/dL and below. Rigorous criteria will be established for the literature review. The work group will then create, in conjunction with the committee, a summary of the evidence for publication."

Scientific and Public Health Context for the WG Review

Prior reviews that compiled the extensive evidence from *in vitro*, animal, and human studies established lead as a multi-organ toxicant, including studies showing health effects at BLLs near 10 µg/dL (ATSDR 1999; WHO 1995; USEPA 1986). The published studies include a large body of literature establishing that

lead is a developmental toxicant and that harmful effects of lead on children's development can occur without clinical signs, symptoms, or abnormal routine laboratory tests. In addition, a growing number of studies suggest that BLLs prevalent in the general population are associated with adverse health effects in adults and in the offspring of pregnant women. Finally, in more recent years, bone-lead levels measured by x-ray fluorescence have been used in epidemiologic studies as a measure of cumulative lead exposure. Although these were not considered in this review, a number of studies showing inverse relations of bone-lead level to health in general population samples (e.g., Cheng et al. 2001) add further evidence that cumulative lead exposure may be harmful to health at typical background exposure levels for the population in the United States.

The observation that available epidemiologic evidence does not demonstrate a threshold below which no effect of lead is possible is not new. A review prepared for a 1986 workshop on lead exposure and child development stated, "There is little evidence for a threshold or no-effect level below which the lead/IQ association is not found. IQ deficits have been reported in studies where the mean lead level is 13 µg/dL (Yule et al. 1981) and similar deficits in the Danish study where the primary measure was tooth lead, but BLLs are lower at around 7 µg/dL." (Smith 1989) A review, meta-regression, and reanalysis of existing data (Schwartz 1994) reached essentially the same conclusion. Available data did not suggest a threshold below which no association between BLLs and intelligence in young children was evident. Recent studies (Canfield et al. 2003; Lanphear et al. 2000; Moss et al. 1999; Wu et al. 2003) provided more direct evidence of an association between BLLs and adverse health effects in the domains of cognitive function, neurologic function, growth, dental caries, and onset of puberty at levels well below 10 µg/dL. Thus, a reexamination of this issue is in order.

As evidence from experimental animal studies and human epidemiologic studies has grown, CDC has lowered the BLL considered elevated for the purpose of interpreting clinical test results of an individual child (Table 1). CDC guidelines also have provided criteria for identifying children who have more severe manifestations of lead toxicity and/or a higher risk of lead-related sequellae. For example, CDC's 1975 and 1978 guidelines defined clinical "lead poisoning" on the basis of BLLs, symptoms, and/or levels of erythrocyte protoporphyrin (EP) or other indicators of lead-related biochemical derangements. CDC's 1985 guidelines used the terms "lead toxicity" and "lead poisoning" interchangeably to refer to BLLs $\geq$25 µg/dL with EP $\geq$35 µg/dL. However, the guidelines acknowledged that "lead poisoning" is generally understood for clinical purposes to refer to episodic, acute, symptomatic illness from lead toxicity. CDC's 1985 guidance also cautioned that blood lead thresholds established to guide follow-up and treatment for individual children "should not be interpreted as implying that a safe level of blood lead has been established." In 1991, CDC guidelines more directly acknowledged the difficulty in assigning terms to specific ranges of BLLs given the different settings in which BLLs are interpreted and given that manifestations of lead toxicity occur along a continuum: "It is not

possible to select a single number to define lead poisoning for the various purposes of all of these groups [e.g. clinicians, public health officials, and policy makers]" (CDC 1991). These guidelines also noted, "Some [epidemiologic] studies have suggested harmful effects at even lower levels [than a BLL of 10 µg/dL]."

In addition to these changes in criteria used to evaluate blood lead test results for individual children, recent analyses by the U.S. Department of Housing and Urban Development (HUD 1999) and the U.S. Environmental Protection Agency (USEPA 2000) to support the development of regulations governing lead exposure have assumed that the relation of increasing blood lead to decrements in children's IQ extends to BLLs <10 µg/dL.

As BLLs considered elevated have fallen, measures to reduce or remove lead from a number of sources, including gasoline, soldered food and beverage containers, paint, drinking water, and industrial emissions have resulted in a dramatic decline in BLLs in the United States since the mid-1970s (Pirkle et al. 1994). The Second National Health and Nutrition Examination Survey (NHANES II) conducted from 1976 to 1980 demonstrated that, among U.S. children ages 6 months through 2 years, 84% of white children and more than 99% of black children had BLLs ≥10 µg/dL, and the median BLLs were 14 and 19 µg/dL, respectively (Mahaffey et al. 1982). A decline in BLLs during the course of that survey was noted, paralleling the falling consumption of leaded gasoline (Annest et al. 1983). A continued decline in BLLs was evident in subsequent NHANES surveys (Pirkle et al. 1994; NCEH 2003) and in clinical blood-lead test data compiled by state and local health agencies (Hayes et al. 1994; CDC 2003). Nationally, it is estimated that by 1999-2000, the prevalence of BLLs ≥10 µg/dL among children 1 to 5 years of age had fallen to 2.2% and the median level to 2.2 µg/dL (NCEH 2003).

Although these reductions in lead exposure represent great progress, scientific advances have shed light on harmful effects of lead at levels of exposure once thought safe. In addition, industrial activity has widely dispersed lead in the environment from naturally occurring deposits. As a result, even at the lower exposure levels that prevail today, typical body burdens of lead are likely to be much higher than those present in pre-industrial humans, which by one estimate corresponded to a BLL of 0.016 µg/dL (Smith et al. 1992). Therefore, the potential for additional subclinical adverse effects of lead from currently prevailing exposures deserves careful study. Finally, although falling BLLs have benefited all demographic groups (Pirkle et al. 1994), stark demographic and geographic disparities continue to reflect the historic pattern; the risk of elevated BLLs in communities where poverty and older (i.e., that built before 1950) housing are prevalent remains several fold higher than the national average (Lanphear et al. 1998).

Review Methods

Scope and Approach

Given the charge to the work group and the scientific and public health context, the WG did not attempt a comprehensive review of all evidence relating lead exposure to health. Instead, the WG set out to answer the following questions:

1. Does available evidence support negative associations between health indicators and children's blood lead levels measured <10 µg/dL?

2. Are the observed associations likely to represent a causal effect of lead on health?

To address these questions, the WG established criteria (see Methods) for published studies that would address the first question. In addition, the work group identified issues relevant to making causal inference from any observed associations. Identifying such issues is an essential step in interpreting evidence relevant to the WG charge. Human studies to assess potential health effects of environmental toxicants, such as lead, are usually observational in design (i.e., the health status of participants is related to some measure of exposure, dose, or body burden that varies on the basis of environmental factors and not experimental manipulations by the investigator). For ethical reasons, the limited number of human experimental studies that have evaluated causal relations between toxicant exposures and health usually have involved attempts to reduce exposure or body burden and assess the impact on health status. Such studies of lead-exposed children are rare, and to date none have focused on children with BLLs <10 µg/dL.

Observational studies have inherent limitations—not specific to studies of lead toxicity—with the potential to produce biased results. Biases from observational studies can obscure true causal effects of toxicant exposures or produce associations between toxicant exposures and health status when no causal relation is present. Thus, statistical associations from individual observational studies or multiple studies subject to similar biases cannot establish causal relationships; additional, non-statistical criteria may be used to evaluate such evidence. Although causal criteria have been stated in various ways, the Surgeon General's Report on Smoking and Health (U.S. Public Health Service 1964) provides a useful set of criteria. They include:

- The consistency of the association. Is a similar association observed across studies with varying methods and populations?

- The strength of the association. The strength of an association is the extent to which the risk of a disease or a measure of health status varies in

relation to exposure and can be expressed, for example, as a relative risk or regression coefficient. It is distinguished from the statistical significance of an association that reflects both the strength of the association and the sample size. An additional criterion, specificity of the association, is closely related to strength of the association and is considered less important in the context of multifactorial health conditions.

- The temporal relationship of associated variables. Does the hypothesized causal exposure occur before the health outcome associated with it?

- Coherence of the association. Is the observed association consistent with other relevant facts including, for example, experimental animal studies and the descriptive epidemiology of the health condition under study?

The application of these criteria does not provide a clear demarcation for concluding definitive proof of causation versus inadequate evidence. Rather, the more the available evidence meets these criteria, the greater the confidence in causal inference about an association. Consistent with these criteria, the WG identified several issues specifically relevant to inferring causality from associations (or the lack of associations) of BLLs to health measures observed in studies of low-level lead exposure. These potential biases are not unique to studies of children with BLLs $\leq$10 µg/dL (e.g., Smith 1989). However, the larger number of human and experimental animal studies (including primate studies) and the nature of observed health effects associated with higher BLLs have conclusively demonstrated the adverse health effects of lead. However, far fewer studies of possible health effects of BLLs <10 µg/dL have been conducted, and the relative importance of some sources of bias may be greater at these lower levels. Therefore, the work group considered several issues in interpreting the findings of available studies (see Discussion).

At the time of the WG's review, a consortium of investigators from several longitudinal studies of lead exposure and cognitive function in children were conducting a reanalysis of data pooled from these studies. These studies included serial measures of blood lead level, cognitive function, and a large number of potential confounders, thus providing stronger evidence than is available from cross-sectional studies. A focus of the pooled reanalysis involved studying the shape of the association between postnatal lead exposure at low levels and measured IQ (B. Lanphear, personal communication, 2003). The WG reviewed published reports from individual cohort studies from which data were pooled, but the final results of this pooled reanalysis were not available for inclusion in the WG report. [Note: Results of the pooled renanlysis were published (Lanphear et al 2005) after the WG finished its review.]

Because of the nature of its charge, the WG did not develop policy recommendations or address questions relevant to such recommendations. Such policy decisions and questions will, if appropriate, be considered by the full ACCLPP after reviewing the findings of this report.

Criteria for Relevant Studies

The WG initially considered, then rejected, limiting its review to studies for which published results provide direct comparisons between children with varying BLLs <10 µg/dL. Such a review would include a relatively small number of studies. Instead, the group decided that the larger number of studies that have included IQ as an outcome could, collectively, indirectly support or refute the existence a threshold near 10 µg/dL for the blood lead–IQ association. The rationale for this approach is based on that used in a review and metaregression reported by Schwartz (1994) and outlined in the following paragraphs.

Suppose that, hypothetically, a threshold exists near 10 µg/dL, above which mean IQ decreases linearly with increasing blood lead, with a slope equal to x and below which mean IQ is not associated with blood lead[1] (see Figure 1—Hypothesized "true" relation A). In studies of children who have BLLs <10 µg/dL, estimated slopes would be, in the absence of sampling error, equal to 0. For studies in which all children have BLLs above the threshold, the estimated slope would be, again ignoring sampling error, equal to x. For studies in which some children have blood lead above and others below the threshold, estimated slopes will vary between 0 and x as shown in Figure 1. Thus, if regression coefficients estimating the IQ–blood lead slope are less negative (approaching 0) in populations with lower mean BLLs than in populations with higher mean levels, a threshold near 10 would be suggested. The absence of such a trend or an increase in slopes with decreasing mean blood lead level of the population studied would provide evidence against such a threshold and instead support "true" relations B and C, respectively. This ideal hypothetical case presumes that effect sizes from the studies compared are based on models that correctly specify the form of the BLL–IQ relation and that factors that might modify the relation do not vary across studies.

Because of this approach, studies that assessed the association between blood lead and measured IQ were included in this review, even if the published results did not examine blood lead–IQ associations limited to BLLs <10 µg/dL (as was true in most cases). An additional reason for considering studies that measured IQ was the relationship of IQ to other outcomes of policy and public health importance including educational success and earnings potential (Grosse et al. 2002). Because the McCarthy Scales of Children's Ability (MSCA) General Cognitive Index (GCI) was used in a number of studies to measure cognitive function in preschool children and because GCI and IQ scores have similar distributions, studies using GCI as an outcome were also included in this review.

---

[1]The concept of a threshold existing for the population makes little sense toxicologically since even if individual thresholds exist, these are likely to vary. Nonetheless, the threshold concept plays a major role in regulatory toxicology, and it only becomes clear in cases like lead that such constructs can be highly problematic.

The following criteria were used to select relevant studies to review for this report:

1. Blood lead levels were measured using graphite furnace atomic absorption spectrophotometry (GFAAS) or anodic stripping voltametry.

2. The study was published in English.

In addition,

For studies in which IQ or GCI was a measured outcome, the

> study analyses included an assessment of the association between BLLs measured in children and IQ or GCI.

For studies in which IQ or GCI was not a measured outcome, the

> study analyses included an assessment of the association between BLLs <10 µg/dL measured in children and a health outcome. The assessment could either be formal (e.g., non-linear modeling, linear modeling restricted to populations with all or at least 95% of children having BLLs <10 µg/dL, statistical comparison of two or more sub-groups with BLLs <10 µg/dL) or informal (e.g., graphical display of results permitting visual assessment of blood lead–outcome relation in the range <10 µg/dL).

Literature Search

To identify potentially relevant articles, a comprehensive report published by the Agency for Toxic Substances and Disease Registry (ATSDR 1999) was reviewed first to identify cited articles that related to low-level lead exposure in children. The list of potentially relevant citations identified in the ATSDR report was supplemented by three computerized literature searches, using Dialog® to search Medline, Toxfile, and other bibliographic databases. Search terms (see Appendix A) were chosen to identify articles reporting on blood lead measurements and one or more domains of health related to lead exposure including neurodevelopment, cognitive function, intelligence, behavior, growth or stature, hearing, renal function, blood pressure, heme synthesis, hematopoiesis, and Vitamin D metabolism. The first search spanned articles published from 1995 through 2002 and indexed as of September 2002, the month and year that the initial search was performed. The second search was performed in April 2003 and spanned the period 2002 through the search date. A third search, spanning the years 1990 through 1996, was performed when a relevant article not cited in the ATSDR toxicological profile was identified by one of the work group members. In addition, potentially relevant articles were identified by work group members and through citations in articles identified previously.

Abstracts were reviewed initially. If they were ambiguous or if they suggested the article was relevant, full articles were checked for relevance. Articles deemed relevant were abstracted for this report. Appendix A summarizes the number of possibly relevant references identified, full articles checked for relevance, and relevant articles abstracted and considered in the review.

Structured Abstracts

For each relevant study, a structured study abstraction was performed that captured the following information: the study location, sample size, age at which blood lead was measured, age at which the outcome was measured, available information about the blood lead distribution (including mean or other measure of central tendency, variance, and percent of participants with BLLs <10 µg/dL), the crude and adjusted regression coefficients relating blood lead to outcome (if available), the type of model fit (linear, log linear, or other), and the covariates included in the adjusted model. If regression coefficients were not available, other measures of association reported (e.g., correlation coefficients) were noted. Because some studies fit multiple blood lead-outcome models (e.g., cohort studies with blood lead and IQ measured at multiple ages), relevant information about each model estimated was abstracted. For IQ studies, covariates measured and not included in adjusted models were recorded when available.

Review of Cohort Study Methods

Among relevant published results were those from cohort studies specifically designed and conducted to study the relation of BLLs to children's cognitive function and other health outcomes. Because these studies had the strongest and best-documented study designs for this review, methods used for blood lead measurement and neuropsychological assessment were summarized for these studies. This information was collected from published studies; in some cases, the studies were supplemented by information provided through correspondence with the investigators.

Results

Studies Relating Postnatal Lead Exposure to IQ or General Cognitive Index

Studies in which IQ or GCI were measured as an outcome and other criteria were met included 23 published reports from 16 separate study populations. Results from these studies are summarized in Table 2 (full scale IQ and GCI), Table 3 (performance IQ), and Table 4 (verbal IQ). Within each table, results are grouped according to the age at blood-lead measurement and age at outcome measurement;

each grouping displays results sorted according to the measure of central tendency of the blood-lead distribution. Because some studies used linear models (BLLs were untransformed) and some used log-linear models (BLLs were log transformed), estimated regression coefficients were, when possible, used to calculate the estimated change in IQ or GCI corresponding to a blood lead increase from 5 to 15 µg/dL to allow for comparisons across studies. Covariates included in adjusted models are grouped into several broad domains that were addressed in most of the published studies.

Among studies that provided results for the size and direction of the associations between BLLs and Full Scale IQ or GCI, regardless of statistical significance, a majority revealed that both crude and adjusted associations were consistent with an adverse effect—IQ decreases with increasing levels of blood lead. In most cases, covariate adjustment attenuated, but did not eliminate, these estimated associations. Findings for performance and verbal IQ were similar, with some studies showing stronger associations of lead with performance IQ and others with verbal IQ.

Notable exceptions to this pattern, however, were found. Results from the Cleveland cohort (Ernhart et al. 1987, 1988, 1989) indicated a crude inverse association between blood lead and IQ but no association with covariate adjustment. In the Cincinnati and Boston cohort studies, BLLs measured at or below 12 months of age showed no association or a slightly positive association with covariate-adjusted IQ (Dietrich et al. 1993; Bellinger et al. 1992). Though published results from a cohort study in Costa Rica (Wolf et al. 1994) did not provide the size and direction of the estimated blood lead–IQ slope, unpublished results provided to the WG did show covariate-adjusted IQ increasing with BLL (B. Lozoff, personal communication 2003). The estimated BLL–IQ association in the Kosovo cohort was strengthened substantially with covariate adjustment (Wasserman et al. 1997).

No trend toward attenuation of the association between blood lead and IQ (or GCI) across studies with decreasing average BLLs is evident (Figures 2 and 3). In one of these studies, analyses were presented that provide more direct information concerning the association between BLL and cognitive function at BLLs <10 µg/dL. The steepest estimates of blood lead–IQ slope from the Rochester (Canfield et al. 2003) studies were based on analyses restricted to children whose measured BLL never exceeded 10 µg/dL. The estimated slope was substantially larger than those estimated from the entire study population (9.2 versus 5.3 IQ point reduction in covariate adjusted IQ for BLL increase from 5 to 15 µg/dL). Canfield and his colleagues (2004) also reported a non-linear model supporting a steeper blood lead–IQ slope at lower levels. Though published as a letter to the editor, rather than in a peer-reviewed article (and therefore not included in the structured review), similar findings were reported for a reanalysis of the Boston cohort: a steeper BLL–IQ slope in the population of children whose measured BLLs never exceeded 10 µg/dL, compared with the entire study population (Bellinger et al. 2003).

Most of the published studies included at least one measure of socio-economic status. All of the published results from cohort studies were adjusted for Home Observation for Measurement Environment (HOME) score and birth weight; all except the Costa Rica cohort were adjusted for a measure of maternal intelligence. A reanalysis of the data from the Costa Rica cohort with adjustment for maternal IQ was consistent with the original finding of a non-significant positive blood lead–IQ slope (B. Lozoff, personal communication, 2003). Prenatal exposure to maternal smoking was adjusted in the majority of studies, whereas only in the Port Pirie cohort was a measure of postnatal environmental tobacco smoke exposure included. Iron deficiency anemia was included as a covariate in results from the Costa Rica study, which found no association of lead and IQ; the inverse blood lead–IQ associations in the Rochester study (Canfield et al. 2003) and the Karachi study (Rahman et al. 2002) were adjusted for serum transferrin saturation and hemoglobin, respectively. In addition, in the Kosovo study (Wasserman et al. 1997), alternative models were fit with adjustment for hemoglobin, resulting in no appreciable change in the lead coefficient.

Not all studies reported regression coefficients that could be used to estimate the change in IQ associated with a BLL change of 5 to 15 µg/dL, and the overall pattern of results summarized above and in Figures 2 and 3 might have been altered had regression coefficients been available from all studies. For example, a member of the WG provided results of reanalysis of the data from the Costa Rica cohort, which showed no evidence of an inverse relation of BLL to IQ with adjustment for maternal IQ and other covariates used in the published result (Wolff et al. 1994; B. Lozoff, personal communication, 2003).

Studies of Health Endpoints Other than IQ and CGI

More stringent criteria were required for inclusion of studies in this review if they assessed health endpoints other than general intelligence as measured by IQ or GCI. These studies are summarized in Table 5 and are described in the following paragraphs.

Cognitive Function

Lanphear et al. (2000) analyzed data on BLLs on performance on standardized tests of cognitive function of 4,853 children age 6 through 16 years who were evaluated as part of the NHANES III survey, a multiphasic health interview and examination survey of a stratified probability sample of the U.S. population, carried out from 1988 through 1994. In this population, with a geometric mean BLL of 1.9 µg/dL and 98% of children having BLLs <10 µg/dL, significant inverse relations were found between BLLs and scores on the Wide Ranging Achievement Test (WRAT) arithmetic and reading scores and on the WISC-R block design and digit span subscales. The relationships were strengthened (the slopes became more negative) as analyses were progressively restricted to children with lower BLLs. Stone et al. (2003) reanalyzed the data used by Lanphear et al. (2000). While the

results they present are largely consistent with the findings of Lanphear et al., they provided a critique of the validity of the NHANES III data for evaluating lead-related impacts on neuropsychological development in children. Their critique did not provide results that could be summarized in the structured abstract format used in this report, so a discussion of the Stone et al. critique is found in Appendix B.

Other Neurobehavioral Measures and Visual Function

Three reports (Altman et al. 1998; Walkowiak et al. 1998; Winneke et al. 1994) describe the relation of blood lead to several neurobehavioral measures and to visual function assessed in 384 school children 5 to 7 years of age in three cities in Eastern Germany. Blood lead levels were generally low, with a geometric mean of 4.25 µg/dL and 95% of children having BLLs <10 µg/dL. Walkowiak et al. (1998) reported a significant negative association between BLLs and WISC vocabulary subscale scores. Continuous performance test false positive and false negative responses increased with increasing BLLs. Other measures inversely related to BLL included performance on a pattern comparison test, finger tapping speed (Winneke et al. 1994), and visual evoked potential interpeak latency (Altman et al. 1998). Mendelsohn and colleagues (1999) found a 6 point deficit in the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development for children aged 12 to 36 months with BLLs 10-24 µg/dL compared with children who had BLLs <10 µg/dL. A scatterplot of covariate-adjusted MDI versus blood lead suggests the association continues at BLLs <10 µg/dL.

Neurotransmitter Metabolite Levels

Among children ages 8 through 12 years with mean BLL of 3.95 µg/dL, a direct relation of blood lead (PbB) to higher urinary homovanillic acid, a neurotransmitter metabolite, was found for the subset of children with BLLs >5 µg/dL (Alvarez Leite et al. 2002).

Growth

Two studies examined the relation of BLLs <10 µg/dL to somatic growth. Ballew et al. (1999), using the NHANES III data, found that BLLs were inversely related to height and to head circumference among children 1 to 7 years of age. A birth cohort of children in Mexico had BLLs and head circumference assessed every 6 months from 6 to 48 months of age, during which time the median BLL varied from 7 to 10 µg/dL (Rothenberg et al. 1999). Most postnatal blood lead measures were inversely correlated with covariate adjusted head circumference, with the strongest relation found between blood lead at age 12 months and head circumference at 36 months. Kafourou and colleagues (1997) reported a significant negative association between BLL and covariate-adjusted head circumference and height in a population of children with a median BLL of 9.8 µg/dL, with a scatterplot suggesting the relation extends to BLLs <10 µg/dL.

Sexual Maturation

Two studies, both based on analyses of the NHANES III data, found an association between BLLs <10 µg/dL and later puberty in girls. Selevan et al. (2003) found that BLLs of 3 µg/dL, compared with 1 µg/dL, were associated with significant delays in breast and pubic hair development in African American and Mexican girls. The trend was similar, but not significant, for non-Hispanic white girls. Age at menarche was also delayed in relation to higher BLLs, but the association was only significant for African-American girls. Wu et al. (2003) reported similar findings for girls in the NHANES III population but did not stratify the analysis by racial/ethnic group. Compared with BLLs 2.0 µg/dL and below, BLLs of 2.1–4.9 µg/dL were associated with significantly lower odds of attaining Tanner 2 stage pubic hair and menarche; whereas no overall association with breast development was noted.

Dental Caries

In the NHANES III population, the odds of having dental caries, comparing children ages 5–17 years in the middle tertile of the BLL distribution (range of BLLs 1.7–4.1 µg/dL) with those in the lowest tertile, was significantly elevated (odds ratio=1.36, 95% confidence interval 1.01–1.83) (Moss et al. 1999). Gemmel et al. (2002) evaluated the association between BLLs and caries in 6–10 year old children from urban communities in eastern Massachusetts (mean BLL=2.9 µg/dL) and a rural community (mean BLL=1.7 µg/dL) in Maine. They found a significant direct relation of BLL to caries in the former, but not the latter population in which a non-significant decrease in caries' frequency was observed with increasing blood lead. In the urban population, the trend of increasing caries with PbB level was evident comparing children with BLLs of 1, 2, and 3 µg/dL.

Blood pressure and renal function

Among 66-month-old children in Kosovo, a graph depicting adjusted mean systolic and diastolic blood pressure versus BLL showed no consistent trend across 4 groups of children (approximately 28 per group) with BLLs spanning a range from approximately 5 to 10 µg/dL (Factor Litvak et al. 1996). In a population of 12- to 15-year-old children living near a lead smelter and a control group, urinary retinal binding protein (U-RBP) was found to be significantly associated with BLL in a stepwise regression. When urinary RBP excretion was examined by BLL tertiles, significantly lower U-RBP was seen in the group with BLL < 8.64 µg/dL compared with BLLs 8.64–12.3 µg/dL.

Heme synthesis biomarkers

Roels et al. (1987) studied the relations of PbB to heme synthesis biomarkers and reported no evident threshold for inhibition of aminolevulinic acid dehydratase synthesis at PbB as low as 8–10 µg/dL, while the threshold for increasing erythrocyte

protoporphyrin levels was evident in the range of 15–20 µg/dL, consistent with other studies, including two meeting criteria for inclusion in this report (Rabinowitz et al. 1986; Hammond et al. 1985).

Discussion

Question 1: Does available evidence support an inverse association between children's blood lead levels <10 µg/dL and children's health?

The weight of available evidence, both indirect and direct, clearly favors an inverse association between these BLLs and cognitive function among children. The indirect evidence comes from the great majority of studies that have examined BLLs in relation to standardized measures of overall cognitive function; these studies reveal an inverse relationship and no trend toward weaker associations in populations with lower BLL distributions. More direct evidence of such an association comes from a recent analysis of data from a cohort designed from the start to study the relation of blood lead to child development (Canfield et al. 2003). This study demonstrated that the inverse relation between BLL and cognitive function exists and is stronger at BLLs <10 µg/dL compared with higher BLLs; it also does not show a threshold within the range of routinely measured BLLs below which no association was present. A recent letter to the editor described a reanalysis of the Boston cohort data (Bellinger et al. 2003) with findings consistent with Canfield et al (2003). Several recent analyses of data from the NHANES III and other populations also provide direct evidence of associations that imply adverse impacts of lead on indicators of children's neurocognitive development, stature, head circumference, dental caries, and sexual maturation in girls, occurring at measured BLLs <10 µg/dL. Though the number of studies providing direct evidence of associations at BLLs <10 µg/dL is limited and most are cross-sectional, they provide supporting evidence of an association in the context of the much larger number of studies that relate slightly higher levels of lead in blood to impairments of children's health.

Question 2: Are the observed associations likely to be causal?

Though the weight of evidence favors an association between children's BLLs <10 µg/dL and health and, indeed, suggests that such relationships become steeper as BLLs decrease, the WG considered a number of concerns that must be addressed in judging whether such associations are likely to be causal. The work group concluded that collectively, these concerns and limitations of the available evidence preclude definitive conclusions about causation and leave considerable uncertainty concerning the magnitude and form of causal relations that may underlie these associations. At the same time, available evidence does not refute the interpretation that these associations are, at least in part, causal. These issues are discussed individually in the following text, followed by overall conclusions.

Biologic Plausibility

Evidence from experimental animal and in vitro studies, which are not subject to confounding influences of concern in human observational studies, can establish causation and identify mechanisms that might be operative in humans assuming a suitable animal model. Thus, evidence from experimental animal and in vitro studies can help to assess potential dose–response relationships and thresholds within the context of any uncertainty added due to interspecies extrapolation. Therefore, an important consideration in judging whether associations between BLLs <10 µg/dL and health outcomes are likely to represent causal relationships is whether such relationships are biologically plausible on the basis of experimental animal and in vitro studies. These studies can also help to assess potential dose–response relationships and thresholds, but extrapolation from in vitro and animal models to human health risk adds additional uncertainty.

Lead is the most extensively studied environmental neurotoxicant. Animal and in vitro studies have provided abundant information concerning biochemical and physiologic changes caused by lead. Along with clinical and epidemiologic data, this evidence has clearly established that lead is toxic to the developing and mature nervous system. These data have been extensively reviewed elsewhere (USEPA 1986; ATSDR 1999; WHO 1995; Davis et al. 1990) and are not exhaustively reviewed here. Rather, this discussion highlights evidence concerning potential mechanisms of lead toxicity and data from animal studies that are relevant to the biologic plausibility of the toxicity of lead, especially to the developing nervous systems of children exposed at BLLs <10 µg/dL.

Although the precise mechanisms of action and their relative importance in different manifestations of lead toxicity are not known definitively, in vitro studies demonstrate that lead can interfere with fundamental biochemical processes. At the most basic level, many of the proposed mechanisms of lead toxicity involve binding to proteins and/or interference with calcium dependent processes (Goldstein 1993).

For some of the adverse health effects of lead (e.g., anemia), the lead-associated biochemical changes that contribute to the effect in humans are well understood. Lead interferes with heme synthesis in part by binding to sulfhydryl groups in the enzyme amino levulinic acid dehydratase (ALAD) (ATSDR 1999), which is especially sensitive to inhibition by lead (less than 0.5 micromoles per liter in vitro) (Kusell et al. 1978; Dresner et al. 1982). This inhibition causes delta amino levulinic acid, a potential neurotoxic agent, to accumulate. Lead also inhibits ferrochelatase, an enzyme catalyzing the incorporation of iron into protoporphyrin to form heme. This inhibition also may involve lead binding to protein sulfhydryl groups.

Although anemia and accumulation of protoporphyrin IX in erythrocytes are the most obvious consequence of impaired heme synthesis, this pathway could play a role in lead-related impairment of cellular function throughout the body (USEPA

1986). By interfering with heme synthesis and perhaps by inducing enzymes that inactivate heme, lead can decrease the levels of heme in body tissues (Fowler et al. 1980). A reduction in the body heme pool may impair heme-dependent biochemical processes, such as cellular respiration, energy production, and the function of the cytochrome p-450 monooxygenase system involved in detoxification of xenobiotics and in transformation of endogenous compounds such as vitamin D precursors (USEPA 1986).

For other more complex health effects of lead, such as impaired neurocognitive development and behavioral change, a number of plausible mechanisms have been demonstrated in animal and in vitro systems. Lead's impact on one or more biochemical systems needed for normal brain development and function could account for the neurobehavioral effects observed at low levels of exposure. Especially sensitive to lead in vitro is the activation of protein kinase C (PKC), a calcium dependent enzyme. Lead binds more avidly to PKC than its physiologic ligand, calcium, causing activation at picomolar concentrations in vitro. (Markovac and Goldstein 1988). The interactions between lead exposure and PKC activity in the brain are complex; chronic lead exposure may reduce activity of PKC associated with cell membranes while increasing cytosolic PKC activity. Lead effects on PKC activity have been proposed to mediate potential impacts of lead on cell growth and differentiation, including that of neural cells (Deng and Poretz 2002), the blood-brain barrier, and long-term potentiation (a process related to memory) (Hussain et al. 2000). Lead also interferes with calcium-dependent control of neurotransmitter release at presynaptic nerve terminals; it may thereby interfere with signaling between neurons and possibly with development of neural networks. In both animal and in vitro studies, lead has been demonstrated to interfere with neurotransmitter systems, including interfering with dopamine binding and the inhibition of N-methyl-D-aspartate (NMDA) receptor activity.

The large body of evidence from animal studies of lead exposure and neurodevelopment supports a causal effect that is persistent following exposure early in life and that generally parallels human studies in terms of the domains of function that are impaired (WHO 1995). Concerning blood lead–effect relationships, direct cross-species comparisons of BLLs cannot be made (Davis et al. 1990), and most animal studies demonstrating lead-related developmental neurotoxicity involved doses that produced BLLs well above 10 µg/dL. However, available studies provide strong evidence of adverse effects in animals with BLLs near 10 µg/dL. It should be noted that BLLs cited in animal studies generally involve mean levels achieved in experimental groups with individual animals varying, sometimes substantially, around that mean.

Non-human primates experimentally exposed to lead early in life demonstrate dose related impairments in learning and behavior (Bushnell and Bowman 1979; Rice 1985; Levin and Boman 1986). One study, involving monkeys dosed during the first 200 days of life with 100 µg/kg/day lead or 50 µg/kg/day lead resulting

in average peak BLLs of 25 and 15 µg/dL respectively, showed deficits relative to control monkeys (dose=0µg/kg/day lead; average peak BLL=3 µg/dL) at age 3 years on "discrimination reversal" tasks (the animals are taught to respond to a cue and then the cue is changed and the ability to learn the new cue, with and without irrelevant cues, is measured). At the time of testing, mean BLLs in the exposed groups had fallen to 13 and 11 µg/dL, respectively. Both exposure groups showed deficits, but deficits in the lower exposed group were evident only with more complex tasks (e.g., including irrelevant cues) (Rice 1985). The same monkeys showed persistent impairments at 9 to 10 years of age (Gilbert and Rice 1987). Experimental studies in rats have demonstrated behavioral effects at mean BLLs of 10–20 µg/dL (Cory-Slechta et al. 1985; Brockel and Cory-Slechta 1998).

There is uncertainty about the relationship of the tissue or cellular levels of lead linked to physiologic changes in animal and in vitro studies to the corresponding human blood lead level required to produce such levels at target sites. Although most (90 to 99%) lead in whole blood is in red cells, plasma lead level likely better reflects lead transferred from bone stores and available for transfer to target tissues (Cake et al. 1996). Because red cells have limited capacity to accumulate lead, the relation of blood lead to plasma or serum lead is non-linear with serum lead increasing more rapidly at higher BLLs (Leggett 1993). In subjects with a mean BLL of 11.9 µg/dL, plasma lead levels ranged from 0.3 to 0.7% of whole BLLs (Hernandez-Avila et al. 1998). The relation of plasma serum levels in intact animals to tissue levels measured in in vitro models is probably more complex. It is also uncertain whether in vitro studies demonstrating possible mechanisms for low-level lead toxicity reflect mechanisms operative in the intact animal. For example, Zhao et al. (1998) found that lead interfered with PKC in choroid plexus endothelial cells in a dose dependent fashion over the concentration range of 0.1-10 micromolar. However, no effect on choroid plexus PKC activity was seen in an in vivo model.

Conclusions: The fundamental nature of biochemical and physiologic changes linked to lead in in vitro and experimental animal studies illustrates potential mechanisms for lead toxicity that might be operative in humans at very low exposure levels. Experimental animal studies support the biologic plausibility of adverse health effects of lead in children at BLLs near 10 µg/dL. However, definite conclusions concerning the relationship of health status of children and BLLs <10 µg/dL cannot be drawn from these studies because of limitations of extrapolating from in vitro systems to intact animals and from animals to humans and because of the limited amount of data available from studies of animals dosed to produce a range of BLLs less than 10 µg/dL. Data from primates, which can most readily be extrapolated to humans, are especially limited.

On the other hand, given the uncertainty in extrapolating across species, the fact that animal test systems cannot match the complexity of learning tasks faced by young children, and the relatively small relative difference in BLLs shown to be harmful in animals and those at issue in children, adverse health effects in children at BLLs <10 µg/dL are biologically plausible.

Blood Lead Measurement

The precision and accuracy of blood-lead measurements performed in an epidemiologic study impacts observed results. If BLLs are systematically over or underestimated, biases in estimated blood lead response relationships and/or no effect thresholds will result. All blood lead measurements involve some random error, which, if a true association between blood lead and health exists, will tend to bias estimates of the relation toward the null (i.e., no effect) value. The quality of blood lead measurements varies between laboratories, between different analytical technologies, and between different specimen collection techniques. In addition, laboratory performance for blood lead has improved markedly over the last three decades and continues to improve as new analytical technologies are developed. Each of these factors becomes important in assessing the quality of blood-lead measurements used in published studies. In this section, specimen collection and laboratory factors that can affect blood-lead precision and accuracy are considered.

The widespread industrial use and dispersal of lead, particularly during the last century, has ensured that it is a ubiquitous contaminant. Therefore, to prevent false-positive results, stringent procedures are necessary to reduce environmental contamination of blood collection devices and supplies. Consequently, venous blood collected using evacuated tubes and needles certified as "lead-free" is considered the most appropriate specimen for blood lead measurements (NCCLS 2001). However, collection of venous blood from pediatric subjects is sometimes difficult; thus, capillary blood from a finger puncture is used widely for screening purposes. Published studies have compared the quality of blood lead results for capillary and venous specimens drawn simultaneously (Schlenker et al. 1994; Schonfeld et al. 1994; Parsons et al. 1997). With stringent precautions, particularly rigorous hand washing, contamination errors can be held to <4% (Parsons et al. 1997). Therefore, although venous blood is preferable for epidemiologic studies of environmental lead exposure, use of capillary blood is acceptable if collected by staff specially trained in the technique using devices certified as "lead-free." Data should be provided showing an acceptably low rate of contamination errors and low mean bias in the capillary BLLs as collected using the study protocol.

Currently, three analytical approaches to blood lead measurement are used: atomic absorption spectrometry (AAS); anodic stripping voltammetry (ASV), and inductively coupled plasma mass spectrometry (ICP-MS). A thorough discussion of these analytical techniques is beyond the scope of this report; however, a comprehensive assessment has been published by the National Committee for Clinical Laboratory Standards (NCCLS 2001). Briefly, the older flame atomization AAS methods, which include MIBK-extraction and Delves cup, are less precise, with a detection limit near 5 µg/dL for Delves cup (Parsons and Slavin. 1993). Thus, they are not well suited for examining relationships between BLLs <10 µg/dL and health. The electrothermal atomization techniques based on the graphite furnace (ETAAS) are more precise and more sensitive and, therefore, have better

detection limits, typically around 1.0 µg/dL. A direct comparison between ASV and ETAAS techniques (Bannon et al. 2001) shows that the latter has better precision and better accuracy. Nonetheless, when operated in experienced hands and with a stringent quality assurance/quality control (QA/QC) program that includes calibration standards traceable to the mole via isotope dilution mass spectrometry (ID-MS), ASV can deliver blood-lead measurements with accuracy and precision sufficient to examine health effects at BLLs <10 µg/dL (Roda et al. 1988).

In order to assess the accuracy and precision of blood-lead measurements made for research purposes, investigators should provide information on the laboratory's performance in measuring external quality control samples and on the between-run standard deviation for routine quality control samples that span the relevant blood lead range for a given study.

Conclusions: The key considerations relevant to judging the accuracy and precision of blood lead measurements in published studies include the type and quality of blood specimen collected, analytical methodology used by the laboratory, and internal and external QA/QC procedures in place. For the purpose of studying the relationship between BLLs <10 µg/dL and health endpoints venous samples are preferred and capillary samples are acceptable with evidence of a rigorous protocol to control contamination errors. Acceptable analytic methods include electrothermal AAS, ASV, and ICP-MS. Information on laboratory performance (i.e., accuracy and precision) from external and internal quality control data should be provided.

To be included in this review, studies were required to have employed suitable measurement methods. In addition, venous samples were used for most postnatal blood lead measurements in the relevant cohort studies (Table 6) and others cited in this report. Given this and the blood lead quality control procedures reported in the most informative studies, it is highly unlikely that systematic errors in measurement in the relevant studies were sufficient to bias the observed blood lead distributions enough that associations observed <10 µg/dL were attributable to BLLs above that threshold. Random variation in BLLs and random error in BLL measurement would make it difficult to collect sufficient data to identify a threshold, if one were to exist.

Blood Lead Age Trend, Tracking, and Inference Concerning Blood Lead — Effect Relations in Children

Age-related changes in children's BLLs and within-child correlation of blood lead measured at different ages may influence observed associations between BLL and health at a given age. In addition, the biologic impact of lead in children is likely determined not only to the BLL measured at any one time but, also, the ages at which a given level occurs and the duration of exposure.

Under most exposure scenarios, children's BLLs show a characteristic age trend. A newborn's BLL will largely reflect the BLL of its mother. Because adult women tend to have lower BLLs than young children, umbilical cord BLLs are generally lower than BLLs during childhood. During the latter half of the first year of life, however, children's BLLs begin to increase as the infant becomes more active, mobile, and exposed to ambient lead. The onset of ambulation during this period is likely to be important, as are play patterns that bring the child into contact with environmental media such as lead-contaminated dust and soils. Other factors that affect exposure include the increased hand-to-mouth activity of children, including the practice of eating "in place," i.e., in play areas. Physiologic factors, such as more efficient absorption of ingested lead in children compared with adults, and their greater food and air intake on a body weight basis might also contribute to the early postnatal rise in BLL.

The mean BLL within a study sample generally peaks during 18 to 36 months of age, and slowly declines over the next few years. This blood lead profile is seen among economically disadvantaged urban minority children (Dietrich et al. 2001) and among children living near lead smelters (Figure 4) (Tong et al. 1996). In cohorts with extremely high exposures, the blood lead decline might be very gradual (e.g., Wasserman et al. 1997). In the Cincinnati Study, the same general profile was evident in each of four strata defined by average lifetime BLL, suggesting that it is, to some extent, independent of the overall level of exposure. This blood lead profile has not been observed in all study cohorts, however. In the Boston Study, for example, mean BLL varied minimally, from 6.2 to 7.6 µg/dL, from birth through 5 years of age (Rabinowitz et al. 1984; Bellinger et al. 1991).

One implication of the typical profile is that maximum level is often associated with age, constituting an obstacle to an effort to identify age-specific vulnerability to lead toxicity. Compounding this challenge is that, under many exposure scenarios (particularly those involving higher exposures), intra-individual stability of BLL tends to be substantial. That is, BLL tends to "track," so that if, at time 1, child A has a higher BLL than child B, child A is likely to have a higher BLL than child B at time 2 as well. Thus, children's rank ordering tends to be similar over time even though, in absolute value, BLL rises and falls over the course of childhood. Again, however, the degree of intra-individual stability varies from cohort to cohort. In the Boston Study cohort, for instance, the extent was limited; this stability is likely attributable to the generally low BLLs of the study population (Rabinowitz et al. 1984).

A BLL measured after 36 months of age will, on average, be lower than the BLL that would have been measured if a child's blood been sampled sometime during the 18 to 36 month period. Suppose, however, that the critical period with regard to producing an adverse health outcome is the 18 to 36 month period, and that, in a study conducted post-36 months, an inverse association is noted between concurrent BLL and a health endpoint. If the concurrent BLL is the only index of lead exposure

history available, basing a dose–effect assessment on it will, to the extent that the natural history of BLLs in the study cohort follows the canonical form illustrated above, result in an underestimate of the BLL responsible for any adverse health effects noted at the time of or subsequent to blood sampling. In other words, one will conclude that adverse health effects occur at lower BLLs than is the case. For instance, assume that the inverse association shown in Figure 5 holds between IQ and concurrent blood lead in a cross-sectional study of 6 year olds.

If, however, the BLL of each child was, on average, 5 µg/dL greater at age 2 than at age 6, and age 2 is the time of greatest toxicologic significance (i.e., it is age at which lead exposure produced the IQ deficit observed at age 6), then the dose–effect relationship that underlies the association seen at age 6 would be more accurately described as in Figure 6.

This dataset would thus not be informative with respect to the functional form of the dose–effect relationship at levels below 10 µg/dL insofar as (hypothetically) all children had a BLL greater than 10 µg/dL at age 2.

Other uncertainties apply to interpreting blood lead–health associations (or lack of associations) observed at any point in time. First, the relation of age to vulnerability to lead toxicity is not well understood. Is BLL during the age period 18 to 36 months more toxicologically critical than a measure of cumulative lifetime exposure, such as the area under the curve or some other exposure index? Also, it is possible that the critical age varies with dose, health endpoint, or sociodemographic factors. Available studies do not provide consistent answers to these questions. For example, in the Boston cohort, blood lead at age 24 months was most strongly related to IQ at age 10 years (Bellinger et al. 1992), whereas in the Port Pirie Cohort, the lifetime average BLL through age 5 years was most predictive of IQ at age 11 to 13 years.

If 18 to 36 months is the critical age of exposure, theoretically, it is possible to "adjust" an observed blood lead distribution measured at age 6 by some function to reflect the downward trend in BLL with age and estimate the blood lead distribution at a different age, (e.g., age 2 years). However, a "one size fits all" adjustment likely is not appropriate for all children. Moreover, the appropriate adjustment is likely to be study-site-specific (i.e., depend on the key exposure sources and pathways of a particular study cohort).

It would be possible to get a general sense of how accurately past peak exposure can be estimated for children in cross-sectional studies by using data collected in prospective studies in which blood lead was measured frequently during the period spanning birth to school-age. Examining the distribution of the differences between BLLs measured at ages 18 to 36 months and at age 6 would suggest the amount of exposure misclassification that would result from applying a constant adjustment factor.

Conclusions: Because of age trends in blood lead and the tendency of BLLs to "track" within individual children, inferences drawn from cross-sectional associations between blood lead and health at a given age should be interpreted cautiously because of the influence of likely higher BLLs occurring earlier in life. It may be possible to apply data on age trends and within-subject correlation of blood lead to estimate, from an observed blood lead–health association, the approximate relation to BLLs at an earlier age. However, because age trends and the extent of "tracking" of blood lead levels vary from one population to another, it is not possible to estimate with confidence the distribution of blood lead levels earlier in life for any given population whose blood lead levels were only measured at one point in time. If the only relevant studies available are based on cross-sectional data (e.g., data from NHANES III), age trends and "tracking" of BLLs would represent a substantial challenge to inferring a causal link between BLLs <10 µg/dL and adverse health impacts. However, recently published results from two cohort studies (Canfield et al. 2003; Bellinger et al. 2003) showed inverse associations between BLLs measured early in life (6 to 24 months and 24 months, etc.) and IQ measured at older ages among children whose measured BLLs did not exceed 10 µg/dL. Therefore, associations observed in cross-sectional studies cited in this report likely do not exclusively result from the impact of higher BLLs experienced earlier in life.

Quality of Neurobehavioral Assessments

As with blood lead (exposure) measurements, the accuracy, precision, and consistency of neurobehavioral assessments can influence observed blood lead-outcome relations. In order to judge whether the data from a study should be considered in characterizing the functional form of the dose–effect relationship at BLLs <10 µg/dL, one would like to have access to the following information about the conduct of the neurobehavioral assessments:

- Assurance that examiners were blinded to all aspects of children's lead exposure histories.

- The assessment setting. Assessments can be standardized when carried out in a hospital, neighborhood health center, or community center, but may be difficult to standardize in a participant's home.

- Essentials of the process by which an examiner was trained, including the criterion used to certify an examiner (e.g., percent agreement on an item-by-item basis with some gold standard, average difference in scores assigned compared with gold standard, correlation with gold standard in terms of scores assigned).

- The plan implemented for supervision of test administration over the course of data collection (e.g., periodic observation of test sessions, live or by videotape).

- The plan implemented for supervision of test scoring over the course of data collection (e.g., double scoring of a sample of protocols).

- The number of neurobehavioral examiners used over the course of data collection.

- If more than one assessor was used, whether the data analysis plan included evaluation of an "assessor" effect (i.e., as a main effect and as a modifier of lead's association with endpoints).

While some have argued that neurobehavioral examiners should have professional qualifications (e.g., Kaufman 2001 cites the need for a clinician with graduate-level training in psychometrics, neuropsychology, etc.), the Practice Committee of the American Academy of Clinical Neuropsychology supports the widespread practice of using non-doctoral level personnel, with appropriate training and supervision by a doctoral-level psychologist, in the administration and scoring of clinical neuropsychological evaluations (Brandt et al. 1999).

Assuming examiners are blinded regarding BLLs, most problems with quality of neurobehavioral assessment would be expected to mask or underestimate true associations rather than create spurious ones. It is possible, for example, that use of non-professional examiners might introduce noise into the data, masking an association between toxicant exposure and performance. In one study of methylmercury (MeHg) exposure (Grandjean et al. 1997), MeHg was inversely associated with children's scores on the Similarities subtest of the WISC-III among children tested by the supervising doctoral-level study examiner. Assuming that blinding was preserved, use of non-professional examiners likely would not introduce a positive bias in effect estimates.

Measurement quality problems causing bias of associations away from the null, without loss of blinding, are theoretically possible. For example, if one examiner consistently yields lower scores than another and that examiner, without knowledge of BLLs, is assigned to assessments of a segment of the study population at higher risk for lead exposure, a spurious inverse association could be created between lead level and neuropsychological test scores.

Conclusions: The key considerations in judging the quality of neurobehavioral assessments in the research setting are the blinding of examiners to lead-exposure history, the training and supervision of examiners, and the setting for examinations. If examiners are truly blinded, other data quality problems generally will bias estimated relationships between blood lead and outcomes toward the null. Therefore, given that examiners were blinded to BLLs in cohort studies demonstrating associations (Table 6) and the NHANES III survey, errors in measurement of neuropsychological function likely did not contribute to observed associations with BLLs <10 µg/dL.

Potential Confounding Factors

Social Factors

Socioeconomic factors influence both lead exposure and many health outcomes, including intellectual development, growth, and a number of chronic conditions, creating the potential for social factors to confound associations between children's lead exposure and health in observational studies. Because cognitive function as reflected in measured intelligence is strongly associated with socioeconomic status (SES) and because cognitive function in children is the most studied health endpoint in studies of lead-exposed children, this discussion is focused on possible SES confounding of associations between BLL and measured intelligence. The potential for reported subtle effects of lead on IQ and related measures of intellect to be attributable to confounding by socioeconomic factors warrants serious consideration (Bellinger et al. 1989). Key relations required for confounding to occur are almost certainly present—SES has been shown to be related to BLLs, presumably because the neighborhoods and homes in which families of lower income reside are associated with higher levels of lead in soil and residences. Socioeconomic status also is clearly related to measures of intelligence, whether through parental stimulation, nutrition, or resources available in the home. With an inverse relationship between socioeconomic factors and lead levels (i.e., higher SES predictive of lower lead levels) and a positive relationship between socioeconomic factors and measures of intelligence (higher SES predictive of higher intelligence test scores), failure to adjust for the confounding effect of socioeconomic factors will result in confounding that overstates the harmful effect of lead on IQ because the socioeconomic effect will be mixed with any true effect of lead exposure. In addition, confounding by social factors may be a concern for some other lead-associated health measures with social gradients such as height (Silventoinen 2003).

Data presented from most of the key studies included in this review strongly suggest that substantial confounding by socioeconomic factors occurs. Even with adjustment for crude measures (e.g., parental education and household income) (Lanphear et al. 2000), the apparent lead effect on cognitive function is greatly reduced. Such a pattern in which adjustment for a crude proxy results in a substantial decrement in the magnitude of association would suggest that "residual confounding" may be present in the adjusted estimate of effect. If residual confounding is indeed present, then tighter control for confounding with more refined measures of the social environment may further attenuate or eliminate the apparent effect (Savitz et al. 1989).

The following factors complicate this scenario:

1. Socioeconomic status is a very elusive construct to fully capture; it is far more complex than is reflected in parental education or income. Socioeconomic status includes many aspects of economic means and associated lifestyle,

so that adjustment for operational measures, such as education or income, will always be incomplete. Adjustment for an imperfect proxy measure of a confounder results in residual confounding (Greenland et al. 1985; Savitz et al. 1989).

2. Long-term lead exposure is imperfectly reflected in a current blood lead measure or to some extent, even from a series of blood lead measures (see Blood Lead Tracking) (Bellinger et al. 1989). Whatever physiologic effect lead might produce, available evidence suggests that the impact is chronic and cumulative. Beyond what is reflected in a blood-lead measure, SES may be indicative of historical exposure; thus, the observed effect of socioeconomic status would partly reflect an effect of lead exposure above and beyond the blood-lead measure.

The nature and magnitude of these associations is less clear when focusing on BLLs <10 µg/dL. Measures of social advantage, including income and parental education, are associated with BLLs <10 µg/dL (e.g., Lanphear et al. 2000). However, the relative importance of different aspects of socioeconomic status and the pathways by which they affect lead exposure are not entirely clear. The association between lower income and deterioration of paint in older housing contributes to variation in BLLs, even BLLs <10 µg/dL. The increase in geometric mean blood lead associated with living in an older home is greater for children from low-income families than for those from middle income families (Pirkle et al. 1998). Nonetheless, with the elimination of lead in gasoline and the continued decline in the proportion of homes with leaded paint (Jacobs et al. 2002), the relative importance of lead exposure sources possibly is changing. It is also possible that the association of social factors with lead exposure is different for populations with BLLs <10 µg/dL than for those above that level.

Several strategies have been applied to address the role of socioeconomic factors and isolate a non-specific effect of socioeconomic factors on IQ from an effect of lead exposure. First, populations can be sought or even constructed in which blood lead is not closely associated with SES as demonstrated most clearly in the Boston cohort (Bellinger et al. 1987). In that population, all in a relatively low blood lead range for that time and the great majority of relatively advantaged SES, there was a weak positive gradient between socioeconomic status and lead. The Kosovo cohort (Wasserman et al. 1997) also departed from the usual trend in that the more SES advantaged of the two communities studied was the site of a lead smelter. As a result, adjustment for social and other covariates actually strengthened the inverse relation of blood lead to IQ in that population.

Second, improved measures of socioeconomic factors have been applied to better control for non-specific effects. That is, by refining and decomposing the construct of socioeconomic status, it is possible to adjust more fully for the confounding dimensions such as nutrition, parental stimulation, attitudes towards achievement,

etc., and not adjust for the aspects that primarily serve as a proxy for lead exposure, such as age of housing and neighborhood. One example among published research of refining and decomposing the construct of socioeconomic status has been the use of the HOME scales to adjust for stimulation provided by caregivers. Use of HOME scales has in some cases further attenuated but not eliminated apparent lead–IQ associations.

A third approach to examine the possibility of confounding of the blood lead–IQ relation at low levels would be to conduct a formal statistical assessment of the extent to which the strength of the observed association across studies varies in relation to control for relevant confounders, using meta-regression, as was applied by Schwartz (1994). This approach could be refined to assess possible residual confounding. One challenge in performing such an analysis using published summary data is the difficulty in operationalizing measures of the tightness of SES adjustment while controlling for other aspects of study design that might influence blood lead–IQ slopes. An alternative approach is discussed later in this report (see Research Needs).

Conclusions: On the basis of available evidence the observed associations between blood lead below 10 µg/dL and cognitive function likely do not entirely result from confounding. This conclusion is supported by the following evidence:

- The studies showing the strongest relationship (Canfield et al. 2003; Bellinger et al. 2003) at low levels employed the HOME scale for adjustment, which is the best available measure for assessing the impact of the home environment on child development.
- Two cohorts, Kosovo and Boston, in which strong associations were found between blood lead and IQ, were characterized by a direct, rather than inverse, correlation of blood lead with social advantage.
- Associations of children's blood lead close to 10 µg/dL and intelligence have been seen in diverse geographic and social settings.
- Animal data have demonstrated effects of lead at BLLs near 10 µg/dL.

On the other hand, the ability to detect confounding by omitted covariates by comparisons across studies is limited because, for most covariates of potential interest, the number of relevant studies in one group being compared is limited. In other words, for a given covariate, either few studies included it (e.g., postnatal ETS exposure) or few excluded it (e.g., SES). At this point, the case for residual confounding by social environment is speculative, but available studies relating blood lead to cognitive function in children cannot entirely exclude the possibility that observed associations are at least partly influenced by it. Such a possibility does increase uncertainty about the actual strength and shape of blood lead relationships at BLLs less than 10 µg/dL.

Iron Status

Nutritional factors, such as iron and zinc intake, that might be correlated with lead uptake and might influence children's health, could confound associations between BLLs and health from observational studies. The potential for iron deficiency to confound the association between blood lead and neurodevelopmental status has been of most concern and is the focus of this discussion. The likelihood of such bias is dependent upon the extent to which iron status was controlled in a given study and the prevalence of iron deficiency in a study population. Iron deficiency may impair neurodevelopment in a manner similar to low-level lead exposure and the populations at increased risk for iron deficiency and lead toxicity may overlap (Lozoff et al. 1991; Wasserman et al. 1999). However, the association between iron deficiency and blood lead is not consistent across populations (CDC 2002). Therefore, the potential for iron to confound an association of blood lead with neurodevelopmental status will vary across populations, depending on both the prevalence of iron deficiency and its association with blood lead level.

For research purposes adequate assessment of iron status entails determination of hemoglobin or hematocrit and at least two other measures of iron status. Generally accepted definitions of iron deficiency and iron deficiency anemia depend on age- and sex-specific normal ranges. The iron status measures most commonly used are mean corpuscular volume (MCV), free erythrocyte protoporphyrin (FEP) or zinc protoporphyrin (ZPP), transferrin saturation, ferritin, and, more recently, transferrin receptor. The standard for defining iron deficiency is values indicating iron deficiency on at least two of these measures and/or response to iron therapy with an increase in hemoglobin to at least 10 g/L. The utility of ferritin in young infants is under debate, making it important that functional measures, such as MCV or ZPP be obtained. There are limitations of each measure (e.g., ferritin goes up with infection, MCV is down in hemoglobinopathies, etc.).

Although iron deficiency with low hemoglobin has been associated with later impairment of cognitive function (Grantham-McGregor et al. 2001), it is not certain which measure(s) of iron status are most strongly related to neurodevelopmental outcomes. In studies of children with higher BLLs, controlling for hemoglobin is problematic because lead toxicity can reduce hemoglobin in the normal range or cause frank anemia. This is less of a concern in studies of children with BLLs <10 µg/dL, a range in which no meaningful impact on hemoglobin levels has been observed.

Conclusions: Measurement of iron deficiency has been absent or suboptimal in most of the studies reviewed. Two studies in which iron status was controlled for using transferrin saturation (Canfield et al. 2003) and serum ferritin (Lanphear et al. 2000) found strong inverse relationships between blood lead and cognitive function, whereas a third study that controlled for the presence of iron-deficiency anemia found the opposite (Wolf et al. 1994). Furthermore, iron-deficiency anemia

is the measure of iron status most clearly linked to impaired cognitive function; therefore, it seems unlikely that the prevalence of iron deficiency anemia could be high enough in the populations showing the strongest inverse relations of blood lead to cognitive function (Canfield et al. 2003; Bellinger et al. 2003; Lanphear et al. 2000) to entirely explain these associations. In the NHANES III data used by Lanphear et al. (2000), the prevalence of iron deficiency ranged from 1% to 9%, depending on the age and sex group (CDC 2002). Finally, in Kosovo, following treatment of iron-deficient children with iron supplements, no association of earlier hemoglobin levels with IQ at age 4 (Wassserman et al. 1994) or age 7 (Wasserman et al. 1997) was found. Thus, iron deficiency likely does not completely explain the inverse associations between BLLs <10 µg/dL and cognitive function.

Tobacco

Blood lead levels in children have been associated with exposure to environmental tobacco smoke (assessed by caregiver report or by urinary cotinine levels) in both general population surveys (Stromberg et al. 2003; Mathee et al. 2002; Lanphear et al. 2000; Mannino et al. 2003) and in studies of children living near lead smelters (Willers et al. 1988; Baghurst et al. 1992; Baghurst et al. 1999). The explanation for this association is not entirely clear; possibilities include enhancement of lead uptake by environmental tobacco smoke (ETS), exposure to lead in ETS itself, and differences in cleaning practices or child supervision between households with and without smokers.

Maternal smoking during pregnancy has been associated with behavioral problems and impaired cognitive development in children; fetal hypoxia is one possible contributing mechanism (Habek et al. 2000). Evidence for an effect of prenatal or postnatal ETS exposure on neurodevelopment is less clear (Eskenazi et al. 1999). As with studies of lead and neurodevelopment, social factors may confound, at least in part, the association between maternal smoking and neurodevelopment (Baghurst et al. 1992). A child's prenatal exposure to maternal smoking or pre- or postnatal exposure to ETS could, if these are causally related to impaired neurodevelopment or other adverse health outcomes, confound the observed associations of lead and health. In addition, if a relationship between postnatal ETS and neurodevelopment is established, lead exposure could be a mediating factor.

Conclusions: Of the studies reviewed, most did not assess prenatal or postnatal ETS as a possible confounding factor. Those that assessed tobacco at all controlled for maternal smoking during pregnancy. However, the two exceptions, Lanphear et al. (2000) in which serum cotinine measurements were used to control for ETS and a study based on the Port Pirie cohort (Tong et al. 1996; Baghurst et al. 1992) which reported postnatal parental smoking, provide no evidence that confounding by tobacco exposure accounts for the associations observed between blood lead and adverse health effects. Limitations in available studies leave some uncertainty as

to what contribution, if any, ETS might make to observed associations between BLL and health.

Causal Direction

Inference of causation from observational epidemiologic studies is sometimes complicated by the possibility that the health outcome under study could be a cause of the exposure or causally related to a third factor which itself is a cause of the exposure under study. Two factors that influence blood lead levels—mouthing behavior and calcium balance—are relevant to assessing causal direction in studies of the health effects of lead at low levels.

Mouthing behavior

An important pathway of lead uptake by young children is ingestion of lead-contaminated dust (Charney et al. 1980; Bornschein et al. 1985), presumably through mouthing of hands, surfaces, and objects on which the dust is deposited. Although mouthing behavior is difficult to measure, children with more reported mouthing behavior have higher BLLs in relation to environmental lead exposure (Lanphear et al. 1998; Bellinger et al. 1986; Baghurst et al. 1999). Pica (purposeful ingestion of non-food items) can be a consequence of impaired neurodevelopment and can predispose one to lead ingestion (Cohen et al. 1976; McElvaine et al. 1992; Shannon et al. 1996), but the relation of variation in "normal" age-appropriate mouthing behavior to neurodevelopment is uncertain. However, in groups of children, average measured or caregiver reported mouthing has been shown to diminish with age (Juberg et al. 2001; Tulve et al. 2002). Nonetheless, it is unclear whether, at the individual level, more frequent mouthing behavior is a marker (independent of its effect on lead ingestion) for delayed neurodevelopment. If such behavior is a marker, then an association between blood lead level and impaired neurodevelopment would result, and failure to adjust for mouthing behavior would result in an overestimate of the blood-lead effect. On the other hand, if measured mouthing behavior is associated with cumulative lead exposure above and beyond that reflected in measured BLLs, then controlling for mouthing behavior could amount to over control, underestimating the true effect of lead on neurodevelopmental measures.

Conclusions: At this point, no direct evidence supports reverse causation by mouthing behavior, and this hypothesis remains speculative. Arguing against this possibility, Tong et al. (1996) reported that an early measure of neurocognitive development, the Bailey MDI, was not predictive of later BLLs.

Calcium balance

Calcium balance changes in relation to growth during childhood and during the rapid expansion of bone mass during puberty and the pubertal growth spurt

(Bronner et al. 1998; van Coeverden et al. 2002; Bailey et al. 2000); estradiol may influence bone mineral deposition in pubertal girls (Cadogan et al. 1998). It is possible that effect of skeletal growth and puberty on calcium balance could cause lower BLLs (Thane et al. 2002), just as the opposite changes in calcium balance during menopause appear to cause an increase in blood lead (Hernandez-Avila et al. 2000; Garrido Latorre et al. 2003). It should be noted that the average age at menarche among U.S. adolescents dropped by approximately 2.5 months between the periods 1963-1970 and 1988-94 and that this trend was accounted for in part by a rising prevalence of obesity (Anderson et al. 2003). Average BLLs were likely falling substantially during this same period.

Conclusions: Because human studies linking blood lead at levels <10 µg/dL to delayed puberty and smaller stature are, with one exception, cross-sectional and evidence is limited on this topic, reverse causation via changes in calcium balance cannot be ruled out as accounting for at least some of the observed associations. While the parallel secular trends in decreasing age at menarche and decreasing BLLs could be explained in part to a causal effect of lead delaying age at menarche, it is also possible that other secular trends (e.g. increasing obesity rates) have caused the trend toward earlier menarche.

Overall Conclusions

Question 1: Does available evidence support an inverse association between children's blood lead levels <10 µg/dL and children's health?

Because of the large number of studies that have assessed cognitive function as an outcome, the review and conclusions by the WG primarily focus on this health domain. The consensus of the WG is that the overall weight of available evidence supports an inverse association between BLLs <10 µg/dL and the cognitive function of children. The evidence for such an association is bolstered by the consistency across both cross-sectional and longitudinal studies in varied settings with blood lead distributions overlapping 10 µg/dL and by the lack of any trend towards a weaker association in studies with lower population mean BLLs. More recent studies and analyses best suited to examining this association (Canfield et al. 2003; Bellinger et al. 2003) have added to, rather than refuted, evidence for such an association noted in prior CDC guidance (1991).

In reaching this conclusion, the WG is mindful of limitations in the available evidence base. Relatively few studies have directly examined the association between BLLs <10 µg/dL and health status among children and many of those that have are cross sectional studies in which data are unavailable on BLLs earlier in life and key covariates. The WG concluded that findings from numerous published studies relating BLL to cognitive function, while not limited to children with BLLs

<10 µg/dL, collectively were not consistent with a threshold for the BLL-cognitive function association at 10 µg/dL. This indirect evidence, however, is less persuasive than cohort studies and analyses that directly assess the relationship between BLL and health <10 µg/dL. These directly relevant studies analyzed data for children whose measured BLLs did not exceed 10 µg/dL (to the investigator's knowledge). Likely included in these analyses were some children who, because of random variation in BLL or age trends, did at some time have a BLL ≥10 µg/dL that was not measured. Such misclassification could produce an apparent inverse association between BLLs <10 µg/dL and health status even if a threshold existed at 10 µg/dL. Such misclassification, however, could not account for the observed BLL–IQ relation in the Canfield (2003) study, in which a steeper slope was observed at BLLs <5 µg/dL than at levels 5–10 µg/dL.

For health endpoints other than cognitive function, including other neurologic functions, stature, sexual maturation, and dental caries, available data are more limited and less replication of findings exists across studies. Nonetheless, the available data from these studies are consistent with associations between higher BLLs and poorer health indicators for values <10 µg/dL .

Question 2: Are the observed associations likely to be causal?

The work group concluded that, while available evidence does not permit a definitive causal interpretation of the observed associations between higher BLLs and adverse health indicators for values <10µg/dL, the weight of available evidence favors, and does not refute, the interpretation that these associations are, at least in part, causal. The WG also concluded that the limitations of the available evidence, including likely residual confounding by social environment, leave uncertainty about the absolute strength and shape of the causal relation at the population level. Even greater uncertainty attends the use of associations observed in the relevant population studies for interpretation of BLLs measured in individual children at a single point in time. Thus, the WG does not believe that the individual children can be classified as "lead poisoned," as the term is used in the clinical setting, on the basis of the associations observed in studies reviewed for this report. The basis of the overall WG conclusions is discussed below and is followed by a summary of the important limitations in the available evidence.

The WG explored other possible explanations (aside from causation) for these associations and concluded that none are likely to fully explain the observed data. The context of evidence from animal, in vitro, and human studies of adult populations, also supports the consensus of the WG conclusion that the observed associations most likely represent, at least in part, causal adverse impacts of lead on children's cognitive function at BLLs <10 µg/dL.

The greatest source of uncertainty in interpreting the relationship between BLLs <10 µg/dL and cognitive function is the potential for residual confounding by social

factors. The conditions for residual confounding appear to be present: BLLs are strongly influenced by SES, SES is clearly related to measured cognitive function, and social factors that could influence BLL and cognitive function are difficult to measure precisely. Other sources of potential bias are, individually, less concerning than social confounding, but collectively they add to the overall uncertainty about the absolute strength and shape of the relation of BLL to impaired cognitive function. These include, random error in blood lead measurement and in a single BLL as a measure of chronic exposure, possible influence of factors that have not been fully addressed in published studies, including blood lead tracking and age trend, which limits cross-sectional studies in particular, tobacco smoke exposure, iron deficiency, and mouthing behavior. Error in measuring lead exposure would bias observed associations towards the null, while failure to adjust for the other factors noted would most likely bias observed associations away from the null.

The recently reported trend of asymptotically increasing slopes of lead-associated decrements in cognitive test scores at lower BLLs (Bellinger et al. 2003; Canfield et al. 2003; Lanphear et al. 2000) would be expected if residual confounding were operative as illustrated in Figure 7. The graph on the left depicts a comparison of two groups of children who live in a high exposure setting. They differ, on average, with respect to aspects of the home and social environment that are not captured in measured covariates. This results in one group ingesting and absorbing twice as much lead and having, after adjustment for measured covariates, a mean IQ 1 point lower than the children raised in a more favorable environment. Assuming a roughly linear relation of lead intake to blood lead, the result is that one group has a mean blood lead twice as high, corresponding to a 10 µg/dL difference in blood lead and an estimated blood lead-IQ slope attributable to residual confounding of 0.1 IQ points per µg/dL. The figure on the right depicts the same hypothetical two populations living in a low exposure setting. The same imperfectly measured differences in social environment contribute to the equivalent covariate-adjusted difference in mean IQ, but in this case, although one group ingests twice as much contaminated dust as before, lower levels of lead contamination result in the two children having a blood lead difference of only 1 µg/dL in blood lead level. The result is an estimated blood lead-IQ slope attributable to residual confounding of 1.0 IQ points per µg/dL. In addition, a convincing and directly relevant biologic mechanism for such a dose response relation has yet to be demonstrated. Though this hypothetical example cannot demonstrate that residual confounding underlies the steep blood lead-IQ slopes observed at low levels, it does support the need for caution in interpreting the absolute value of the estimated effect sizes.

The available data for these other health endpoints, taken mostly from cross-sectional studies, are more limited and firm conclusions concerning causation cannot be made at this time.

Research Needs

Resolving residual confounding through observational studies

It may be somewhat easier to identify study populations with BLLs <10 µg/dL in which socioeconomic factors are not associated with exposure as compared to populations with more widely varying blood lead levels within many low SES children, but few high SES children, may have blood lead levels above 20 or 30 µg/dL. Configuring a cohort similar to the one in Boston or assembling one from the pieces of others already studied could be helpful in isolating socioeconomic and lead effects from one another. Another formal statistical approach that could be applied to pooled data across multiple studies is the application of a hierarchical modeling approach as proposed by Schwartz et al. (2003, in press).

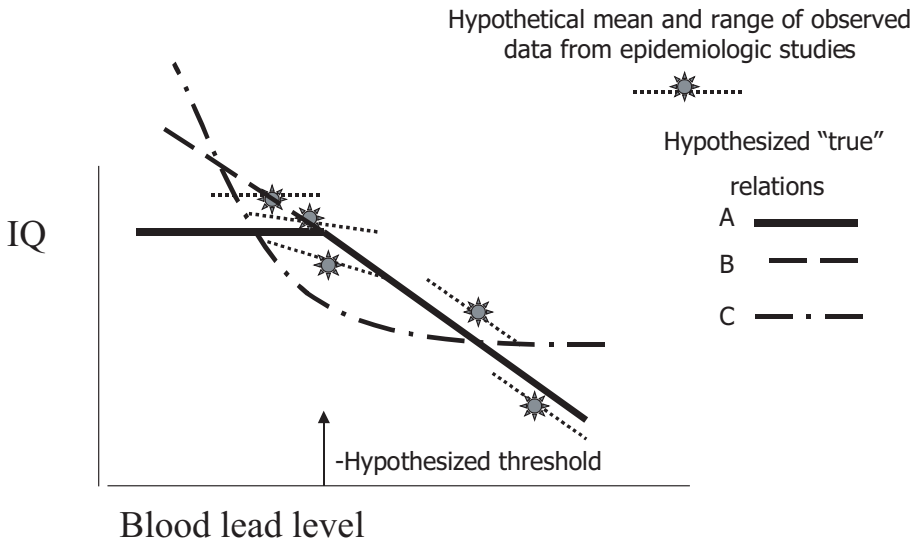
Controlled intervention trials

While experimental designs can establish causation with greater confidence than observational studies, intentionally exposing some children to higher BLLs in a randomized controlled design would be unethical. However, randomized trials in which interventions are tested for their ability to reduce BLLs <10 µg/dL or prevent their increase provide an opportunity to support or refute a causal relationship between BLLs <10 µg/dL and adverse health outcomes. Studies testing such interventions should measure covariates relevant to assessing health effects, allowing a test of the causal hypothesis should they be successful at sufficiently reducing BLLs.

Animal and in vitro studies to explore mechanisms and dose-response relations

While the overall evidence from animal or in vitro models supports the biologic plausibility of adverse effects of lead at BLLs <10 µg/dL, the WG is unaware of directly relevant animal or in vitro studies that demonstrate a steeper slope for adverse effects of lead exposure at lower BLLs than observed at higher levels. Demonstrating such a relationship in experimental studies and identifying possible mechanisms would increase confidence in a causal interpretation of the observed blood lead-response relationship in studies such as Canfield et al. (2003).

Figure 1. Expected variation in regression slopes given hypothetical "true" threshold blood lead - IQ relation (A).



Notes: Figures 2 and 3

Selected estimates of change in outcome (Full Scale IQ or McCarthy General Cognitive Index (GCI) derived from regression coefficients and listed in Table 2 and the corresponding mean BLLs of the study population are displayed in Figures 2 and 3. Figure 2 contains results from studies where the BLLs were measured at ages $\leq$2 years, and outcome measures were measured at ages $\geq$4 years. Figure 3 contains the results when both the BLLs and outcome measures were measured at ages $\geq$4 years. Both the crude (open dot) and adjusted (solid dot) coefficients are displayed in the figures when both are available. (The Kosovo and European Multicenter Study papers did not provide the crude coefficient). Although multiple models for a single study population may have been fit to results from differing ages within the defined age categories, only the regression coefficients for the highest age at which blood lead was measured (per study population) are included in the figures. (The highest outcome measure age was used as a tiebreaker when necessary.) Also, when models for both a concurrent blood lead measure and a lifetime average blood lead measure existed for the highest age at which blood lead was measured (Port Pirie and Rochester), the concurrent results were included. For the study that provided multiple models for the same highest-age blood lead versus outcome measure (Lavrion, Greece), the results from the model that included the most covariates were included. Any studies not providing both a regression coefficient and blood lead mean were excluded. Three-letter abbreviations for each study population, defined in the legends below, were used on the plots.

Legend for Figure 2

Abbreviation	Study population	Reference number	Blood lead and outcome ages
Bos	Boston, Massachusetts	7	24 months / 10 years
Cin	Cincinnati, Ohio	13	15-24 months / 6.5 years
Kos	Kosovo, Serbia	37	24 months / 4 years
Por	Port Pirie, Australia	23	24 months / 4 years
Roc	Rochester, New York	11	6-24 months / 5 years

Legend for Figure 3

Abbreviation	Study population	Reference number	Blood lead and outcome ages
Bos	Boston, Massachusetts	7	10 years / 10 years
Cin	Cincinnati, Ohio	13	51-60 months / 6.5 years
Eur	European Multicenter Study	39	6-11 years / 6-11 years
Kar	Karachi, Pakistan	28	6-8 years / 6-8 years
Kos	Kosovo, Serbia	37	48 months / 4 years
Lav	Lavrion, Greece	20	primary school / primary school
Por	Port Pirie, Australia	35	11-13 years / 11-13 years
Roc	Rochester, New York	11	5 years / 5 years

Figure 2. Cognitive Function Regression Coefficients for Blood Lead Age ≤2 years and Outcome Age ≥4 years.

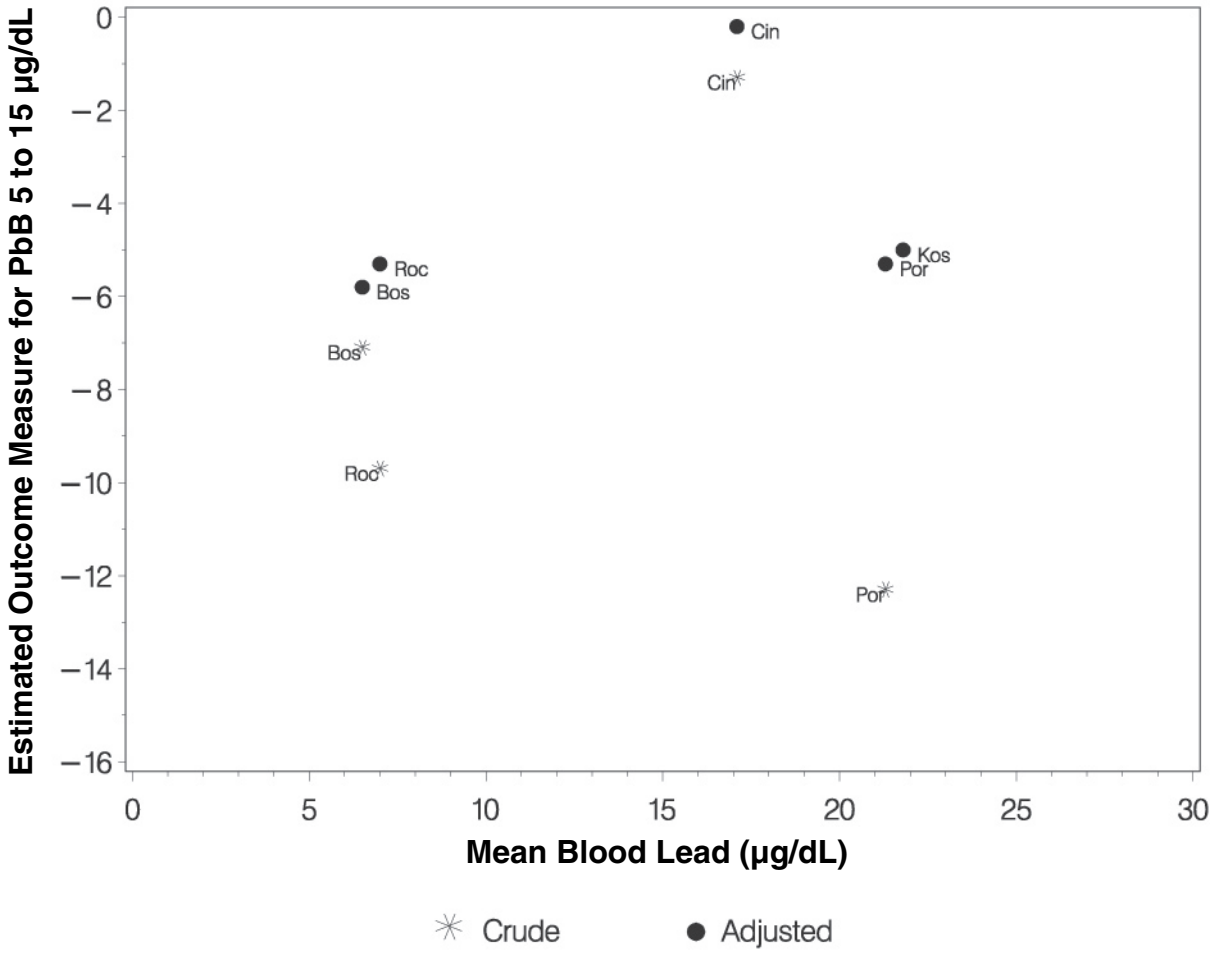


Figure 3. Cognitive Function Regression Coefficients for Blood Lead Age ≥4 years and Outcome Age ≥4 years.

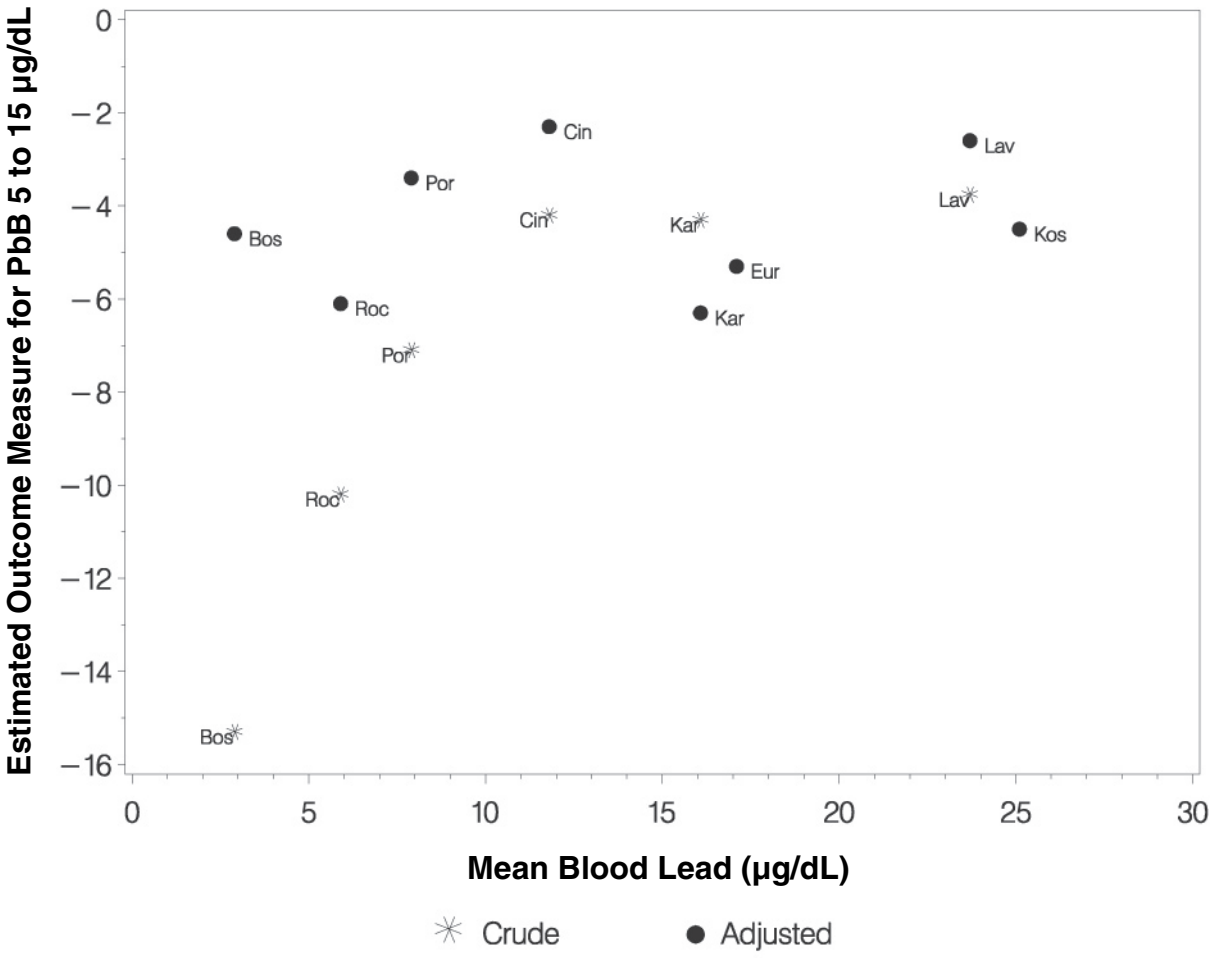
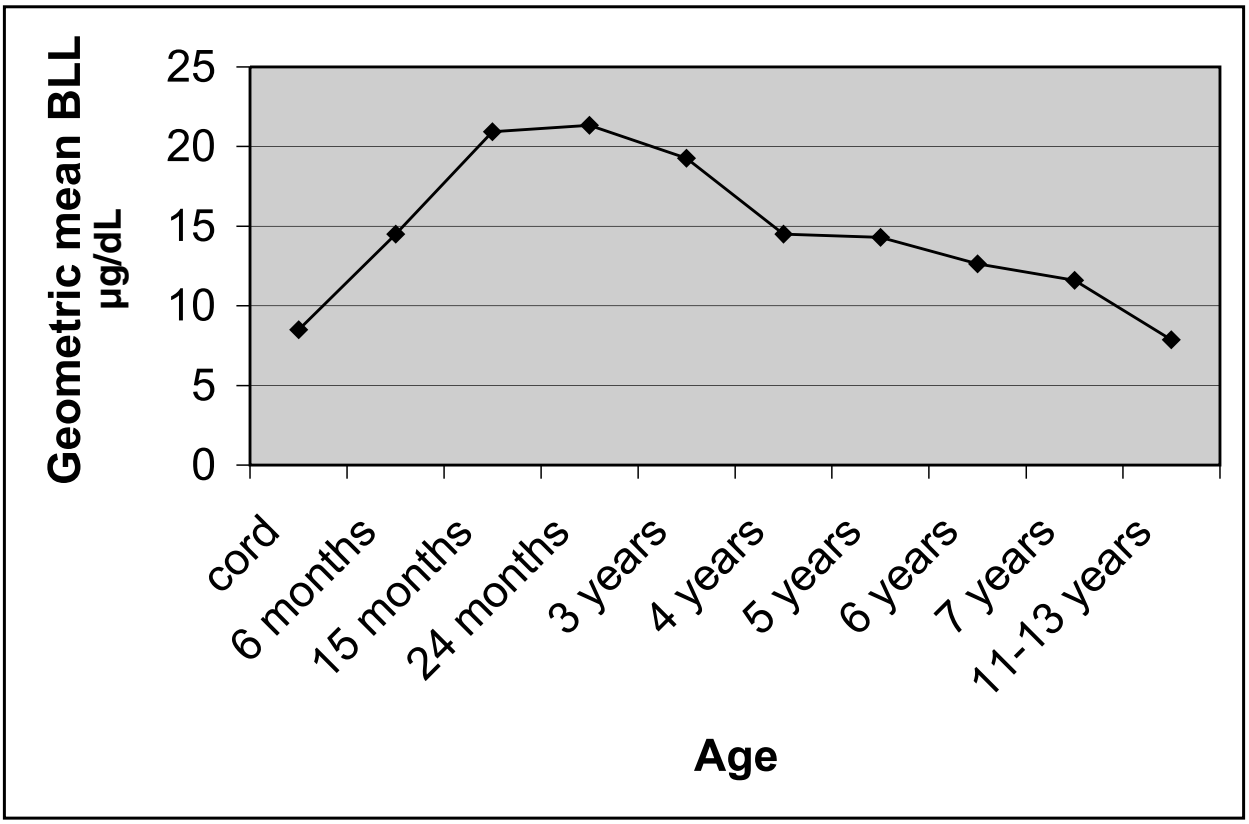


Figure 4. Age trend in blood lead levels (BLLs).



Source: Tong et al. 1996.

Figure 5. Hypothetical observed association between blood lead and IQ.

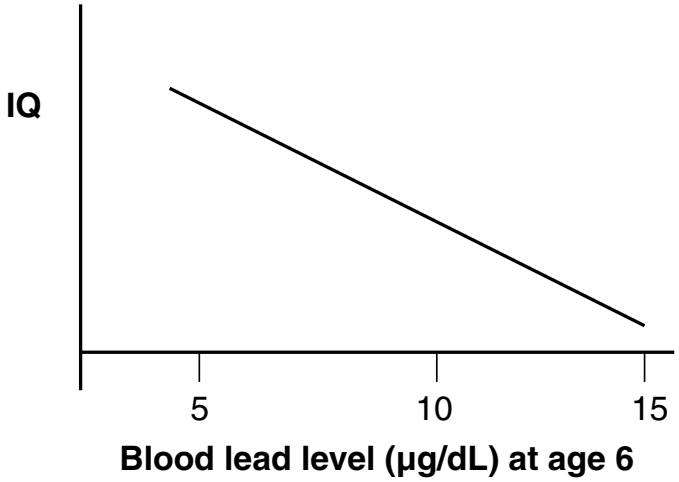


Figure 6. Hypothetical "true" association between blood lead and IQ.

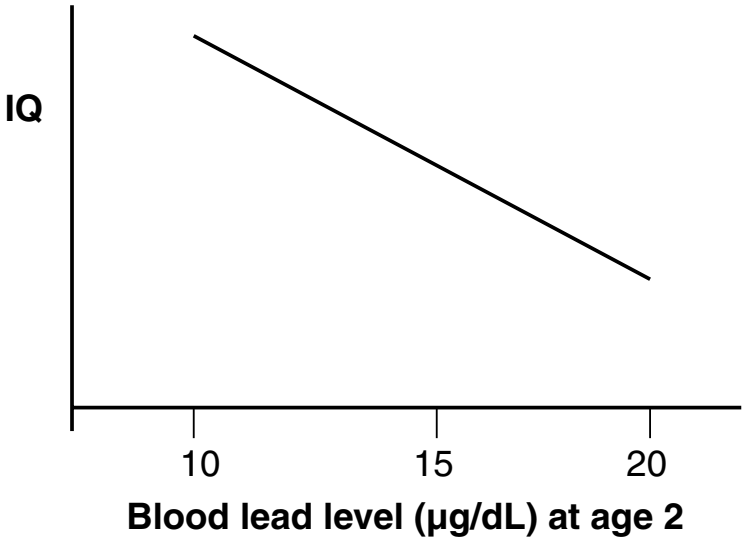


Figure 7. Hypothetical slopes of the relationship between blood lead and IQ associated with residual confounding (see Overall Conclusions).

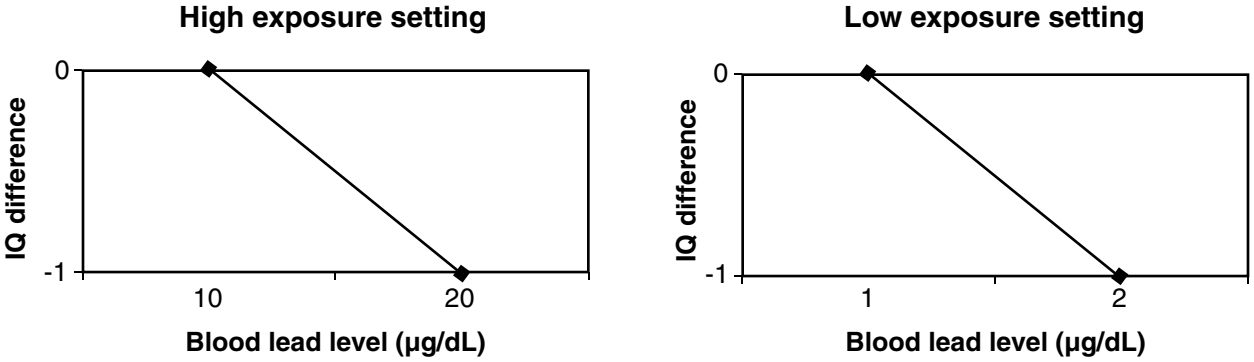


Table 1. Lowest blood lead level (BLL) considered elevated by CDC and the US Public Health Service

Year and Reference	BLL (µg/dL)
1971 (Surgeon General)	40
1975 (CDC)	30
1978 (CDC)	30
1985 (CDC)	25
1991 (CDC)	10

Table 2. Summary of studies estimating association of postnatal PbB with cognitive function

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
	(<= 2 years)	(>= 4 years)												
Kosovo (37, L ,332)	24 months	# 4 years	21.8 (GM)	Not stated	-5 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Port Pirie (23, L ,537)	24 months	# 4 years	21.3 (GM)	-12.3 (log10)^	-5.3 (log10)^	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight, Gestation	Marital Status, Maternal Age	Unspecified		Maternal		Maternal Medication/Drug Use, Postnatal Factors, Birth Order, Birth Type, Birth Problems, Child's Sex, Residence in Regions, Child's Medical History, Mother's Work Site
Port Pirie (23, L ,537)	15 months	# 4 years	20.9 (GM)	-6.8 (log10)^	-1.7 (log10)	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight, Gestation	Marital Status, Maternal Age	Unspecified		Maternal		Maternal Medication/Drug Use, Postnatal Factors, Birth Order, Birth Type, Birth Problems, Child's Sex, Residence in Regions, Child's Medical History, Mother's Work Site
Port Pirie (35, L ,367)	15 months	11-13 years	20.9 (GM)	-6.8 (ln)^	-2 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Port Pirie (4, L ,494)	Lifetime average - 2 years	7 years	16.6-20.5 (means of 2nd & 3rd quartiles) (GM)	Not stated	-5.1 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Kosovo (37, L ,332)	18 months	# 4 years	20.0 (GM)	Not stated	-2.3 (log10)	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Port Pirie (4, L ,494)	Lifetime average - 15 months	7 years	14.3-18.0 (means of 2nd & 3rd quartiles) (GM)	Not stated	-4.4 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Kosovo (37, L ,332)	12 months	# 4 years	17.2 (GM)	Not stated	-3.6 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Cincinnati (13, L ,253)	Mean 15-24 months	6.5 years	17.1	-1.3	-0.2		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cleveland (16, L ,149)	2 years	4 years 10 months	16.70	r=-.38^	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Sydney (12, L ,318)	Mean 18,24 months	# 48 months	15.8 (GM)	Not stated	Not stated	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education		Gestation		Total at 48 months		Maternal		
Sydney (12, L ,318)	Mean 6,12 months	# 48 months	15.2 (GM)	Not stated	Not stated	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education		Gestation		Total at 48 months		Maternal		
Kosovo (37, L ,332)	6 months	# 4 years	15.0 (GM)	Not stated	-2 (log10)	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Port Pirie (23, L ,537)	6 months	# 4 years	14.5 (GM)	-7.2 (log10)^	-4.1 (log10)	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight, Gestation	Marital Status, Maternal Age	unspecified		Maternal		Maternal Medication/Drug Use, Postnatal Factors, Birth Order, Birth Type, Birth Problems, Child's Sex, Residence in Regions, Child's Medical History, Mother's Work Site
Costa Rica (41, L ,184)	12-23 months	5 years	11.0	r=.06	Not stated									
Cincinnati (13, L ,253)	Mean 3-12 months	6.5 years	10.6	-2.2	0.1		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Mexico City (31, L ,112)	Mean 6-18 months	# 36-60 months	10.1 (GM)	Not stated	Mean square = 87.81 (neg) (ln)	Family Socioeconomic Level, Maternal Education		Birth Weight				Maternal		Postnatal Factors, Birth Order, Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Cleveland (16, L ,122)	6 months	4 years 10 months	9.99	r=-.06	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse
Boston (6, L ,170)	18 months	# 57 months	8.0	-3.3 (ln)^	-1.8 (ln)	Hollingshead Index of Social Class		Birth Weight	Family Structure, Marital Status, Residence Changes, Day Care	Total	Child	Maternal		Birth Order, Child's Sex, Medication Used by Child, Preschool Attendance
Boston (6, L ,170)	12 months	# 57 months	7.8	-2.4 (ln)	-1.6 (ln)	Hollingshead Index of Social Class		Birth Weight	Family Structure, Marital Status, Residence Changes, Day Care	Total	Child	Maternal		Birth Order, Child's Sex, Medication Used by Child, Preschool Attendance
Boston (7, L ,116)	18 months	10 years	7.8	-2.8	-1.2	Hollingshead Four-Factor Index of Social Class			Family Stress, Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Boston (7, L ,116)	12 months	10 years	7.7	-2	0	Hollingshead Four-Factor Index of Social Class			Family Balance, Family Stress, Marital Status	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Parents' Sense Competence, Birth Order, Child's Sex
Boston (6, L ,170)	24 months	# 57 months	7.0	-3.4 (ln)^	-3.2 (ln)^	Hollingshead Index of Social Class		Birth Weight	Family Structure, Marital Status, Residence Changes, Day Care	Total	Child	Maternal		Birth Order, Child's Sex, Medication Used by Child, Preschool Attendance

*** L=Longitudinal cohort, X=Cross-sectional.**
**** (ln)/(log10) = Original coefficient reported in log scale.**
 # = McCarthy GCI, all unmarked are full-scale IQ measures.
^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Rochester (11, L ,172) [all]	Average in infancy - 6-24 months	5 years	7.0	-9.7^	-5.3^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Boston (6, L ,170)	6 months	# 57 months	6.8	0.3 (ln)	0.3 (ln)	Hollingshead Index of Social Class		Birth Weight	Family Structure, Marital Status, Residence Changes, Day Care	Total	Child	Maternal		Birth Order, Child's Sex, Medication Used by Child, Preschool Attendance
Boston (7, L ,116)	6 months	10 years	6.7	-2	-1.3	Hollingshead Four-Factor Index of Social Class			Marital Status	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Boston (7, L ,116)	24 months	10 years	6.5	-7.1^	-5.8^	Hollingshead Four-Factor Index of Social Class			Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Cincinnati (13, L ,253)	10 Days	6.5 years	5	-1	-0.3		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Boston (34, L ,148)	24 months	10 years	< 8	Not stated	-5.8^	Hollingshead Four-Factor Index of Social Class			Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Rochester (11, L ,105) [<10 group]	Average in infancy - 6-24 months	5 years	Not stated	-15.8^	-9.2	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
	(>2 - <4 years)	**(>= 4 years)**												
Kosovo (37, L ,332)	36 months	# 4 years	24.1 (GM)	Not stated	-4.5 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Kosovo (37, L ,332)	42 months	# 4 years	23.2 (GM)	Not stated	-5 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Kosovo (37, L ,332)	30 months	# 4 years	22.1 (GM)	Not stated	-4.6 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Port Pirie (4, L ,494)	Lifetime average - 3 years	7 years	17.4-21.7 (means of 2nd & 3rd quartiles) (GM)	Not stated	-5.3 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Port Pirie (23, L ,537)	36 months	# 4 years	19.5 (GM)	-12 (log10)^	-6.3 (log10)^	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight, Gestation	Marital Status, Maternal Age	Unspecified		Maternal		Maternal Medication/Drug Use, Postnatal Factors, Birth Order, Birth Type, Birth Problems, Child's Sex, Residence in Regions, Child's Medical History, Mother's Work Site
Port Pirie (35, L ,372)	3 years	11-13 years	19.3 (GM)	-10.8 (ln)^	-4.2 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cleveland (16, L ,155)	3 years	4 years 10 months	16.70	r=-.31^	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Cincinnati (13, L ,253)	Mean 27-36 months	6.5 years	16.3	-2.6^	-1.3		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Sydney (12, L ,318)	Mean 30,36 months	# 48 months	12.4 (GM)	Not stated	Not stated	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education		Gestation		Total at 48 months		Maternal		
Cleveland (16, L ,212)	Mean 0.5-3 years	4 years 10 months	9.99 at 6 months & 16.70 at both 2 years & 3 years	r=-.25	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse
Mexico City (31, L ,112)	Mean 24-36 months	# 36-60 months	9.7 (GM)	Not stated	Mean square = 101.62 (neg) (ln)	Family Socioeconomic Level, Maternal Education		Birth Weight				Maternal		Postnatal Factors, Birth Order, Child's Sex
Port Pirie (35, L ,326)	Lifetime average - 3 years	11-13 years	Not stated	-10.4 (ln)^	-4.7 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
	(>= 4 years)	**(>= 4 years)**												
Kosovo (37, L ,332)	48 months	# 4 years	25.1 (GM)	Not stated	-4.5 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Lavrion, Greece (20, X ,509) [cov. model b]	Primary school children - not specified years	Primary school children - not specified years	23.7	-3.76^	-2.66^	Maternal Education, Paternal Education, Paternal Occupation			Family Structure			Both		Birth Order, History Alcohol Abuse, Father's Age
Lavrion, Greece (20, X ,509) [cov. model c]	Primary school children - not specified years	Primary school children - not specified years	23.7	-3.76^	-2.7^	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight	Family Structure, Marital Status, Life Events			Both		Birth Order, Child's Age, Child's Medical History, History Alcohol Abuse, Father's Age, Bilingualism, Length of Child's Hospital Stay after Birth
Lavrion, Greece (20, X ,509) [cov. model d]	Primary school children - not specified years	Primary school children - not specified years	23.7	-3.76^	-2.6^	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight	Family Structure, Marital Status, Life Events			Both		Birth Order, Child's Sex, Child's Age, Residence in Regions, Child's Medical History, History Alcohol Abuse, Mouthing Behavior, Father's Age, Bilingualism, Length of Child's Hospital Stay after Birth
Lavrion, Greece (20, X ,509) [cov. model e]	Primary school children - not specified years	Primary school children - not specified years	23.7	-3.76^	-2.4^	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight	Family Structure, Marital Status, Life Events			Both		Birth Order, Child's Age, School Grade, Child's Medical History, History Alcohol Abuse, Father's Age, Bilingualism, Length of Child's Hospital Stay after Birth

*** L=Longitudinal cohort, X=Cross-sectional.**
**** (ln)/(log10) = Original coefficient reported in log scale.**
 # = McCarthy GCI, all unmarked are full-scale IQ measures.
^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Port Pirie (4, L ,494)	Lifetime average - 4 years	7 years	17.6-21.5 (means of 2nd & 3rd quartiles) (GM)	Not stated	-5.1 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Port Pirie (4, L ,494)	Lifetime average - 7 years	7 years	15.7-19.7 (means of 2nd & 3rd quartiles) (GM)	Not stated	-4.1 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Mexico City II (26, X ,139)	7-9 years	7-9 years	19.4	r=-.33 (ln)	r=-.32 (ln)	Income, Maternal Education, Paternal Education								Child's Sex, Type of Housing, Nutritional Status (weight for height & height for age)
European Multicenter Study (39, M ,1639)	6-11 years	6-11 years	17.1 (GM)	Not stated	-5.3	Maternal Education, Paternal Occupation								Child's Sex, Child's Age
Port Pirie (23, L ,537)	48 months	# 4 years	16.4 (GM)	-9.6 (log10)^	-2.6 (log10)	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight, Gestation	Marital Status, Maternal Age	Unspecified		Maternal		Maternal Medication/Drug Use, Postnatal Factors, Birth Order, Birth Type, Birth Problems, Child's Sex, Residence in Regions, Child's Medical History, Mother's Work Site
Karachi (28, X ,138)	6-8 years	6-8 years	16.08	-4.3^	-6.3^								Haemoglobin	Child's Height for Age

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Port Pirie (35, L ,368)	5 years	11-13 years	14.3 (GM)	-9.8 (ln)^	-4.4 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Port Pirie (35, L ,326)	Lifetime average - 11-13 years	11-13 years	14.1 (GM)	-12.7 (ln)^	-4.7 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cincinnati (13, L ,253)	Mean 39-48 months	6.5 years	14.0	-3.1^	-1.5		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cincinnati (13, L ,253)	Mean 51-60 months	6.5 years	11.8	-4.2^	-2.3^		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Port Pirie (35, L ,360)	7 years	11-13 years	11.6 (GM)	-9.8 (ln)^	-3.7 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Dunedin, New Zealand (33, L ,579)	11 years	11 years	11.1	r=-0.05 (ln)	Not stated									
Sassuolo, Italy (8, X ,211)	7-8 years	7-8 years	10.99 (GM)	r = -0.064 (log10)	Not stated									

*** L=Longitudinal cohort, X=Cross-sectional.**
**** (ln)/(log10) = Original coefficient reported in log scale.**
 # = McCarthy GCI, all unmarked are full-scale IQ measures.
^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Sydney (12, L ,318)	Mean 42,48 months	# 48 months	10.4 (GM)	Not stated	Not stated	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education		Gestation		Total at 48 months		Maternal		
San Luis Potosi, Mexico (10, X ,39) [reference group]	6-9 years	6-9 years	9.73 (GM)	r=.06 (ln)	r=.02 (ln)	Bronffman Index of Socioeconomic Status, Maternal Education, Paternal Education								Child's Sex, Child's Age
San Luis Potosi, Mexico (10, X ,41) [exposed group]	6-9 years	6-9 years	8.98 (GM)	r=-.14 (ln)	r=-.12 (ln)	Bronffman Index of Socioeconomic Status, Maternal Education, Paternal Education								Child's Sex, Child's Age
Mexico City (31, L ,112)	Mean 42-54 months	# 42-54 months	8.4 (GM)	Not stated	Mean square = 6.23 (neg) (ln)	Family Socioeconomic Level, Maternal Education		Birth Weight				Maternal		Postnatal Factors, Birth Order, Child's Sex
Port Pirie (35, L ,326)	11-13 years	11-13 years	7.9 (GM)	-7.1 (ln)^	-3.4 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Rochester (11, L ,172) [all]	Lifetime average - 5 years	5 years	7.4	-10^	-5.7^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Boston (6, L ,170)	57 months	# 57 months	6.4	-4.7 (ln)^	-2.5 (ln)	Hollingshead Index of Social Class		Birth Weight	Family Structure, Marital Status, Residence Changes, Day Care	Total	Child	Maternal		Birth Order, Child's Sex, Medication Used by Child, Preschool Attendance
Boston (7, L ,116)	57 months	10 years	6.3	-9^	-2.6	Hollingshead Four-Factor Index of Social Class		Birth Weight	Family Stress, Marital Status, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Rochester (11, L ,171) [all]	Concurrent - 5 years	5 years	5.9	-10.2^	-6.1^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Boston (7, L ,116)	10 years	10 years	2.9	-15.3^	-4.6	Hollingshead Four-Factor Index of Social Class		Birth Weight	Family Stress, Marital Status, Day Care, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Kosovo (38, L ,258)	Mean AUC7 years	7 years	PbB at age 7 years = 21.2; cumulative PbB through age 7 years = 1.21	-1.4 (log10)	-4.1 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Rochester (11, L ,101) [<10 group]	Concurrent - 5 years	5 years	Not stated	-25.6^	-17.9^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,101) [<10 group]	Lifetime average - 5 years	5 years	Not stated	-25.4^	-15.2^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Sydney (12, L ,318)	Lifetime average - 48 months	# 48 months	Not stated	Not stated	Not stated	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education		Gestation		Total at 48 months		Maternal		
Port Pirie (35, L ,326)	Lifetime average - 5 years	11-13 years	Not stated	-11.1 (ln)^	-5.6 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Port Pirie (35, L ,326)	Lifetime average - 7 years	11-13 years	Not stated	-11 (ln)^	-5.1 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cincinnati (13, L ,253)	Mean 66-72 months	6.5 years	Not stated	-5.8^	-3.3^		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cincinnati (13, L ,253)	Lifetime average - 72 months	6.5 years	Not stated	-3.1^	1.3		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
	(Other)	**(Other)**												
Cleveland (15, L ,167)	3 years	3 years	16.95	r=-.27^	Not stated	Maternal Education			Authoritarian Family Ideology	Total	Child	Maternal		Birth Order, Child's Sex, Child's Age

*** L=Longitudinal cohort, X=Cross-sectional.**
**** (ln)/(log10) = Original coefficient reported in log scale.**
 # = McCarthy GCI, all unmarked are full-scale IQ measures.
^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Cleveland (14, L ,153)	2 years	3 years	16.74	r=-.31^	Not stated	Maternal Education	Maternal Cigarettes per Day	Birth Weight	Authoritarian Family Ideology	Preschool Inventory at 3 years	Child	Maternal		Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, Child's Age
Cleveland (15, L ,153)	2 years	3 years	16.74	r=-.31^	Not stated	Maternal Education			Authoritarian Family Ideology	Total	Child	Maternal		Birth Order, Child's Sex, Child's Age
Cleveland (14, L ,165)	3 years	3 years	16.68	r=-.29^	Not stated	Maternal Education	Maternal Cigarettes per Day	Birth Weight	Authoritarian Family Ideology	Preschool Inventory at 3 years	Child	Maternal		Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, Child's Age
Rochester (11, L ,172) [all]	Peak - 5 years	5 years	11.3	-4.7^	-2.6^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Cleveland (14, L ,126)	6 months	3 years	10.05	r=-.04	Not stated	Maternal Education	Maternal Cigarettes per Day	Birth Weight	Authoritarian Family Ideology	Preschool Inventory at 3 years	Child	Maternal		Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, Child's Age
Cleveland (15, L ,126)	6 months	3 years	10.05	r=-.04	Not stated	Maternal Education			Authoritarian Family Ideology	Total	Child	Maternal		Birth Order, Child's Sex, Child's Age
Rochester (11, L ,172) [all]	Lifetime average - 3 years	3 years	7.7	-7.4^	-3.5	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Rochester (11, L ,172) [all]	Average in infancy - 6-24 months	3 years	7.0	-7.3^	-3.2	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,172) [all]	Average in infancy - 6-24 months	3 & 5 years	7.0	-8.5^	-4.3^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,172) [all]	Lifetime average - 3 & 5 years	3 & 5 years	Not stated	-8.7^	-4.6^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,172) [all]	Peak - 3 years	3 years	Not stated	-4^	-1.9	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,171) [all]	Concurrent - 3 years	3 years	Not stated	-6^	-3.1^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,171) [all]	Concurrent - 3 & 5 years	3 & 5 years	Not stated	-8.1^	-4.6^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,172) [all]	Peak - 3 & 5 years	3 & 5 years	Not stated	-4.4^	-2.3^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Rochester (11, L ,101) [<10 group]	Lifetime average - 3 years	3 years	Not stated	-23^	-12.2	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,101) [<10 group]	Lifetime average - 3 & 5 years	3 & 5 years	Not stated	-24.2^	-13.7^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,101) [<10 group]	Peak - 3 years	3 years	Not stated	-20.9^	-13.6^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,101) [<10 group]	Peak - 5 years	5 years	Not stated	-21.2^	-14.4^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,101) [<10 group]	Peak - 3 & 5 years	3 & 5 years	Not stated	-21^	-14^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,101) [<10 group]	Concurrent - 3 & 5 years	3 & 5 years	Not stated	-23.8^	-15.8^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,105) [<10 group]	Average in infancy - 6-24 months	3 years	Not stated	-12.9	-5.8	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age #	Mean PbB (ug/dL)	Estimated Delta for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental Intelligence	Iron Status	Other
Rochester (11, L ,105) [<10 group]	Average in infancy - 6-24 months	3 & 5 years	Not stated	-14.3^	-7.5	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex
Rochester (11, L ,101) [<10 group]	Concurrent - 3 years	3 years	Not stated	-21.9^	-13.6^	Yearly Household Income, Maternal Education	Tobacco Use during Pregnancy (user/nonuser)	Birth Weight		Total	Mother	Maternal	Serum Transferrin Saturation	Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

 # = McCarthy GCI, all unmarked are full-scale IQ measures.

^ statistically significant (p < 0.05)

Table 3. Summary of studies estimating association of postnatal PbB with performance scale IQ

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
	(<= 2 years)	(>= 4 years)												
Port Pirie (35, L ,367)	15 months	11-13 years	20.9 (GM)	-5.7 (ln)^	-0.7 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Port Pirie (4, L ,494)	Lifetime average - 2 years	7 years	16.6-20.5 (means of 2nd & 3rd quartiles) (GM)	Not stated	-2.6 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Port Pirie (4, L ,494)	Lifetime average - 15 months	7 years	14.3-18.0 (means of 2nd & 3rd quartiles) (GM)	Not stated	-2.5 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Cincinnati (13, L ,253)	Mean 15-24 months	6.5 years	17.1	-2^	-1		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cleveland (16, L ,149)	2 years	4 years 10 months	16.70	r=-.34	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Costa Rica (41, L ,184)	12-23 months	5 years	11.0	r=.05	Not stated									
Cincinnati (13, L ,253)	Mean 3-12 months	6.5 years	10.6	-3.9^	-1.6		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cleveland (16, L ,122)	6 months	4 years 10 months	9.99	r=-.06	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse
Boston (7, L ,116)	18 months	10 years	7.8	Not stated	0	Hollingshead Four-Factor Index of Social Class			Family Stress, Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Boston (7, L ,116)	12 months	10 years	7.7	Not stated	1.4	Hollingshead Four-Factor Index of Social Class			Family Balance, Family Stress, Marital Status	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Parents' Sense Competence, Birth Order, Child's Sex
Boston (7, L ,116)	6 months	10 years	6.7	Not stated	0.3	Hollingshead Four-Factor Index of Social Class			Marital Status	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Boston (7, L ,116)	24 months	10 years	6.5	Not stated	-3.9	Hollingshead Four-Factor Index of Social Class			Family Stress, Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Cincinnati (13, L ,253)	10 Days	6.5 years	5	-4	-2.2		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Boston (34, L ,148)	24 months	10 years	< 8	Not stated	-3.9	Hollingshead Four-Factor Index of Social Class			Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 mo	Child	Maternal		Child Stress, Birth Order, Child's Sex
	(>2 - <4 years)	(>= 4 years)												
Port Pirie (4, L ,494)	Lifetime average - 3 years	7 years	17.4-21.7 (means of 2nd & 3rd quartiles) (GM)	Not stated	-3.1 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Port Pirie (35, L ,372)	3 years	11-13 years	19.3 (GM)	-10.3 (ln)^	-4.6 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cleveland (16, L ,155)	3 years	4 years 10 months	16.70	r=-.28	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse
Cincinnati (13, L ,253)	Mean 27-36 months	6.5 years	16.3	-3.4^	-2.2^		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Cleveland (16, L ,212)	Mean 0.5-3 years	4 years 10 months	9.99 at 6 months & 16.70 at both 2 years & 3 years	r=-.25	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse
Port Pirie (35, L ,326)	Lifetime average - 3 years	11-13 years	Not stated	-8.6 (ln)^	-3.5 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
	(>= 4 years)	**(>= 4 years)**												
Lavrion, Greece (20, X ,509)	Primary school children - not specified years	Primary school children - not specified years	23.7	Not stated	-2.3^	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight	Family Structure, Marital Status, Life Events			Both		Birth Order, Child's Age, Child's Medical History, History Alcohol Abuse, Father's Age, Bilingualism, Length of Child's Hospital Stay after Birth
Port Pirie (4, L ,494)	Lifetime average - 4 years	7 years	17.6-21.5 (means of 2nd & 3rd quartiles) (GM)	Not stated	-3.6 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Port Pirie (4, L ,494)	Lifetime average - 7 years	7 years	15.7-19.7 (means of 2nd & 3rd quartiles) (GM)	Not stated	-2.5 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Mexico City II (26, X ,139)	7-9 years	7-9 years	19.4	r=-.24 (ln)	r=-.28 (ln)	Income, Maternal Education, Paternal Education								Child's Sex, Type of Housing, Nutritional Status (weight for height & height for age)
Port Pirie (35, L ,368)	5 years	11-13 years	14.3 (GM)	-7.9 (ln)^	-4.1 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Port Pirie (35, L ,326)	Lifetime average - 11-13 years	11-13 years	14.1 (GM)	-11.9 (ln)^	-5.2 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cincinnati (13, L ,253)	Mean 39-48 months	6.5 years	14.0	-4.3^	-2.7^		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cincinnati (13, L ,253)	Mean 51-60 months	6.5 years	11.8	-5.5^	-3.8^		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Port Pirie (35, L ,360)	7 years	11-13 years	11.6 (GM)	-9.4 (ln)^	-4.2 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Dunedin, New Zealand (33, L ,579)	11 years	11 years	11.1	r=-0.03 (ln)	Not stated									
Sassuolo, Italy (8, X ,211)	7-8 years	7-8 years	10.99 (GM)	r = -0.100 (log10)	Not stated									
San Luis Potosi, Mexico (10, X ,39) [reference group]	6-9 years	6-9 years	9.73 (GM)	r=.04 (ln)	r=-.10 (ln)	Bronffman Index of Socioeconomic Status, Maternal Education, Paternal Education								Child's Sex, Child's Age
San Luis Potosi, Mexico (10, X ,41) [exposed group]	6-9 years	6-9 years	8.98 (GM)	r=-.08 (ln)	r=.005 (ln)	Bronffman Index of Socioeconomic Status, Maternal Education, Paternal Education								Child's Sex, Child's Age
Port Pirie (35, L ,326)	11-13 years	11-13 years	7.9 (GM)	-6.8 (ln)^	-2.2 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Boston (7, L ,116)	57 months	10 years	6.3	Not stated	-4.4	Hollingshead Four-Factor Index of Social Class		Birth Weight	Family Stress, Marital Status, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Boston (7, L ,116)	10 years	10 years	2.9	Not stated	-1.7	Hollingshead Four-Factor Index of Social Class		Birth Weight	Family Stress, Marital Status, Day Care, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Kosovo (38, L ,261)	Mean AUC7 years	7 years	PbB at age 7 years = 21.2; cumulative PbB through age 7 years = 1.21	Not stated	-4.5 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Port Pirie (35, L ,326)	Lifetime average - 7 years	11-13 years	Not stated	-9.6 (ln)^	-4.7 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Port Pirie (35, L ,326)	Lifetime average - 5 years	11-13 years	Not stated	-9.4 (ln)^	-4.8 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cincinnati (13, L ,253)	Mean 66-72 months	6.5 years	Not stated	-7.5^	-5.2^		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cincinnati (13, L ,253)	Lifetime average - 72 months	6.5 years	Not stated	-4.3^	-2.6^		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Table 4. Summary of studies estimating association of postnatal PbB with verbal scale IQ

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
	(<= 2 years)	(>= 4 years)												
Port Pirie (35, L ,367)	15 months	11-13 years	20.9 (GM)	-7 (ln)^	-3.2 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Port Pirie (4, L ,494)	Lifetime average - 2 years	7 years	16.6-20.5 (means of 2nd & 3rd quartiles) (GM)	Not stated	-6.4 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Port Pirie (4, L ,494)	Lifetime average - 15 months	7 years	14.3-18.0 (means of 2nd & 3rd quartiles) (GM)	Not stated	-5.5 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Cincinnati (13, L ,253)	Mean 15-24 months	6.5 years	17.1	-0.3	0.2		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cleveland (16, L ,149)	2 years	4 years 10 months	16.70	r=-.37	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Costa Rica (41, L ,184)	12-23 months	5 years	11.0	r=.06	Not stated									
Cincinnati (13, L ,253)	Mean 3-12 months	6.5 years	10.6	0	1.2		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cleveland (16, L ,122)	6 months	4 years 10 months	9.99	r=-.05	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse
Boston (7, L ,116)	18 months	10 years	7.8	Not stated	-2	Hollingshead Four-Factor Index of Social Class			Family Stress, Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Boston (7, L ,116)	12 months	10 years	7.7	Not stated	-1.3	Hollingshead Four-Factor Index of Social Class			Family Balance, Family Stress, Marital Status	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Parents' Sense Competence, Birth Order, Child's Sex
Boston (7, L ,116)	6 months	10 years	6.7	Not stated	-2.4	Hollingshead Four-Factor Index of Social Class			Marital Status	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Boston (7, L ,116)	24 months	10 years	6.5	Not stated	-6.3^	Hollingshead Four-Factor Index of Social Class			Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Cincinnati (13, L ,253)	10 Days	6.5 years	5	-0.1	1.1		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Boston (34, L ,148)	24 months	10 years	< 8	Not stated	-6.3^	Hollingshead Four-Factor Index of Social Class			Marital Status, Residence Changes, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
	(>2 - <4 years)	(>= 4 years)												
Port Pirie (4, L ,494)	Lifetime average - 3 years	7 years	17.4-21.7 (means of 2nd & 3rd quartiles) (GM)	Not stated	-6.3 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Port Pirie (35, L ,372)	3 years	11-13 years	19.3 (GM)	-9.3 (ln)^	-2.9 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cleveland (16, L ,155)	3 years	4 years 10 months	16.70	r=-.37	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse
Cincinnati (13, L ,253)	Mean 27-36 months	6.5 years	16.3	-1.4	-0.4		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**
**** (ln)/(log10) = Original coefficient reported in log scale.**
^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Cleveland (16, L ,212)	Mean 0.5-3 years	4 years 10 months	9.99 at 6 months & 16.70 at both 2 years & 3 years	r=-.29	Not stated	Maternal Education	Cigarettes per Day	Birth Weight, Gestation	Authoritarian Family Ideology	Total (mean of 1, 2, 3, and 4 years 10 months)	Child	Maternal		Child Stress, Maternal Medication/Drug Use, Maternal Alcohol Consumption, Birth Order, Child's Sex, History Alcohol Abuse
Port Pirie (35, L ,326)	Lifetime average - 3 years	11-13 years	Not stated	-10.2 (ln)^	-5.1 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
	(>= 4 years)	**(>= 4 years)**												
Lavrion, Greece (20, X ,509)	Primary school children - not specified years	Primary school children - not specified years	23.7	Not stated	-2.52^	Maternal Education, Paternal Education, Paternal Occupation		Birth Weight	Family Structure, Marital Status, Life Events			Both		Birth Order, Child's Age, Child's Medical History, History Alcohol Abuse, Father's Age, Bilingualism, Length of Child's Hospital Stay after Birth
Port Pirie (4, L ,494)	Lifetime average - 4 years	7 years	17.6-21.5 (means of 2nd & 3rd quartiles) (GM)	Not stated	-5.5 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Port Pirie (4, L ,494)	Lifetime average - 7 years	7 years	15.7-19.7 (means of 2nd & 3rd quartiles) (GM)	Not stated	-4.7 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education, Paternal Education	Parental Smoking	Birth Weight	Family Structure, Maternal Age	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex
Mexico City II (26, X ,139)	7-9 years	7-9 years	19.4	r=-.24 (ln)	r=-.19 (ln)	Income, Maternal Education, Paternal Education								Child's Sex, Type of Housing, Nutritional Status (weight for height & height for age)
Port Pirie (35, L ,368)	5 years	11-13 years	14.3 (GM)	-9.2 (ln)^	-4.1 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Port Pirie (35, L ,326)	Lifetime average - 11-13 years	11-13 years	14.1 (GM)	-11.9 (ln)^	-4.3 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cincinnati (13, L ,253)	Mean 39-48 months	6.5 years	14.0	-1.4	-0.2		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cincinnati (13, L ,253)	Mean 51-60 months	6.5 years	11.8	-2.2	-0.7		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Port Pirie (35, L ,360)	7 years	11-13 years	11.6 (GM)	-8.7 (ln)^	-3.1 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Dunedin, New Zealand (33, L ,579)	11 years	11 years	11.1	r=-0.06 (ln)	Not stated									
Sassuolo, Italy (8, X ,212)	7-8 years	7-8 years	10.99 (GM)	r = -0.101 (log10)	Not stated									
San Luis Potosi, Mexico (10, X ,39) [reference group]	6-9 years	6-9 years	9.73 (GM)	r=.04 (ln)	r=.07 (ln)	Bronffman Index of Socioeconomic Status, Maternal Education, Paternal Education								Child's Sex, Child's Age
San Luis Potosi, Mexico (10, X ,41) [exposed group]	6-9 years	6-9 years	8.98 (GM)	r=-.12 (ln)	r=-.25 (ln)	Bronffman Index of Socioeconomic Status, Maternal Education, Paternal Education								Child's Sex, Child's Age
Port Pirie (35, L ,326)	11-13 years	11-13 years	7.9 (GM)	-6.3 (ln)^	-2.6 (ln)	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Boston (7, L ,116)	57 months	10 years	6.3	Not stated	-0.7	Hollingshead Four-Factor Index of Social Class		Birth Weight	Family Stress, Marital Status, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Study Population* (ref., type, n)	PbB Age	Outcome Age	Mean PbB (ug/dL)	Estimated Delta IQ for PbB 5 -> 15**		Covariates in Model								
				Crude	Adj	SES	Smoking	Fetal Growth	Family Environment	HOME	Race	Parental IQ	Iron Status	Other
Boston (7, L ,116)	10 years	10 years	2.9	Not stated	-5.9	Hollingshead Four-Factor Index of Social Class		Birth Weight	Family Stress, Marital Status, Day Care, Maternal Age	Scales V & VI at 120 months, Total at 57 months	Child	Maternal		Child Stress, Birth Order, Child's Sex
Kosovo (38, L ,259)	Mean AUC7 years	7 years	PbB at age 7 years = 21.2; cumulative PbB through age 7 years = 1.21	Not stated	-3.4 (log10)^	Maternal Education		Birth Weight	Family Structure, Maternal Age	Unspecified	Child	Maternal		Child's Sex
Port Pirie (35, L ,326)	Lifetime average - 5 years	11-13 years	Not stated	-10.8 (ln)^	-5.5 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Port Pirie (35, L ,326)	Lifetime average - 7 years	11-13 years	Not stated	-10.5 (ln)^	-4.7 (ln)^	Daniel's Scale of Prestige of Occupations in Australia, Maternal Education	Parental Smoking Habits	Birth Weight	Family Structure, Family Functioning, Marital Status, Maternal Age, Life Events	Unspecified		Maternal		Breast Feeding, Feeding Method, Birth Order, Child's Sex, Child's Age, School Grade, School Absence
Cincinnati (13, L ,253)	Mean 66-72 months	6.5 years	Not stated	-3.3^	-1.2		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex
Cincinnati (13, L ,253)	Lifetime average - 72 months	6.5 years	Not stated	-1.3	-0.1		Cigarette Consumption during Pregnancy	Birth Weight, Birth Length		Unspecified		Maternal		Child's Sex

*** L=Longitudinal cohort, X=Cross-sectional.**

**** (ln)/(log10) = Original coefficient reported in log scale.**

^ statistically significant (p < 0.05)

Table 5. Studies of health endpoints other than IQ or GCI in relation to BLLs <10 µg/dL.

Study population (ref., type, n)	Health outcome	Age at measurement: BLL	Age at measurement: Outcome	BLL distribution	Covariates	Results on BLL-outcome association <10 µg/dL
NHANES III (22, X, 4853)	Cognitive function and academic achievement	6-16 years	6-16 years	Geometric mean (GM)=1.9 µg/dL, 98% <10 µg/dL	Sex, race/ethnicity, poverty, region, parent/caregiver education and marital status, serum ferritin, serum cotinine.	Significant inverse relationships between BLL and WRAT arithmetic, WRAT reading, WISC R block design, WISC-R digit span. For all but block design, regression slopes became more negative with restriction of analyses to children with BLL <10, < 7.5, < 5.0, and < 2.5 µg/dL.
Leipzig, Gardelegen, Duisberg, Germany (36, X, 384)	Attention, sensorimotor function, and cognitive function	5-7 years	5-7 years	GM=4.25 µg/dL, 95 % <9 µg/dL	For WISC vocabulary and block design: Study area, visual acuity and contrast sensitivity, parental education, sex, breastfeeding, height, nationality. For NES2 pattern comparison, pattern memory, tapping, simple reaction time, and continuous performance test: study area, visual acuity and contrast sensitivity, age, parental education, sex, birthweight, smoking in pregnancy, number of siblings, height, computer familiarity.	Significant negative association between WISC vocabulary and CPT results. Associations strongest in Gardelegen, community with lowest mean BLL.
Leipzig, Gardelegen, Duisberg, Germany (40, X, 367)	Neurobehavioral and neurophysiologic function	6 years	6 years	Median=5 µg/dL, 95 % <10 µg/dL	For NES2 tapping, benton (pattern memory), reaction time, pattern comparison: age, sex, parental education, study area. For Visual Evoked Potentials: age, gender, study area.	Significant negative association of log transformed blood lead with tapping speed and with pattern comparison. No significant association of log-transformed BLL with visual evoked potential peak latencies.

Study population (ref., type, n)	Health outcome	Age at measurement		BLL distribution	Covariates	Results on BLL-outcome association <10 µg/dL
		BLL	Outcome			
New York (24, X, 68)	Mental development	12-36 months	12-36 months	Mean=10.3 µg/dL	Receives public assistance, maternal education, HOME - Stim Q, child race, maternal IQ, anemia or low MCV, birth order, sex, age	Significantly lower Bayley MDI for children ≥10 µg/dL vs <10; scatterplot of adjusted MDI vs. BLL suggests relation linear relation continues at BLL <10.
Leipzig, Gardelegen, Duisberg, Germany (1, X, 746)	NES1 – Tapping Test and pattern recognition	5 and 6 years	5 and 6 years	Median=5 µg/dL and 95th percentile of overall frequency distribution for PbB was <10 µg/dL	Maternal education, child's sex, child's age	Authors report that after adjustment for confounders a significant deficit for tapping and pattern comparison in relation to BLL ($p<0.05$) was found, but no regression coefficient or dose-response analyses are presented.
Leipzig, Gardelegen, Duisberg, Germany (2, X, 384)	Visual function	5-7 years	5-7 years	GM=4.25 µg/dL, 95% <9 µg/dL	Child's age, assessment site, birth weight, child's medical history, head circumference, child weight, quality of fixation	Visual evoked potential interpeak latencies were significantly prolonged in relation to BLL for one of three visual stimuli tested and non-significantly prolonged for a second stimulus. No significant association between BLL and contrast sensitivity was seen.
Study location not stated (3, X, 400)	Neurotransmitter and neuroendocrine levels	8.5-12.3 years	8.5-12.3 years	Mean=3.95 µg/dL		No significant correlation overall between BLL and serum prolactin (Pro-S) or urinary homovanillic acid (HVA-U). Analysis performed on only those children BLL >5 µg/dL showed a weak but statistically direct relation to BLL.
NHANES III (5, X, 4391)	Stature and head circumference	1-7 years	1-7 years		Ethnic group, iron status, dietary intake, medical history, sociodemographic factors, and household characteristics	Significant inverse association of BLL to stature and head circumference (estimated decrease of 1.57 cm in stature and 0.52 cm in head circumference for each 10 µg/dL increase in BLL).

Study population (ref., type, n)	Health outcome	Age at measurement: BLL	Age at measurement: Outcome	BLL distribution	Covariates	Results on BLL-outcome association <10 µg/dL
Mexico City (30, L, 119-199)	Head circumference	every 6 months from 6-48 months	every 6 months from 6-48 months	Median postnatal varied from 7-10 µg/dL	Birth problems, child's race, maternal head circumference, head circumference at birth	Natural log of blood lead at 12, 18, and 24 months significantly related to head circumference at 36 months; Natural log of blood lead at 12 months significantly related to head circumference at 42 months. Most other partial correlations between postnatal blood were negative. Plot of covariate adjusted head circumference at 36 months vs. natural log of blood lead at 12 months shows inverse relation that appears to continue below 10 µg/dL.
Lavrion, Elefsina, Loutraki Greece (21, X, 522)	Somatic growth, including head circumference, height, and chest circumference	6-9 years	6-9 years	Mean=12.3 µg/dL, Median=9.8 µg/dL	Paternal education, paternal occupation, child's sex, child's age, iron status, assessment site, father's height, mother's height	Significant negative association of BLL and head circumference and height with scatterplot suggesting relation continues below 10 µg/dL. No significant association with chest circumference.
NHANES III (32, X, 2186) girls: 1964 with pubic hair stage, 1986 with breast development stage and 1796 with age at menarche.) (African American only)	Pubertal development in girls	8-18 years	8-18 years	GMs: Non-Hispanic whites:=1.4 µg/dL; African Americans: = 2.1; Mexican Americans= 1.7µg/dL. BLLs >5 µg/dL: 2.7%, 11.6% and 12.8%, respectively	Family income, ever smoked 100 cigarettes, child's age, iron status, child's medical history, height, BMI, age squared For age at menarche: height, family income, ever smoked 100 cigarettes, child's age, iron status, child's medical history, height, MI, age squared	Blood lead levels of 3 µg/dL (compared with BLLs of 1 µg/dL) were associated with significant delays in breast and pubic hair development in African American and Mexican girls. The trend was similar, but not significant, for non-Hispanic white girls. Age at menarche was also delayed in relation to higher BLLs, but the association was only significant for African-American girls.

Study population (ref., type, n)	Health outcome	Age at measurement: BLL	Age at measurement: Outcome	BLL distribution	Covariates	Results on BLL-outcome association <10 µg/dL
NHANES III (42, X, Sample I: 1706 ages 8-16 years with pubic hair and breast development info; Sample II: 1235 girls aged 10-16 had info on menarche) (all races)	Pubertal development in girls	8-16 years	8-16 years	98.5% <10; 54.3% 0-2.0	Poverty income ratio, family size, metro residence, child's age, child's race, BMI	Compared with BLLs 2.0 µg/dL and below, BLLs of 2.1-4.9 were associated with significantly lower odds of attaining Tanner Stage 2 pubic hair (0R=0.48, 95% CI 0.25-0.92) and menarche (OR=0.42, 95% CI 0.18-0.97); no significant association with breast development was noted.
NHANES III (25, X, 24901)	Dental caries	2+ years	2+ years	GMs: Age 2-5 years=2.9 µg/dL, Age 6-11 years=2.1 µg/dL; Age 12+ years=2.5 µg/dL; 74-88% of participants with BLL <5 µg/dL in each age group	Poverty income ratio, maternal education, exposure to cigarette smoke, child's sex, child's age, child's race, assessment site, child's medical history, days since last dental visit, usual frequency of dental visits	Comparing children 5-17 years of age in middle tertile of BLL (range of BLLs: 1.7-4.1) to those in lowest tertile, odds ratio for dental caries was 1.36 (1.01-1.83)
Boston & Cambridge, MA and Farmington, ME (18, X, 543)	Dental caries	6-10 years	6-10 years	Means: Cambridge/ Boston 2.9 µg/dL, Farmington 1.7 µg/dL	Age, sex, family income, education of female guardian, ethnicity, maternal smoking, tooth brushing frequency, tooth brush bristle hardness, gum chewing	In Cambridge/Boston, number of carious surfaces increased significantly with log BLL in linear regression and in graph comparing children with BLL of 1, 2, and 3µg/dL. In Farmington, non-significant decrease in carious surfaces with increasing BLL
Kosovo (17, L, 281)	Blood pressure	66 months	66 months	K. Mitrovica: mean=37.3 µg/dL (sd=12.0); Pristina: mean=8.7 µg/dL (sd=2.8)	For systolic blood pressure: birth order, child's sex, child's race, height, BMI For diastolic blood pressure: birth order, child's race	Figures showing adjusted mean systolic and diastolic blood pressure for 10 blood lead groups with approximately equal numbers in each ordered by blood lead shows no consistent trend among the 4 blood lead groups with BLL approximately 5-10 µg/dL.

Study population (ref., type, n)	Health outcome	Age at measurement: BLL	Age at measurement: Outcome	BLL distribution	Covariates	Results on BLL-outcome association <10 µg/dL
Belgium (29, X, 143)	Heme synthesis biomarkers	10-13 years	10-13 years	Means: Boys: <1 km: 28.7 µg/dL (SD=8); 2.5 km: 15.6 (2.9); urban: 10.6 (2.0); rural: 9.2 (2.3) Girls: <1 km: 20.7 (7.6); 2.5 km: 9.8 (3.8); urban: 9 (2.0); rural: 8.7 (17)	Not specified	Dose-effect relationships are plotted for FEP, ALAD, and ALAU. No threshold evident for ALAD inhibition. Authors state if it exists, it must be below 8-10 µg/dL. A BLL 5 threshold for increasing FEP evident at 15-20 µg/dL Pb.
Boston (27, L, 249 originally recruited; 201 at 2 years)	Heme synthesis biomarkers	6-24 months	6-24 months	Mean=7 µg/dL	Not specified	No relationship between incidence of elevated erythrocyte protoporphyrin levels and BLLs below 15 µg/dL
Cincinnati (19, L, 165)	Heme synthesis biomarkers	6-30 months	6-30 months	Not presented	None presented, crude results only	Significant positive association reported for FEP and ZPP and log transformed BLL at all ages. Threshold for relationship at BLL between 15 and 20 µg/dL.
Pribam, Czech Republic (9, X, 246)	Renal function	12-15 years	12-15 years	Mean ranged from 8.39 µg/dL in girls in the control area to 14.9 µg/dL in boys in polluted area 2	None presented, crude results only	Urinary RBP was found to be significantly associated with BLL in a stepwise regression. When urinary RBP excretion was examined by BLL tertiles, significantly lower U-RBP was seen in the group with BLL <8.64 µg/dL compared with BLL 8.64-12.3.

Table 6. Selected methodologic details from cohort studies

Study Population	Quality Assurance Comments	
	Blood-lead Measurement	**Cognitive Function Measurement**
Boston (6, 7, 34)	Samples were measured by capillary and venous and were analyzed by ASV and GFAAS. Blood specimens for 6-, 12-, 18, and 24-month specimens were collected in capillary tubes by trained technicians. Blood samples were assayed in duplicate or triplicate. The analytical system was calibrated with aqueous standards of known lead concentrations. Each batch of samples was accompanied by a blood sample of known lead concentrations to quantify intralaboratory reliability. Several standardized blood samples with lead concentrations also were included after they became available in 1982 from CDC. (Rabinowitz, et al., 1985) 57-month venous blood samples were obtained. Lead was measured in duplicate by GFAAS. An aliquot of a standardized blood sample provided by the National Bureau of Standards was included in each batch of samples. (Bellinger, et al., 1991)	MDI was administered at 6-month intervals beginning at 6 months of age, by examiners blind to the infants' lead levels. (Bellinger, et al., 1985) For WISC-R , most children were tested in a single session, 2 were seen in a second session to complete testing, and 7 were tested in their homes by parental request. Psychologists were blind to all aspects of child's developmental and lead exposure histories.
Cincinnati (13)	Samples were measured by venipuncture, heel stick, and finger stick for infants and were analyzed by ASV. Blood samples were obtained using either venipuncture or heel stick. Approximately 72% of all samples are venipuncture. For heel stick, two capillary tubes were filled for duplicate PbB determination. If venipuncture was possible, pediatric vacutainer tubes were filled, one for PbB determination and a second for serum iron and total iron binding capacity (TIBC) analyses. The sample was aliquoted and duplicate analyses performed according to a predetermined protocol using ASV. The laboratory participates in both the CDC and PA State Blood Lead and Protoporphyrin Programs. A series of bench-top QC samples and blind QC samples were analyzed with each run. (Bornschein et al., 1985)	For WISC-R, one experienced psychometrician performed all the assessments. Children were tested at a pediatric clinic. The examiner was blind to the exposure levels of the child. For MDI, all assessments took place in a prenatal and child welfare clinic. Psychometric tests were administered at an inner-city health clinic by the study leader or trained assistant with whom inter-tester reliability had been previously established. Testers were blind to children's blood-lead levels.
Cleveland (14, 15, 16)	Samples were measured by venous and were analyzed by GFAAS. Blood samples were collected in heparinized plastic syringes which had been determined to be free of trace metals. The concentration of lead in whole blood samples was determined by GFAAS. All samples were run in duplicate. The within-run (same day) reproducibility was evaluated for a sample of adult whole blood. The obtained values were 55.2 ug/dl, 1.34, and 2.4%, respectively, for the mean, SD, and coefficient of variation. Regular assessment of accuracy and precision using CDC samples of bovine blood were conducted and found to be within the certified range. Two inter-laboratory reviews were conducted for further determination of accuracy. Blood-lead levels were not adjusted for hematocrit. (Emhart, et al., 1985)	WPPSI, MDI, and Stanford Binet IQ tests were conducted by well-trained examiners blind to all risk and background information. Home testing was used to control attrition, to minimize bias in attrition, and to facilitate administration of the HOME Inventory. Inter-observer agreement was checked through observation and duplicate scoring by a supervisor for approximately one out of every 26 examinations. Agreement was maintained at r=.99. Answer sheets were checked for possible irregularities by the supervisor within a few days of each administration.
Costa Rica (41)	Samples were measured by venous and were analyzed by GFAAS. Venipuncture samples were taken and red blood cells were promptly separated and frozen for future analysis in the U.S. The frozen red cells were analyzed using GFAAS in a laboratory that participates in CDC's Maternal and Child Health Resources Development Proficiency Testing Program for Blood Lead. Quality control was monitored through certified controls obtained from the National Bureau of Standards. Red cell lead values were converted to whole blood-lead levels using the formula of Rosen et al.(1974).	Spanish versions of Bayley MDI and WPPSI were used in the assessment. A single tester, trained by one of the primary investigators and the most senior research psychologist in the country, administered the assessments. The tester was blind to the children's iron status and never knew the blood-lead levels (these were performed in the U.S.). (Lozoff, personal communication)
Kosovo (37, 38)	Samples were measured by venous and were analyzed by GFAAS. All blood specimens were refrigerated on site and transported on wet ice to Columbia University where all assays were performed. The laboratory participates in CDC's PBB QC program and is certified by OSHA. Over the study period, interclass correlation with QC values was computed, with correlation coefficients of .95 for PbB.	Three Yugoslavian psychologists scored the WISC-R and the McCarthy GCI independently. All interviews and assessment instruments were translated and administered in the two dominant languages of the region, Serbo-Croatian and Albanian. Training and reliability visits occurred. The average interclass correlation for 96 tests over study period was calculated.
Mexico City (31)	Samples were measured by venous and were analyzed by ASV. Samples were analyzed at Environmental Sciences Associates (ESA) Laboratories, Inc., which is a CDC reference lab for the Blood Lead Proficiency Testing Program and also participates in the New York State Department of Control Program. All samples were analyzed using ASV. Samples with mean duplicate values < 5 ug/dl were reanalyzed in duplicate by graphite furnace AAS. Mean values of the duplicates were used as data. (Rothenberg, et al., 1994)	Four trained psychologists blind to children's lead levels administered the McCarthy GCI. As there were no norms for the McCarthy scale in the Mexican population, the U.S. norms were used to calculate GCI, with a Spanish translation of the test. Interexaminer reliability was assessed by calculating the correlation in GCI scores assigned by two of the psychologists with the scores of a third psychologist whom they observed applying the test in all possible combinations with 10 subjects for each combination. Mean observer-examiner correlation was .99.

APPENDIX A:

LITERATURE REVIEW AND CLASSIFICATION UPDATE

The literature review began with the Agency for Toxic Substances and Disease Registry's Toxicological Profile for Lead (ATSDR Tox Profile), published July 1999. The Health Effects chapter was thoroughly read and all articles relating to low blood lead levels in children were chosen, regardless of whether they demonstrated significant results. New literature searches were then performed by Battelle's Technical Information Center. The year 1995 was chosen as the cutoff date for the new searches because the WG felt that, before this time, research rarely focused on BLLs <10 µg/dL, and that most relevant articles before 1995 were cited in the ATSDR Toxicological Profile. Searches were performed on a variety of databases using DIALOG and a set of keywords.

The following is an example of the DIALOG, including databases and keywords:

SYSTEM:OS - DIALOG OneSearch
File 6:NTIS 1964-2003/May W3 (c) 2003 NTIS, Intl Cpyrght All Rights Res
File 103:Energy SciTec 1974-2003/May B1 (c) 2003 Contains copyrighted material
File 266:FEDRIP 2003/Mar Comp & dist by NTIS, Intl Copyright All Rights Res
File 161:Occ.Saf.& Hth. 1973-1998/Q3 (c) Format only 1998 The Dialog Corp.
File 156:ToxFile 1965-2003/May W2 (c) format only 2003 The Dialog Corporation
File 155:MEDLINE(R) 1966-2003/May W2 (c) format only 2003 The Dialog Corp.
File 162:Global Health 1983-2003/Apr (c) 2003 CAB International
File 71:ELSEVIER BIOBASE 1994-2003/May W3 (c) 2003 Elsevier Science B.V.
File 40:Enviroline(R) 1975-2003/May
File 73:EMBASE 1974-2003/May W1 (c) 2003 Elsevier Science B.V.
File 34:SciSearch(R) Cited Ref Sci 1990-2003/May W2 (c) 2003 Inst for Sci Info
File 5:Biosis Previews(R) 1969-2003/May W2 (c) 2003 BIOSIS

Set	Items	Description
S1	512735	NATAL? OR PRENATAL? OR PERINATAL? OR POSTNATAL?
S2	1244432	INFANT? ? OR INFANCY
S3	2607491	CHILD? ? OR CHILDREN? ?
S4	253558	LEAD/TI,DE,ID
S5	184354	PB
S6	68959	RN=7439-92-1
S7	5798237	BLOOD
S8	14048	(S1:S3) AND (S4:S6) AND S7
S9	2153692	GROWTH/TI,DE,ID
S10	31450	STATURE
S11	634981	NUTRITION
S12	169948	HEARING
S13	200409	(RENAL OR KIDNEY)(3N)FUNCTION?
S14	669012	BLOOD()PRESSURE
S15	13	HEMESYNTHESIS
S16	61334	HEMATOPOIESIS
S17	20269	(VITAMIN()D)(3N)METABOLI?
S18	1441	S8 AND (S9:S17)
S19	438	S18 AND PY=1990:1996
S20	422	S19/ENG OR (S19 AND LA=ENGLISH)
S21	353	S20/HUMAN
S22	190	RD (unique items)
S23	190	Sort S22/ALL/PY,D

S24 19583 NEUROBEHAVIO?
S25 272980 NEUROLOGICAL?
S26 166224 NEUROLOGIC
S27 148942 NEUROTOXIC?
S28 15459 NEURODEVELOPMENT?
S29 7061 COGNITIVE()DEVELOPMENT
S30 2878983 BEHAVIOR? OR BEHAVIOUR?
S31 3 IMPULSITIVITY
S32 54987 HYPERACTIVITY
S33 10725 ADHD
S34 31451 IQ OR (INTELLIGENCE()QUOTIENT? ?)
S35 3350 WISC
Ref Items Index-term
E1 715223 *DC=A8.186. (Central nervous system)
E2 645734 DC=A8.186.211. (Brain)
E3 23250 DC=A8.186.211.132. (Brain stem)
S36 715223 DC='A8.186.':DC='A8.186.211.132.'
S37 2936 (S8 AND (S24:S36)) NOT S18
S38 964 S37 AND PY=1990:1996
S39 941 S38/ENG OR (S38 AND LA=ENGLISH)
S40 808 S39/HUMAN
S41 415 RD (unique items)

This literature search was first run for the years 1995-2002. In spring, 2003, the search was rerun for the years 2002-2003 to determine the relevance of recently published articles. Also at this time, the search was rerun for the years 1990-1996 for relevant articles that were not cited in the ATSDR Toxicological Profile. Titles and abstracts from each literature search were reviewed, and relevant articles were ordered for further review. Additional articles were identified while reviewing the selected articles and were added to the list of references, as were several articles recommended by workgroup members.

The table below provides a summary of all the articles obtained from the various sources. This table shows when the search was performed, the years covered in the search, the number of articles found in the literature search, the number of articles ordered after the titles and abstracts had been reviewed, and the number of articles that were relevant for abstraction.

Summary of Literature Review Results

Date of Search	Years Covered	Number of Unique References Found	Number of reviewed for relevance	Number of Articles Abstracted into the Database
9/02	1995-2002	327	79	12
4/03	2002-2003	119	14	4[a]
5/03	1990-1996	605	25	4
ATSDR Tox Profile	Prior to 1996	-	107	24
Referrals[b]	various	10	12	6
		Total:	**235**	**50**
Relevant articles cited in Tables 2- 5				**42**

[a]A 5th article, Stone et al. 2003, was obtained from this search and is not abstracted into the database but its relevance is discussed elsewhere in the report.

[b]Referrals include articles that were recommended by workgroup members, as well as those articles cited as references in studies identified in the ATSDR Tox Profile or literature searches.

APPENDIX B:

DISCUSSION OF CRITIQUE OF NHANES III DATA BY STONE ET AL. (2003)

Stone et al. (2003) reanalyzed the data used by Lanphear et al. (2000). While the results they present are largely consistent with the findings of Lanphear et al. (2000), they provided a critique of the validity of the NHANES III data for evaluating lead-related impacts on neuropsychological development in children. Because their critique cuts across on neuropyschological measurements performed in the survey, the main points of their paper are summarized in this appendix, as follows.

- Stone et al. note that the weighted mean values for the four measures used by Lanphear et al. are below the predicted mean based on standardization data for these tests collected in the early 1970s for the WISC-R) and early 1980s for the WRAT. Stone et al. argue that the mean values should be higher than predicted by the standardization means because of secular improvements in cognitive test scores. One possible reason cited for the discrepancy is that NHANES tests were not administered by a psychologist. It is unclear, however, if the population sample used in the standardization data was equally representative of the U.S. population at that time or if changes in the population composition since then would lead to an increase or decrease in overall mean test performance. More importantly, it is unclear how a bias in mean score, even if real, and the use of non-psychologists for testing could produce associations between BLLs and test scores, given that examiners could not have known the BLLs of participants. If non-psychologists produced less precise test results than psychologists would have, the expected impact on regression coefficients would be a bias toward the null.
- The age-adjusted scores used in NHANES are correlated with age, and they should not be. Stone et al. show that age is negatively correlated with arithmetic, block design, and digit span and positively correlated with reading. However, since BLLs decrease with age across the age range studied, the negative correlations would tend to produce a trend towards higher scores with increasing blood lead for those tests, the opposite of the findings of Stone et al.
- Imputation of missing covariate values was performed for a substantial proportion of observations in the analyses performed by Lanphear et al. While imputation could increase covariate mismeasurement and residual confounding, analyses presented by Stone et al. demonstrate essentially similar findings when analyses are restricted to observations with full rank data.
- Relevant covariates, including whether a child has repeated a grade, whether interviews were in Spanish, and several other factors, were not included in analyses. However, two problems are evident in alternative “two stage” analysis provided by Stone et al. First, it uses predicted rather than residual blood lead level as an independent variable in a model relating blood lead to test scores. This amounts to testing the relation to test scores of a linear combination of covariates, many included in the model with test score as the outcome. In addition at least one variable – having to repeat a grade – is included as a covariate, possibly result serious over control as

discussed earlier. Lead associated cognitive and behavioral effects have, not surprisingly, been associated with an increased risk of failure to complete high school. Thus, controlling for failure to complete a grade could amount to controlling for an effect of, rather than a confounder of the lead effect.

As a whole, the Stone et al. critique of the NHANES III data do not provide a convincing argument that the findings reported by Lanphear et al. (2000) result from problems with the sample or testing methods. However, the WG did consider the limitations of the Lanphear et al. study, including its cross-sectional design and limited data on potential confounders. This study was weighed in the overall context of other relevant studies, including the more persuasive cohort studies, which are largely consistent with the associations Lanphear et al. report.

REFERENCES

Note: *Table R-1, which follows this alphabetical listing of references, identifies the numbered references that are used in Tables 2 through 6 (which also are included in the alphabetical listing).*

Agency for Toxic Substances and Disease Registry. Toxicological profile for lead. Atlanta: U.S. Department of Health and Human Services, 1999.

Al-Saleh, I., Nester, M., DeVol, E., Shinwari, N., Munchari, L., Al-Shahria, S. Relationships between blood lead concentrations, intelligence, and academic achievement of Saudi Arabian schoolgirls. Int J Hyg Environ Health. 2001;204:165–174.

Altmann, L., Sveinsson, K., Kramer, U., Weishoff-Houben, M., Turfeld, M., Winneke, G., et al. Visual functions in 6-year old children in relation to lead and mercury levels. Neurotoxicol Teratol. 1998;20:9–17.

Altmann, L., Sveinsson, K., Kramer, U., Winneke, G., Wiegand, H. Assessment of neurophysiologic and neurobehavioral effects of environmental pollutants in 5- and 6-year-old children. Environ Res. 1997;73:125–131.

Alvarez Leite, E.M., Leroyer, A., Nisse, C., Haguenoer, J.M., de Burbure, C.Y., Buchet, J.P., et al. Urinary homovanillic acid and serum prolactin levels in children with low environmental exposure to lead. Biomarkers. 2002;7:49–57.

Anderson, S.E., Dallal, G.E., Must, A. Relative weight and race influence average age at menarche: results from two nationally representative surveys of U.S. girls studied 25 years apart. Pediatrics. 2003;111:844–850.

Annest, J.L., Pirkle, J.L., Makuc, D., Neese, J.W., Bayse, D.D., Kovar, M.G. Chronological trend in blood lead levels between 1976 and 1980. N Engl J Med. 1983;308:1373–1377.

Baghurst, P.A., McMichael, A.J., Wigg, N.R., Vimpani, G.V., Robertson, E.F., Roberts, R.J., et al. Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study. N Engl J Med. 1992;327:1279–1284.

Baghurst, P.A., Tong, S.L., Sawyer, M.G., Burns, J.M., McMichael, A.J. Sociodemographic and behavioural determinants of blood lead concentrations in children aged 11-13 years. The Port Pirie Cohort Study. Med J Aust. 1999;170:63–67.

Bailey, D.A., Martin, A.D., McKay, H.A., Whiting, S., Mirwald, R. Calcium accretion in girls and boys during puberty: a longitudinal analysis. J Bone Miner Res. 2000;15:2245–2250.

Ballew, C., Khan, L.K., Kaufmann, R., Mokdad, A., Miller, D.T., Gunter, E.W. Blood lead concentration and children's anthropometric dimensions in the third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. J Pediatr. 1999;134:623–630.

Bannon, D.I., Chisolm, J.J. Anodic stripping voltammetry compared with graphite furnace atomic absorption spectrophotometry for blood lead analysis. Clin Chem. 2001;47:1703–1704.

Bellinger, D.C. Interpreting the literature on lead and child development: the neglected role of the "experimental system." Neurotoxicol Teratol. 1995;17:201–212.

Bellinger, D.C., Leviton, A., Rabinowitz, M.B., Needleman, H.L., Waternaux, C. Correlates of low-level lead exposure in urban children at 2 years of age. Pediatrics. 1986;77:826–833.

Bellinger, D.C., Leviton, A., Waternaux, C. Lead, IQ and social class. Int J Epidemiol. 1989;18:180–185.

Bellinger, D.C., Leviton, A., Waternaux, C., Allred, E. Methodological issues in modeling the relationship between low-level lead exposure and infant development: examples from the Boston Lead Study. Environ Res. 1985;38:119–129.

Bellinger, D.C., Leviton, A., Waternaux, C., Needleman, H.L., Rabinowitz, M.B. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. N Engl J Med. 1987;316:1037–1043.

Bellinger, D.C., Leviton, A., Waternaux, C., Needleman, H.L., Rabinowitz, M.B. Low-level lead exposure and early development in socioeconomically advantaged urban infants. In: Smith M, Grant L.D.; Sors A Ieds. Lead Exposure and Child Development: An International Assessment. Lancaster, UK: Kluwer Publishers. 1989:345–356.

Bellinger, D.C., Leviton, A., Waternaux, C., Needleman, H.L., Rabinowitz, M.B. Low-level lead exposure, social class, and infant development. Neurotoxicol Teratol. 1988;10:497–503.

Bellinger, D.C., Needleman, H.L. Correspondence: Intellectual Impairment and blood lead levels. N Engl J Med. 2003;349:500–502.

Bellinger, D.C., Sloman, J., Leviton, A., Rabinowitz, M.B., Needleman, H.L., Waternaux, C. Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics. 1991;87:219–227.

Bellinger, D.C., Stiles, K.M., Needleman, H.L. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics. 1992;90:855–861.

Bergomi, M., Borella, P., Fantuzzi, G., Vivoli, G., Sturloni, N., Cavazzuti, G., et al. Relationship between lead exposure indicators and neuropsychological performance in children. Dev Med Child Neurol. 1989;31:181–190.

Bernard, A., Vyskocil, A., Roels, H.A., Kriz, J., Kodl, M., Lauwerys, R. Renal effects in children living in the vicinity of a lead smelter. Environ Res. 1995;68:91–95.

Bornschein, R.L., Succop, P.A., Dietrich, K.N., Clark, S.C., Que Hee, S., Hammond, P.B. The influence of social and environmental factors on dust lead, hand lead, and blood lead levels in young children. Environ Res. 1985;38:108–118.

Brandt, J., Van Gorp, W. American Academy of Clinical Neuropsychology policy on the use of non-doctoral level personnel in conducting clinical neuropsychological evaluations. J Clin Exp Neuropsychol. 1999;21:1–1.

Brockel, B.J., Cory-Slechta, D.A. Lead, attention, and impulsive behavior: changes in a fixed-ratio waiting-for-reward paradigm. Pharmacol Biochem Behav. 1998;60:545–552.

Bronner, F., Abrams, S.A. Development and regulation of calcium metabolism in healthy girls. J Nutr. 1998;128:1474–1480.

Bushnell, P.J., Bowman, R.E. Persistence of impaired reversal learning in young monkeys exposed to low levels of dietary lead. J Toxicol Environ Health. 1979;5:1015–1023.

Cadogan, J., Blumsohn, A., Barker, M.E., Eastell, R. A longitudinal study of bone gain in pubertal girls: anthropometric and biochemical correlates. J Bone Miner Res. 1998;13:1602–1612.

Cake, K.M., Bowins, R.J., Vaillancourt, C., Gordon, C.L., MacNutt, R.H., Laporte, R., et al. Partition of circulating lead between serum and red cells is different for niternal and external sources of exposure. Am J Ind Med. 1996;29:440–445.

Calderon, J., Navarro, M.E., Jimenez-Capdeville, M.E., Santos-Diaz, M.A., Golden, A., Rodriguez-Leyva, I., et al. Exposure to arsenic and lead and neuropsychological development in Mexican children. Environ Res. 2001;85:69–76.

Canfield, R.L., Henderson, C.R., Cory-Slechta, D.A., Cox, C., Jusko, T.A., Lanphear, B.P. Intellectual impairment in children with blood lead concentrations below 10 µg per deciliter. N Engl J Med. 2003;348:1517–1526.

Centers for Disease Control and Prevention. Managing Elevated Blood Lead Levels Among Young Children: Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention. Nutritional Interventions. Atlanta: U.S. Department of Health and Human Services, 2002. Available at http://www.cdc.gov/nceh/lead/CaseManagement/caseManage_chap4.htm. Accessed February 23, 2004.

Centers for Disease Control and Prevention. Second National Report on Human Exposure to Environmental Chemicals. Atlanta: U.S. Department of Health and Human Services, 2003. NCEH Pub. No. 02-0716. Available at http://www.cdc.gov/exposurereport/2nd/pdf/secondner.pdf. Accessed February 23, 2004.

Centers for Disease Control and Prevention. Preventing Lead Poisoning in Young Children. Atlanta: U.S. Department of Health and Human Services, 1991. Available at http://www.cdc.gov/nceh/lead/publications/books/plpyc/contents.htm. Accessed February 23, 2004.

Charney, E., Sayre, J., Coulter, M. Increased lead absorption in inner city children: Where does the lead come from? Pediatrics. 1980;65:226–231.

Cheng, Y., Schwartz, J., Sparrow, D., Aro, A., Weiss, S., Hu, H. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: The Normative Aging Study. Am J Epidemiol. 2001;153:164–171.

Cohen, D.J., Johnson, W.T., Caparulo, B.K. Pica and elevated blood lead level in autistic and atypical children. Am J Dis Child. 1976;130:47–48.

Cooney, G.H., Bell, A., McBride, W., Carter, C. Low-level exposures to lead: the Sydney lead study. Dev Med Child Neurol. 1989;31:640–649.

Cory-Slechta, D.A., Weiss, B., Cox, C. Performance and exposure indices of rats exposed to low concentrations of lead. Toxicol Appl Pharmacol. 1985;78:291–299.

Davis, J.M., Otto, D.A., Weil, D.E., Grant, L.D. The comparative developmental neurotoxicity of lead in humans and animals. Neurotoxicol Teratol. 1990;12:215–229.

Deng, W., Poretz, R.D. Protein kinzse C activation is required for the lead-induced inhibition of proliferation and differentiation of cultured oligodendrglial progenitor cells. Brain Res. 2002;929:87–95.

Dietrich, K.N., Berger, O.G., Succop, P.A., Hammond, P.B., Bornschein, R.L. The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry. Neurotoxicol Teratol. 1993;15:37–44.

Dietrich, K.N., Ris, M.D., Succop, P.A., Berger, O.G., Bornschein, R.L. Early exposure to lead and juvenile delinquency. Neurotoxicol Teratol. 2001;23:511–518.

Dietrich, K.N., Succop, P.A., Bornschein, R.L., Krafft, K.M., Berger, O.G., Hammond, P.B., et al. Lead exposure and neurobehavioral development in later infancy. Environ Health Perspect. 1990;89:13–19.

Dresner, D.L., Ibrahim, N.G., Mascarenhas, B.R., Levere, R.D. Modulation of bone marrow heme and protein synthesis by trace elements. Environ Res. 1982;28:55–66.

Ernhart, C.B., Morrow-Tlucak, M., Marler, M.R., Wolf, A.W. Low level lead exposure in the prenatal and early preschool periods: early preschool development. Neurotoxicol Teratol. 1987;9:259–270.

Ernhart, C.B., Morrow-Tlucak, M., Wolf, A.W. Low level lead exposure and intelligence in the preschool years. Sci Total Environ. 1988;71:453–459.

Ernhart, C.B., Morrow-Tlucak, M., Wolf, A.W., Super, D., Drotar, D. Low level lead exposure in the prenatal and early preschool periods: intelligence prior to school entry. Neurotoxicol Teratol. 1989;11:161–170.

Ernhart, C.B., Wolf, A.W., Sokol, R.J., Brittenham, G.M., Erhard, P. Fetal lead exposure: antenatal factors. Environ Res. 1985;38:54–66.

Eskenazi, B., Castorina, R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. Environ Health Perspect. 1999;107:991–1000.

Factor-Litvak, P., Kline, J.K., Popovac, D., Hadzialjevic, S., Lekic, V., Preteni-Rexhepi, E., et al. Blood lead and blood pressure in young children. Epidemiology. 1996;7:633–637.

Fowler, B.A., Kimmel, C.A., Woods, J.S., McConnell, E.E., Grant, L.D. Chronic low-level lead toxicity in the rat: III. An integrated assessment of long-term toxicity with special reference to the kidney. Toxicol Appl Pharmacol. 1980;56:59–77.

Fulton, M., Raab, G., Thomson, G., Laxen, D., Hunter, J., Hepburn, W. Influence of blood lead on the ability and attainment of children in Edinburgh. Lancet. 1987;1:1221–1226.

Garrido Latorre, E., Hernandez-Avila, M., Tamayo Orozco, J., Albores Medina, C.A., Aro, A., Palazuelos, E., et al. Relationship of blood and bone lead to menopause and bone mineral density among middle-age women in Mexico City. Environ Health Perspect. 2002;110:A625–A630.

Gemmel, A., Tavares, M., Alperin, S., Soncini, J., Daniel, D., Dunn, J., et al. Blood lead level and dental caries in school-age children. Environ Health Perspect. 2002;110:A625–A630.

Gilbert, S.G., Rice, D.C. Low-level lifetime exposure produces behavioral toxicity (spatial discrimination reversal) in adult monkeys. Toxicol Appl Pharmacol. 1987;91:484–490.

Goldstein, G.W. Evidence that lead acts as a calcium substitute in second messenger metabolism. Neurotoxicology. 1993;14:97–101.

Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol. 1997;19:417–428.

Grantham-McGregor, S., Ani, C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr. 2001;131:649s–668s.

Greenland, S., Robins, J. M. Confounding and misclassification. Am J Epidemiol. 1985;122:495–506.

Grosse, S.D., Matte, T.D., Schwartz, J., Jackson, R.J. Economic gains resulting from the reduction of children's exposure to lead in the United States. Environ Health Perspect. 2002;110:563–569.

Hammond, P.B., Bornschein, R.L., Succop, P.A. Dose-effect and dose-response relationships of blood lead to erthryocytic protoporphyrin in young children. Environ Res. 1985;38:187–196.

Hatzakis, A., Kokkevi, A., Katsouyanni, K., Maravelias, K., Salaminios, F., Kalandi, A., et al. Psychometric intelligence and attentional performance deficits in lead-exposed children. In: Lindberg S.E., Hutchinson T.C., eds. International Conference on Heavy Metals in the Environment, Vol. 1. Edinburgh, UK: CEP Consultants, 1987;204–209.

Hayes, E.B., McElvaine, M.D., Orbach, H.G., Fernandez, A.M., Lyne, S., Matte, T.D. Long-term trends in blood lead levels among children in Chicago: relationship to air lead levels. Pediatrics. 1994;93:195–200.

Hernandez-Avila, M., Smith, D., Meneses, F., Sanin, L. H., Hu, H. The influence of bone and blood lead on plasma lead levels in environmentally exposed adults. Environ Health Perspect. 1998;106:473–477.

Hussain, R.J., Parsons, P.J., Carpenter, D.O. Effects of lead on long-term potentiation in hippocampal CA3 vary with age. Brain Res Dev Brain Res. 2000;121:243–252.

Jacobs, D.E., Clickner, R.P., Zhou, J.D., Viet, S.M., Marker, D.A., Rogers, J.W., et al. The prevalence of lead-based paint hazards in U.S. housing. Environ Health Perspect. 2002;110:A599–A606.

Juberg, D.R., Alfano, K., Coughlin, R.J., Thompson, K.M. An observational study of object mouthing behavior by young children. Pediatrics. 2001;107:135–142.

Kafourou, A., Touloumi, G., Makropoulos, V., Loutradi, A., Papanagioutou, A., Hatzakis, A. Effects of lead on the somatic growth of children. Archives Env Health. 1997;52:377–383.

Kaufman, A.S. Do low levels of lead produce IQ loss in children? A careful examination of the literature. Archives of Clinical Neuropsychology. 2001;16:303–341.

Kusell, M., Lake, L., Anderson, L.A., Gerschenson, L.E. Cellular and molecular toxicology of lead. II. Effect of lead on d-aminolevulinic acid synthetase of cultured cells. J Toxicol Environ Health. 1978;4:515–525.

Lanphear, B.P., Byrd, R. S., Auinger, P., Schaffer, S.J. Community characteristics associated with elevated blood lead levels in children. Pediatrics. 1998;101:264–271.

Lanphear, B.P., Dietrich, K.N., Auinger, P., Cox, C. Cognitive deficits associated with blood lead concentrations <10 ug/dL in US children and adolescents. Public Health Rep. 2000;115:521–529.

Lanphear B.P., Hornung R., Khoury J., Yolton K., Baghurst P., Bellinger D.C., et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect. 2005;113:894–899.

Leggett, R.W. An age-specific kinetic model of lead metabolism in humans. Environ Health Perspect. 1993;101:598–616.

Levin, E.D., Bowman, R.E. Long-term lead effects on the Hamilton Search Task and delayed alternation in monkeys. Neurobehav Toxicol Teratol. 1986;8:219–224.

Lozoff, B., Jimenez, E., Wolf, A.W. Long-term developmental outcome of infants with iron deficiency. N Engl J Med. 1991;325:687–694.

Mahaffey, K.R., Rosen, J.F., Chesney, R.W., Peeler, J.T., Smith, C.M., DeLuca, H.F. Association between age, blood lead concentration, and serum 1,25-dihydroxycholecalciferol levels in children. N Engl J Med. 1982;307:573–579.

Mannino, D.M., Albalak, R., Grosse, S.D., Repace, J. Second-hand smoke exposure and blood lead levels in U.S. children. Epidemiology. 2003;14:719–727.

Markovac, J., Goldstein, G.W. Picomolar concentrations of lead stimulate brain protein kinase C. Nature. 1988;334:71–73.

Matthee, A., von Schirnding, Y.E., Levin, J., Ismail, A., Huntley, R., Cantrell, A. A survey of blood lead levels among young Johannesburg school children. Environ Res. 2002;90:181–184.

McElvaine, M.D., DeUngria, E.G., Matte, T.D., Copley, C.G., Binder, S. Prevalence of radiographic evidence of paint chip ingestion among children with moderate to severe lead poisoning; St. Louis, Missouri, 1989 through 1990. Pediatrics. 1992;89:740–742.

McMichael, A.J., Baghurst, P.A., Wigg, N. R., Vimpani, G. V., Robertson, E. F., Roberts, R. J. Port Pirie Cohort Study: environmental exposure to lead and children's abilities at the age of four years. N Engl J Med. 1988;319:468–475.

Mendelsohn, A. L., Dreyer, B. P., Fierman, A. H., Rosen, C. M., Legano, L. A., Kruger, H. A., Lim, S. W., Barasch, S., Au, L., Courtlandt, C. D. Low-level lead exposure and cognitive development in early childhood. J Dev Behav Pediatr. 1999;20:425–431.

Meyer, P.A., Pivetz, T., Dignam, T.A., Homa, D.M., Schoonover, J, Brody, D. Surveillance for elevated blood lead levels among children—United States, 1997–2001. In: CDC Surveillance Summaries. MMWR 2003;52(No. SS-10):1–21.

Moss, M.E., Lanphear, B.P., Auinger, P. Association of dental caries and blood lead levels. J Am Med Assoc. 1999;281(24):2294–2298.

Munoz, H., Meneses-Gonzalez, F., Romieu, I., Hernandez-Avila, M., Palazuelos, E., Mancilla-Sanchez, T. Blood lead level and neurobehavioral development among children living in Mexico City. Arch Environ Health. 1993;48:132–138.

Parsons, P.J., Reilly, A.A., Esernio-Jenssen, D. Screening children exposed to lead: an assessment of the capillary blood lead fingerstick test. Clin Chem. 1997;43:302–311.

Parsons, P.J., Slavin, W. A rapid Zeeman graphite furnace atomic absorption spectrometric method for the determination of lead in blood. Spetrochim Acta B. 1993;48:925–939.

Paschal, D.C., Caldwell, K.L., Ting, B.G. Determination of lead in whole blood using inductively coupled argon plasma mass spectrometry with isotope dilution. J Anal At Spectrom. 1995;10:367–370.

Pirkle, J.L., Brody, D., Gunter, E.W., Kramer, R.A., Paschal, D.C., Flegal, K.M., et al. The decline in blood lead levels in the United States—The National Health and Nutrition Examination Surveys (NHANES). JAMA 1994;272:284–291.

Pirkle, J.L., Kaufmann, R., Brody, D., Hickman, T., Gunter, E.W., Paschal, D.C. Exposure of the U.S. population to lead, 1991–1994. Environ Health Perspect. 1998;106:745–750.

Rabinowitz, M.B., Leviton, A., Needleman, H.L. Occurrence of elevated protoporphyrin levels in relation to lead burden in infants. Environ Res. 1986;39:253–257.

Rabinowitz, M.B., Leviton, A., Needleman, H.L. Variability of blood lead concentrations during infancy. Arch Environ Health. 1984;39:74–77.

Rabinowitz, M.B., Leviton, A., Needleman, H.L., Bellinger, D.C., Waternaux, C. Environmental correlates of infant blood lead levels in Boston. Environ Res. 1985;38:96–107.

Rahman, A., Maqbool, E., Zuberi, H.S. Lead-associated deficits in stature, mental ability and behaviour in children in Karachi. Ann Trop Paediatr. 2002;22:301–311.

Rice, D.C. Chronic low-level lead exposure from birth produces deficits in discrimination reversal in monkeys. Toxicol Appl Pharmacol. 1985;77:201–210.

Roda, S.M., Greenland, R.D., Bornschein, R.L., Hammond, P.B. Anodic stripping voltammetry procedure modified for improved accuacy of blood lead analysis. Clin Chem. 1988;34:563–567.

Roels, H.A., Lauwerys, R. Evaluation of dose-effect and dose-response relationships for lead exposure in different Belgian population groups (fetus, child, adult men and women). Trace Elem Med. 1987;4:80–87.

Rosen, J.F., Zarate-Salvador, C., Trinidad, E.E. Plasma lead levels in normal and lead-intoxicated children. Pediatrics. 1974;84:45–48.

Rothenberg, S.J., Karchmer, S., Schnaas, L., Perroni, E., Zea, F., Alba, J.F. Changes in serial blood lead levels during pregancy. Environ Health Perspect. 1994;102:876–880.

Rothenberg, S.J., Schnaas, L., Perroni, E., Hernandez, R.M., Martinez, S., Hernandez, C. Pre- and postnatal lead effect on head circumference: a case for critical periods. Neurotoxicol Teratol. 1999;21:1–11.

Savitz, D.A., Baron, A.E. Estimating and correcting for confounder misclassifcation. Am J Epidemiol. 1989;129:1062–1071.

Schlenker, T.L., Fritz, C.J., Mark, D., Layde, M., Linke, G., Murphy, A., et al. Screening for pediatric lead poisoning. Comparability of simultaeously drawn capillary and venous blood samples. JAMA. 1994;271:1346–1348.

Schnaas, L., Rothenberg, S.J., Perroni, E., Martinez, S., Hernandez, C., Hernandez, R.M. Temporal pattern in the effect of postnatal blood lead level on intellectual development of young children. Neurotoxicol Teratol. 2000;22:805–810.

Schonfeld, D.J., Cullen, M.R., Rainey, P.M., Berg, A.T., Brown, D.R., Hogan Jr., J.C., et al. Screening for lead poisoning in an urban pediatric clinic using samples obtained by fingerstick. Pediatrics. 1994;94:174–179.

Schwartz, J. Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ Res. 1994;65:42–55.

Selevan, S.G., Rice, D.C., Hogan, K.A., Euling, S.Y., Pfahles-Hutchens, A., Bethel, J. Blood lead concentration and delayed puberty in girls. N Engl J Med. 2003;348:1527–1536.

Shannon, M., Graef, J.W. Lead intoxication in children with pervasive developmental disorders. J Toxicol Clin Toxicol. 1996;34:177–181.

Shen, X.M., Guo, D., Xu, J.D., Wang, M.X., Tao, S.D., Zhou, J.D., et al. The adverse effect of marginally higher lead level on intelligence development of children: A Shanghai Study. Indian J Pediatr. 1992;59:233–238.

Silva, P.A., Hughes, P., Williams, S., Faed, J.M. Blood lead, intelligence, reading attainment, and behavior in eleven year old children in Dunedin, New Zealand. J Child Psych Psychiatry. 1988;29:43–52.

Silventoinen, K. Determinants of variation in adult body height. J Biosoc Sci. 2003; 35:263–285.

Smith, D.R., Fleegal, A.R. The public health implications of humans' natural levels of lead. Am J Public Health. 1992;82:1565–1566.

Smith, M.A. The effects of low-level lead exposure in children. In: Smith, M.A., Grant, L.D. Sors, A.I, eds. Lead Exposure and Child Development, An International Assessment. Lancaster, UK: Kluwer Publishers, 1989:1–45.

Sovcikova, E., Ursinyova, M., Wsolova, L., Rao, V., Lustik, M. Effects on the mental and motor abilities of children exposed to low levels of lead in Bratislava. Toxic Subst Mechanisms. 1997;16:221–236.

Stiles, K.M., Bellinger, D.C. Neuropsychological correlates of low-level lead exposure in school-age children: A prospective study. Neurotoxicol Teratol. 1993;15:27–35.

Stone, B.M., Reynolds, C.R. Can the National Health and Nutrition Examination Survey III (NHANES III) data help resolve the controversy over low blood lead levels and neuropsychological development in children? Arch Clin Neuropsychol. 2003;18:219–244.

Stromberg, U., Lundh, T., Schutz, A., Skerfving, S. Yearly measurements of blood lead in Swedish children since 1978: an update focusing on the petrol lead free period 1995–2001. Occup Environ Med. 2003;60:370–372.

Thane, C.W., Bates, C.J., Prentice, A. Menarche and nutritional status in pubescent British girls. Nutr Res. 2002;22:423–432.

Tong, S.L., Baghurst, P.A., McMichael, A.J., Sawyer, M.G., Mudge, J. Lifetime exposure to environmental lead and children's intelligence at 11–13 years: the Port Pirie cohort study. BMJ. 1996;312:1569–1575.

Tulve, N.S., Suggs, J.C., McCurdy, T., Cohen Hubal, E.A., Moya, J. Frequency of mouthing behavior in young children. J Expo Anal Environ Epidemiol. 2002;12:259–264.

U.S. Environmental Protection Agency. Air Quality Criteria for Lead. Research Triangle Park, NC. U.S. Environmental Protection Agency, Office of Research and Development, 1986. EPA Publication No. 600/8-83-028F. Accessed February 23, 2004.

U.S. Environmental Protection Agency. Risk Analysis to Support Standards for Lead in Paint, Dust, and Soil: Supplemental Report. Washington, D.C.: U.S. Environmental Protection Agency. 2000. EPA 747-R-00-004. Available at http://www.epa.gov/opptintr/lead/403risksupp.htm. Accessed February 23, 2004.

U.S. Department of Health, Education and Welfare. Smoking and Health—Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, D.C.: U.S. Department of Health, Education and Welfare, Public Health Service, 1964

U.S. Department of Housing and Urban Development. Economic Analysis of the Final Rule on Lead-Based Paint: Requirements for Notification, Evaluation, and Reduction of Lead-Based Paint Hazards in Federally-Owned Residential Property and Housing Receiving Federal Assistance. Washington, D.C.: U.S. Department of Housing and Urban Development, 1999. Available at http://www.hud.gov/offices/lead/leadsaferule/completeRIA1012.pdf. Accessed February 23, 2004.

van Coeverden, S.C., Netelenbos, J.C., de Ridder, C.M., Roos, J.C., Popp-Snijders, C., Delemarre-van de Waal, H.A. Bone metabolism markers and bone mass in healthy pubertal boys and girls. Clin Endocrinol. 2002;57:107–116.

Walkowiak, J., Altmann, L., Kramer, U., Sveinsson, K., Turfeld, M., Weishoff-Houben, M., et al. Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. Neurotoxicol Teratol. 1998;20:511–521.

Wasserman, G.A., Graziano, J.H., Factor-Litvak, P., Popovac, D., Morina, N., Musabegovic, A., et al. Independent effects of lead exposure and iron deficiency anemia on developmental outcome at age 2 years. J Pediatr. 1999;121:695–703.

Wasserman, G.A., Graziano, J.H., Factor-Litvak, P., Popovac, D., Morina, N., Musabegovic, A., et al. Consequences of lead exposure and iron supplementation on childhood development at age 4 years. Neurotoxicol Teratol. 1994;16:233–240.

Wasserman, G.A., Liu, X., Lolacono, N.J., Factor-Litvak, P., Kline, J.K., Popovac, D., et al. Lead exposure and intelligence in 7-year-old children: the Yugoslavia Prospective Study. Environ Health Perspect. 1997;105:956–962.

Willers, S., Schutz, A., Attewell, R., Skerfving, S. Relation between lead and calcium in blood and the involuntary smoking of children. Scand J Work Environ Health. 1988;14:385-389.

Winneke, G., Altmann, L., Kramer, U., Turfeld, M., Behler, R., Gutsmuths, F. J., et al. Neurobehavioral and neurophysiological observations in six year old children with low lead levels in East and West Germany. Neurotoxicology. 1994;15:705-713.

Winneke, G., Brockhaus, A., Ewers, U., Kramer, U., Neuf, M. Results from the European Multicenter Study on lead neurotoxicity in children: implications for risk assessment. Neurotoxicol Teratol. 1990;12:553–559.

Wolf, A.W., Jimenez, E., Lozoff, B. No evidence of developmental ill effects of low-level lead exposure in a developing country. J Dev Behav Pediatr. 1994;15:224–231.

World Health Organization, International Programme on Chemical Safety. Environmental Health Criteria 165. Inorganic Lead. Geneva: World Health Organization. 1995.

Wu, T., Buck, G.M., Mendola, P. Blood lead levels and sexual maturation in US girls: the Third National Health and Nutritional Examination Survey, 1988–1994. Environ Health Perspect. 2003;111:1–28.

Yule, W., Lansdown, R., Millar, I.B., Urbanowicz, M.A. The relationship between blood lead concentrations, intelligence and attainment in a school population: a pilot study. Dev Med Child Neurol. 1981;23:567–576.

Zhao, Q., Slavkovich, V., Zheng, W. Lead exposure promotes translocation of protein kinase C activites in rat choroid plexus in vitro, but not in vivo. Toxicol Appl Pharmacol. 1998;149:99–106.

Table R-1. Numbered references used in Tables 2 through 6.

Reference Number	First Author	Publication Date	Journal Title
1	Altmann, L.	1997	Assessment of neurophysiologic and neurobehavioral effects of environmental pollutants in 5- and 6-year-old children
2	Altmann, L.	1998	Visual functions in 6-year old children in relation to lead and mercury levels
3	Alvarez Leite, E. M.	2002	Urinary homovanillic acid and serum prolactin levels in children with low environmental exposure to lead
4	Baghurst, P. A.	1992	Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study
5	Ballew, C.	1999	Blood lead concentration and children's anthropometric dimensions in the third National Health and Nutrition Examination Survey (NHANES III), 1988-1994
6	Bellinger, D. C.	1991	Low-level lead exposure and children's cognitive function in the preschool years
7	Bellinger, D. C.	1992	Low-level lead exposure, intelligence and academic achievementµ a long-term follow-up study
8	Bergomi, M.	1989	Relationship between lead exposure indicators and neuropsychological performance in children
9	Bernard, A.	1995	Renal effects in children living in the vicinity of a lead smelter
10	Calderon, J.	2001	Exposure to arsenic and lead and neuropsychological development in Mexican children
11	Canfield, R. L.	2003	Intellectual Impairment in Children with Blood Lead Concentrations below 10 µg per deciliter
12	Cooney, G. H.	1989	Low-level exposures to leadµ the Sydney lead study
13	Dietrich, K. N.	1993	The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry

Table R-1. Numbered references used in Tables 2 through 6. ***(Continued)***

Reference Number	First Author	Publication Date	Journal Title
14	Ernhart, C. B.	1987	Low level lead exposure in the prenatal and early preschool periods: early preschool development
15	Ernhart, C. B.	1988	Low level lead exposure and intelligence in the preschool years
16	Ernhart, C. B.	1989	Low level lead exposure in the prenatal and early preschool periods: intelligence prior to school entry
17	Factor-Litvak, P.	1996	Blood lead and blood pressure in young children
18	Gemmel, A.	2002	Blood lead level and dental caries in school-age children
19	Hammond, P. B.	1985	Dose-effect and dose-response relationships of blood lead to erthryocytic protoporphyrin in young children
20	Hatzakis, A.	1987	Psychometric intelligence and attentional performance deficits in lead-exposed children
21	Kafourou, A.	1997	Effects of lead on the somatic growth of children
22	Lanphear, B. P.	2000	Cognitive deficits associated with blood lead concentrations
23	McMichael, A. J.	1988	Port Pirie Cohort Study: environmental exposure to lead and children's abilities at the age of four years
24	Mendelsohn, A. L.	1999	Low-level lead exposure and cognitive development in early childhood
25	Moss, M. E.	1999	Association of dental caries and blood lead levels
26	Munoz, H.	1993	Blood Lead Level and Neurobehavioral Development among Children Living in Mexico City
27	Rabinowitz, M. B.	1986	Occurrence of elevated protoporphyrin levels in relation to lead burden in infants
28	Rahman, A.	2002	Lead-associated deficits in stature, mental ability and behaviour in children in Karachi

Table R-1. Numbered references used in Tables 2 through 6. *(Continued)*

Reference Number	First Author	Publication Date	Journal Title
29	Roels, H. A.	1987	Evaluation of dose-effect and dose-response relationships for lead exposure in different Belgian population groups (fetus, child, adult men and women)
30	Rothenberg, S. J.	1999	Pre- and postnatal lead effect on head circumference: a case for critical periods
31	Schnaas, L.	2000	Temporal pattern in the effect of postnatal blood lead level on intellectual development of young children
32	Selevan, S. G.	2003	Blood lead concentration and delayed puberty in girls
33	Silva, P. A.	1988	Blood lead, intelligence, reading attainment, and behavior in eleven year old children in Dunedin, New Zealand
34	Stiles, K. M.	1993	Neuropsychological correlates of low-level lead exposure in school-age children: A prospective study
35	Tong, S. L.	1996	Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study
36	Walkowiak, J.	1998	Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing
37	Wasserman, G. A.	1994	Consequences of lead exposure and iron supplementation on childhood development at age 4 years
38	Wasserman, G. A.	1997	Lead exposure and intelligence in 7-year-old children: the Yugoslavia Prospective Study
39	Winneke, G.	1990	Results from the European Multicenter Study on lead neurotoxicity in children: implications for risk assessment
40	Winneke, G.	1994	Neurobehavioral and neurophysiological observations in six year old children with low lead levels in East and West Germany

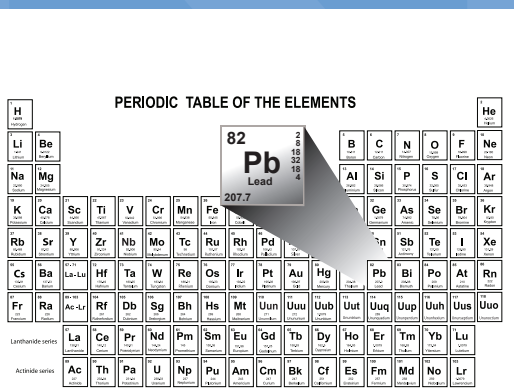
Table R-1. Numbered references used in Tables 2 through 6. ***(Continued)***

Reference Number	First Author	Publication Date	Journal Title
41	Wolf, A. W.	1994	No Evidence of Developmental III Effects of Low-Level Lead Exposure in a Developing Country
42	Wu, T.	2003	Blood lead levels and sexual maturation in US girls: the Third National Health and Nutritional Examination Survey, 1988-1994

EPA/600/R-10/075F | June 2013 | www.epa.gov

United States
Environmental Protection
Agency

Integrated Science Assessment for Lead



Office of Research and Development
National Center for Environmental Assessment, Research Triangle Park, NC

United States Environmental Protection Agency

June 2013
EPA/600/R-10/075F

Integrated Science Assessment for Lead

National Center for Environmental Assessment-RTP Division
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency (EPA) policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

CONTENTS

Lead Project Team

Executive Direction

Dr. John Vandenberg (Director)—National Center for Environmental Assessment-RTP Division, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Debra Walsh (Deputy Director)—National Center for Environmental Assessment-RTP Division, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Mary Ross (Branch Chief)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Reeder Sams III (Acting Deputy Director)—National Center for Environmental Assessment-RTP Division, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Doug Johns (Acting Branch Chief)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Scientific Staff

Dr. Ellen Kirrane (Team Leader, ISA for Lead)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. James Brown—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Allen Davis—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jean-Jacques Dubois—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Tara Greaver—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Erin Hines—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Dennis Kotchmar—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Meredith Lassiter—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Stephen McDow—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Qingyu Meng—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Elizabeth Oesterling Owens—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Molini Patel—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr Joseph P. Pinto—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jennifer Richmond-Bryant—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Lindsay Stanek—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. David Svendsgaard—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Lisa Vinikoor-Imler—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Technical Support Staff

Ms. Marieka Boyd—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Kenneth J. Breito–Senior Environmental Employment Program, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Gerald Gurevich—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Ryan Jones—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Ellen Lorang—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. J. Sawyer Lucy–Student Services Authority, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Deborah Wales—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Richard N. Wilson–National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Barbara Wright—Senior Environmental Employment Program, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Authors, Contributors, and Reviewers

Authors

Dr. Ellen Kirrane (Team Leader, ISA for Lead)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Robyn Blain— Energy, Environment and Transportation, Environmental Science & Policy, ICF International, Lexington, MA

Dr. James Brown—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Philip Bushnell, National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Allen Davis—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Gary Diamond—Syracuse Research Corporation, Akron, NY

Dr. Rodney Dietert—Cornell University College of Veterinary Medicine, Veterinary Medical Center, Ithaca, NY

Dr. Jean-Jacques Dubois—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Anne Fairbrother—Exponent, Inc., Bellevue, WA

Dr. Jay Gandy—Department of Environmental and Occupational Health, University of Arkansas for Medical Sciences, Little Rock, AR

Dr. Harvey Gonick—David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, CA

Dr. Margaret Graham—School of Geosciences, University of Edinburgh, Edinburgh, Scotland

Dr. Tara Greaver—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Erin Hines—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Dennis Kotchmar—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Meredith Lassiter—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Stephen McDow—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Qingyu Meng—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Bill Mendez—Energy, Environment and Transportation, Environmental Science & Policy, ICF International, Fairfax, VA

Dr. Howard Mielke—Center for Bioenvironmental Research, Tulane/Xavier Universities, New Orleans, LA

Ms. Chandrika Moudgal— Energy, Environment and Transportation, Environmental Science & Policy, ICF International, Dublin, CA

Dr. Elizabeth Oesterling Owens—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Katherine Palmquist—Exponent, Inc., Bellevue, WA

Dr. Molini Patel—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr Joseph P. Pinto—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jennifer Richmond-Bryant—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Stephen Rothenberg—National Institute of Public Health, Cuernavaca, Morelos, Mexico

Dr. MaryJane Selgrade—Energy, Environment and Transportation, Environmental Science & Policy, ICF International, RTP, NC

Dr. Lindsay Stanek—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. David Svendsgaard—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Lisa Vinikoor-Imler—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Virginia Weaver—Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Dr. Marc Weisskopf—Department of Environmental Health and Department of Epidemiology, Harvard School of Public Health, Harvard University, Boston, Massachusetts

Dr. John Pierce Wise, Sr.—Maine Center for Toxicology and Environmental Health, Department of Applied Medical Sciences, Portland, ME

Dr. Rosalind Wright—Harvard Medical School and School of Public Health, Harvard University, Boston, MA

Dr. Robert Wright—Harvard Medical School and School of Public Health, Harvard University, Boston, MA

Contributors

Mr. Brian Adams—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Halil Cakir— Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Ye Cao—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Laura Datko—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Josh Drukenbrod—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, RTP, NC

Ms. Meagan Madden—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Mark Schmidt—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Katie Shumake—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Kaylyn Siporin—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Lauren Tuttle—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Adrien Wilkie—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Brianna Young—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Reviewers

Dr. David Bellinger – Harvard Medical School and Department of Environmental Health, Harvard School of Public Health, Boston, MA

Dr. Christal Bowman—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. David Buchwalter—Department of Toxicology, North Carolina State University, Raleigh, NC

Dr. Barbara Buckley—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Kevin Cavender—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Rebecca C. Dzubow—Office of Children's Health Protection, U.S. Environmental Protection Agency, Washington, DC

Dr. David DeMarini—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Pam Factor-Litvak—Department of Epidemiology, Mailman School of Public Health, New York, NY

Dr. Gabriel Filippelli—Department of Earth Sciences, Indiana University-Purdue University, Indianapolis, IN

Dr. Andrew Friedland—Environmental Studies Program, Dartmouth College, Hanover, NH

Dr. Barbara Glenn—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC

Dr. Jeff Herrick—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Marion Hoyer—Office of Transportation and Air Quality, Office of Air and Radiation, U.S. Environmental Protection Agency, Ann Arbor, MI

Dr. Joseph Jacobson – Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

Dr. Douglas Johns—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jay S. Kaufman – Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada

Dr. Thomas Luben—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Karen Martin—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Connie Meacham—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Marie Lynn Miranda—Environmental Sciences and Policy, Nicholas School of the Environment, Duke University, Durham, NC

Dr. Deirdre Murphy—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Paul Mushak—PB Associates, Durham NC

Dr. Kris Novak—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. David Orlin—Air and Radiation Law Office, Office of General Counsel, U.S. Environmental Protection Agency, Washington, DC

Dr. Meredith Pedde—Office of Transportation and Air Quality, Office of Air and Radiation, U.S. Environmental Protection Agency, Ann Arbor, MI

Dr. Pradeep Rajan—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Joanne Rice—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Mary Ross—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Joel Schwartz—Department of Environmental Health, Harvard School of Public Health, Boston, MA

Mr. Jason Sacks—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Ginger Tennant—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jay Turner—Environmental and Chemical Engineering Department, Washington University, St. Louis, MO

Dr. John Vandenberg—National Center for Environmental Assessment-RTP Division, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Robert W. Vanderpool—National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Nosratola Vaziri—Division of Nephrology and Hypertension, School of Medicine, University of California, Irvine, Irvine, CA

Ms. Debra Walsh—National Center for Environmental Assessment-RTP Division, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Nasser Zawia—Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI

Clean Air Scientific Advisory Committee Lead NAAQS Review Panel

Chair of the Lead Review Panel

Dr. Christopher H. Frey*, North Carolina State University, Raleigh, NC

Lead Review Panel Members

Mr. George A. Allen*, Northeast States for Coordinated Air Use Management (NESCAUM), Boston, MA

Dr. Herbert Allen, University of Delaware, Newark, DE

Dr. Richard Canfield, Cornell University, Ithaca, NY

Dr. Deborah Cory-Slechta, University of Rochester, Rochester, NY

Dr. Cliff Davidson, Syracuse University, Syracuse, NY

Dr. Philip E. Goodrum, Cardno ENTRIX, Syracuse, NY

Dr. Sean Hays, Summit Toxicology, Allenspark, CO

Dr. Philip Hopke, Clarkson University, Potsdam, NY

Dr. Chris Johnson, Syracuse University, Syracuse, NY

Dr. Susan Korrick, Harvard Medical School, Boston, MA

Dr. Michael Kosnett, University of Colorado School of Medicine, Denver, CO

Dr. Roman Lanno, Ohio State University, Columbus, OH

Mr. Richard L. Poirot, Vermont Agency of Natural Resources, Waterbury, VT

Dr. Joel Pounds, Pacific Northwest National Laboratory, Richland, WA

Dr. Michael Rabinowitz, Marine Biological Laboratory, Newport, RI

Dr. William Stubblefield, Oregon State University, Corvallis, OR

Dr. Ian von Lindern, TerraGraphics Environmental Engineering, Inc., Moscow, ID

Dr. Gail Wasserman, Columbia University, New York, NY

Dr. Michael Weitzman, New York University School of Medicine, New York, NY

* Members of the statutory Clean Air Scientific Advisory Committee (CASAC) appointed by the EPA Administrator

Science Advisory Board Staff

Mr. Aaron Yeow, Designated Federal Officer, U.S. Environmental Protection Agency, Science Advisory Board (1400R), 1200 Pennsylvania Avenue, NW, Washington, D.C. 20460-0001, Phone: 202-564-2050, Fax: 202-565-2098, (yeow.aaron@epa.gov)

Acronyms and Abbreviations

Acronym/Abbreviation	Meaning
α	alpha
αT	the extent of DNA denaturation per cell
Å	Ångström (10^{-10} meter)
AA	African American; arachidonic acid, atomic absorption
AALM	All Ages Lead Model
AAS	atomic absorption (spectrophotometry, spectrometry, spectroscopy)
Ab	amyloid-beta peptide
ABL	atmospheric boundary layer
ACE	angiotensin converting enzyme
ACF	Apalachicola, Chattahoochee, and Flint River Basin
ACh	acetylcholine
ACP	acid phosphatase
ACR	acute to chronic ratio
Acyl-CoA	acyl-coenzyme A
AD	axial diffusivity
ADHD	attention deficit hyperactivity disorder
ADP	adenosine diphosphate
AE	anion exchanger
AEC	adenylate energy charge
AERMOD	atmospheric dispersion model
AF	absorbed fraction; absorption fraction
aff'd	affirmed
A/G	albumin/globulin
Ag	silver
AGL	above-ground level
A-horizon	Topsoil horizon (surface soil)
AKI	acute kidney injury
Al	aluminum
ALA	aminolevulinic acid
ALAD	aminolevulinic acid dehydratase;

Acronym/Abbreviation	Meaning
ALAD 1-1	aminolevulinate delta-dehydratase 1-1
ALAD-2	aminolevulinate delta-dehydratase-2
ALD	aldehyde dehydrogenase
ALM	Adult Lead Methodology
ALP	alkaline phosphatase
ALS	Amyotrophic Lateral Sclerosis (Lou Gehrig's disease)
ALT	alanine aminotransferase
AM	Alveolar macrophages
AMF	arbuscular mycorrhizal fungi
AMP	adenosine monophosphate
ANC	acid neutralizing capacity; absolute neutrophil counts
ANF	atrial natriuretic factor
AngII	renal angiotensin II
ANOVA	analysis of variance
ANPR	advance notice of proposed rulemaking
AOP	adverse outcome pathway
AP-1	activator protein-1
ApaI	polymorphism of the VDR in humans
APC	antigen-presenting cell
APOE	Apolipoprotein E
APRT	adenine phosphoribosyltransferase
AQCD	Air Quality Criteria Document
AQS	(U.S. EPA) Air Quality System (database)
Ar	argon
As	arsenic
AST	aspartate aminotransferase
ASV	anode stripping voltammetry
ATLD	ataxia-telangiectasia-like disorder

Acronym/Abbreviation	Meaning
ATOFMS	aerosol time-of-flight mass spectrometry
ATP	adenosine-triphosphate
ATPase	adenosine triphosphatase; adenosine triphosphate synthase
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Research
Au	gold
avg	average
AVS	acid-volatile sulfides
a-wave	initial negative deflection in the electroretinogram
AWQC	Ambient Water Quality Criteria
β	Beta; Beta coefficient; regression coefficient; standardized coefficient
3β-HSD	3-beta-hydroxysteroid dehydrogenase
17β-HSD	17-beta-hydroxysteroid dehydrogenase
Ba	barium
BAF	bioaccumulation factors
BAL	2,3-dimercaptopropanol
BASC	Behavior Assessment System for Children
BASC-PRS	Behavior Assessment System for Children-Parent Ratings Scale
BASC-TRS	Behavior Assessment System for Children-Teacher Rating Scale
BC	black carbon, soot
BCB	blood cerebrospinal fluid barrier
B-cell	Bone marrow-derived lymphocytes, B lymphocyte
BCF	bioconcentration factors
Bcl-x	member of the B-cell lymphoma-2 protein family
Bcl-xl	B-cell lymphoma-extra large
B-horizon	subsoil horizon
bio	biological
Bi_2S_3	bismuth (III) sulfide
BK	biokinetics
BLM	biotic ligand model
BMD	benchmark dose; bone mineral density
BMDL	benchmark dose limit
BMI	body mass index
BMP	bone morphogenetic protein
BMS	Baltimore Memory Study
BMW	battery manufacturing workers
BP	blood pressure
Br	bromine
BR	bronchial responsiveness
BrdU	bromo-2'-deoxyuridine
8-Br-GMPc	8-bromo-cyclic guanosine monophosphate
Bs-horizon	subsoil horizon with accumulation of sesquioxides
BSI	Brief Symptom Inventory
BSID-II	Bayley Scale for Infant Development-II
BsmI	polymorphism of the VDR in humans
Bt20	Birth-to-age Twenty (cohort)
BUN	blood urea nitrogen
bw	body weight
b-wave	initial positive deflection in the electroretinogram
C	carbon; Celsius; soil or dry sediment Pb concentration; Caucasian; Cysteine
Ca	calcium
Ca^{2+}	calcium ion
CAA	Clean Air Act
CaBP	calcium binding protein
$CaCl_2$	calcium chloride
$CaCO_3$	calcium carbonate; calcite
CaEDTA	calcium ethylenediaminetetraacetic acid
CaMKII	calmodulin-dependent protein kinase II

Acronym/Abbreviation	Meaning
cAMP	cyclic adenosine monophosphate
CASAC	Clean Air Scientific Advisory Committee
CASM	Comprehensive Aquatic Systems Model
$CaSO_4$	calcium sulfate
$CaSO_4 \cdot 2H_2O$	gypsum
CAT	catalase
CBLI	cumulative blood Pb index
CBSA	core based statistical area
CCSEM	computer-controlled scanning electron microscopy
CD	cluster of differentiation
Cd	cadmium
Cd(II)	cadmium (II)
Cd^{2+}	cadmium ion
CD3+	T lymphocyte
CD4+	T helper cell
CDC	Centers for Disease Control
CEA	carcinoembryonic antigen
CEC	cation exchange capacity
cent	central
cert.	certiorari
cf	correction factor; latin abbreviation for conferre (used as "compared with)
CFL	constant flux layer
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
C-H	carbon-hydrogen (bond)
CHAD	Consolidated Human Activity Database
ChAT	chlorine acetyltransferase
CHD	coronary heart disease
CHL	Chinese hamster lung
CHO	Chinese hamster ovary cell line
C-horizon	Soil horizon underneath A- and B-horizons, may contain lumps or shelves of rock and parent material

Acronym/Abbreviation	Meaning
CHV79	Chinese hamster lung cell line
CI	confidence interval
Cir.	circuit
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	confidence limit
Cl	chlorine
Cl^-	chlorine ion
Cl_2	molecular chlorine
CLACE 5	Fifth Cloud and Aerosol Characterization Experiment in the Free Troposphere campaign
CLS	Cincinnati Lead Study
CO	carbon monoxide
CO_2	carbon dioxide
CO_3^{2-}	carbonate ion
Co	cobalt
CoA	coenzyme A
COD	coefficient of difference
Coeff	coefficient
COMP aT	The percentage of sperm with increased sensitivity to DNA denaturation
Con	control
Conc.	concentration
Cong.	congress
Corr	correlation
COX	cyclooxygenase; cytochrome oxidase subunits
COX-2	cyclooxygenase-2
$cPLA_2$	cytosolic phospholipidase A_2
CPRI	coarse particle rotary impactor
CPRS-R	Conners' Parent Rating Scale-Revised
Cr	chromium; creatine
C-R	concentration-response (relaltionship)
Cr III	chromium III
CRAC	Ca^{2+} release activated calcium

Acronym/Abbreviation	Meaning
CRACI	calcium release activated calcium influx
CREB	cyclic adenosinemonophosphate (cAMP) response element-binding
CRP	C-reactive protein
CSF	colony-stimulating factor
CSN	Chemical Speciation Network
CT	zinc-adequate control
Cu	copper
Cu(II)	copper (II)
CV	coefficient of variation
CVD	cardiovascular disease
CYP	cytochrome
CYP 1A1, Cyp1A1	cytochrome P450 family 1 member A1
CYP 1A2, Cyp1A2	cytochrome P450 family 1 member A2
CYP P450	cytochrome P450
Δ	delta, difference, change
Δ5-3β-HSD	delta-5-3-beta-hydroxysteroid dehydrogenase
δ-ALA	5-aminolevulinic acid; delta-aminolevulinic acid
δ-ALAD	delta-aminolevulinic acid dehydratase
D_2, D_3	dopamine receptors
D50	size at 50% efficiency
d	day(s); depth
db, dB	decibel
DbH	dopamine beta-hydroxylase
DBP	diastolic blood pressure
DENA	Denali National Park and Preserve, Alaska
dep	dependent
dev.	deviation
DEX	exogenous dexamethasone
DG	degenerate gyrus
2-dG	2-deoxyguanosine
DHAA	dehydroascorbate
diff	differentiation
DIT	developmental immunotoxicity
DMPS	2,3-dimercaptopropane-l-sulfonic acid
DMSA	dimercaptosuccinic acid
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DoAD	developmental origins of adult disease
DOC	dissolved organic carbon
DOM	dissolved organic matter
DP-109	metal chelator
DP-460	metal chelator
DR	diet-restricted
DRD4	dopamine 4 receptor
DRD4.7	dopamine 4 receptor repeat alleles
DRUM	Davis Rotating Unit for Monitoring
D-serine	neuronal signal
DSM-IV	Diagnostic Statistical Manual-IV
DTH	delayed-type hypersensitivity
DTPA	diethylene triamine pentaacetic acid; technetium-diethylenetriamine-pentaacetic acid
E	east; expression for exposure
E2	estradiol
e	exponential function
EC	elemental carbon, endothelial cell
EC_{10}	effect concentration for 10% of test population
EC_{20}	effect concentration for 20% of test population
EC_{50}	effect concentration for 50% of test population
ECG	electrocardiography; electrocardiogram
ECOD	7-ethoxycoumarin-o-deethylase
Eco-SSLs	ecological soil screening levels
ED_{10}	effect dose for 10% of population

Acronym/Abbreviation	Meaning
EDTA	ethylenediaminetetraacetic acid
EFS	electrical field stimulus
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
Eh	electrochemical potential
E-horizon	Eluviated horizon; soil horizon which is eluviated or leached of mineral and/or organic content
EI-MS	electron impact ionization mass spectrometry
ELPI	electrical low-pressure impactor
eNOS	endothelial nitric oxide synthase
EOG	end-of-grade
EPA	U.S. Environmental Protection Agency
EPT	ephemeroptera, plecoptera, trichoptera
ER	endoplasmic reticulum
Erg-1	ether-a-go-go related gene
ERG	electroretinogram
ERK	extracellular signal regulated kinase
ERK1/2	extracellular signal-regulated kinases 1 and 2
EROD	7-ethoxyresorufin-o-deethylase
ESCA	electron spectroscopy for chemical analysis
ESI-MS	electrospray ionization mass spectrometry
ESRD	end stage renal disease
ET	endothelin
ET-1	vasoconstrictor endothelin-1
ET_A-type receptors	endothelin type A receptors
ETS	environmental tobacco smoke
EU	European Union
EURO	European emission standard
eV	electronvolts
EXAFS	X-ray absorption fine structure spectroscopy
F_0	filial “zero” generation (parental stock)
F_1	first filial generation (offspring of F_0)
F_2	second filial generation (offspring of F_1)
FAA	Federal Aviation Agency
FAI	free androgen index
FAS	apoptosis stimulating fragment
Fas-L	apoptosis stimulating fragment ligand
Fe	iron
Fe(III)	iron III
FEM	Federal equivalence method
FEV1	forced expiratory volume in 1 second
FI	fixed interval
FI-Ext	fixed interval with extinction
Fl	fluoride
FokI	polymorphism of the VDR in humans
FR	Federal Register (Notice)
FrA	fractional anisotropy
FR-FI	fixed ratio-fixed interval
FRM	Federal reference method
FSH	follicle-stimulating hormone
FSIQ	full scale intelligence quotient (IQ)
FT3	free triiodothyronine
FT4	free thyroxine
G	pregnancy; guanine
G2	gap 2 Phase
g, kg, mg, µg, ng, pg	gram(s), kilogram(s), milligram(s), microgram(s), nanogram(s), picogram(s)
G93A	mouse model
GAAR	Gates of the Arctic National Park and Preserve, Alaska
GABA	γ-aminobutyric acid; gamma aminobutyric acid

Acronym/Abbreviation	Meaning
GABAergic	inhibitory neurons that release the neurotransmitter GABA
GAD	generalized anxiety disorder
GC	gas chromatography
G-CSF	granulocyte colony-stimulating factor
GD	gestational day
GEE	generalized estimating equations
GFAAS	graphite furnace atomic absorption spectrometry
GFAP	glial fibrillary acidic protein
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
GH	growth hormone
GHRH	growth-hormone releasing hormone
GI	gastrointestinal
GIS	Geographic Information System
G+L	pregnancy plus lactation
GLAC	Glacier National Park, Montana
GLE	gestationally-lead exposed
GM	geometric mean
GMR	geometric mean blood Pb ratio
GnRH	gonadotropin-releasing hormone
G6PD	glucose-6-phosphate dehydrogenase
GPEI	glutathione transferase P (GST-P) enhancer I
GPT	glutamate pyruvate transaminase
GPx	glutathione peroxidase
GPX1	gene encoding for glutathione peroxidase 1
GR	glutathione reductase
GRP78	glucose-regulated protein 78
GRP94	glucose-regulated protein 94
Grp	glucose-regulated protein
GSD	geometric standard deviation
GSH	glutathione
GSSG	glutathione disulfide
GST	glutathione S-transferase
GSTM1	glutathione S-transferase Mu 1
GST-P	glutathione transferase P
GTP	guanosine-5'-triphosphate; guanine triphosphate
H	hydrogen
H^+	hydrogen ion
h	hour(s)
ha	hectare
HAD	hydroxy-alkenals
HAP	hazardous air pollutant
Hb	hemoglobin
HC_5	acute toxicity hazardous concentration for 5% of species
HC_{10}	acute toxicity hazardous concentration for 10% of species
HCl	hydrochloric acid
HCO_3^-	bicarbonate; hydrogen carbonate
Hct	hematocrit
HDL	high-density lipoprotein
HERO	Health and Environmental Research online (database)
HEW	U.S. Department of Health, Education, and Welfare
HF	hydrogen fluoride
HFE	hemochromatosis gene
HFE C282Y	hemochromatosis gene with C282Y mutation
HFE H63D	hemochromatosis gene with H63D mutation
Hg	mercury
$HgCl_2$	mercury(II) chloride
5-HIAA	5-hydroxyindoleacetic acid
HIV	human immunodeficiency virus
HLA-DRB	human leukocyte antigen genes
HMEC	human dermal microvascular endothelial cells

Acronym/Abbreviation	Meaning
HMGR	3-hydroxy-3-methylglutaryl-CoA reductase
HMOX-1	heme oxygenase-1
HNO_3	nitric acid
HO-1	heme oxygenase; heme oxidase-1
H_2O	water
H_2O_2	hydrogen peroxide
HOME	Home Observation for Measurement of the Environment
HPA	hypothalamic-pituitary-adrenal
HPb, h-Pb	high Pb
HPG	hypothalamic-pituitary-gonadal
HPLC	high-performance liquid chromatography
HPRT	hypoxanthine-guanine phosphoribosyltransferase
HPT	hyperparathyroidism; hypothalamic-pituitary-thyroid
HR	heart rate; hazard ratio
HRV	heart rate variability
hsp	heat shock proteins
5HT	serotonin
5-HT	5-hydroxytryptamine
5-HT2B	5-hydroxytryptamine receptor 2B
hTERT	telomerase reverse transcriptase
HVA	homovanillic acid
I	interstate
IARC	International Agency for Research on Cancer
IC_{50}	half maximal inhibitory concentration
ICAP	inductively coupled argon plasma
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
ICPMS, ICP-MS	Inductively coupled plasma mass spectrometry
ICR	imprinting control region
ICRP	International Commission on Radiological Protection
ID	identification
IDA	iron-deficiency anemia
IDE	insulin-degrading enzyme
IEPA	Illinois Environmental Protection Agency
IEUBK	Integrated Exposure Uptake Biokinetic
IFN-γ	interferon-gamma
Ig	immunoglobulin
IgA	immunoglobulin A
IgE	immunoglobulin E
IGF-1	insulin-like growth factor 1
IgG	immunoglobulin G
IgM	immunoglobulin M
IHD	ischemic heart disease
IL	interleukin
IL-1β	interleukin-1 Beta
IL-2	interleukin-2
IL-4	interleukin-4
IL-5	interleukin-5
IL-6	interleukin-6
IL-8	interleukin-8
IL-10	interleukin-10
IL-12	interleukin-12
IMPROVE	Interagency Monitoring of Protected Visual Environment
IMT	intimal medial thickening
INL	inner neuroblastic layers of the retina
iNOS	inducible nitric oxide synthase
IOM	Institute of Medicine (provides health information to the NAS [National Academy of Sciences])
i.p.	intraperitoneal (route)
IQ	intelligence quotient
IQR	interquartile range
IRE1	inositol-requiring enzyme-1
IRP	integrated review plan
ISA	Integrated Science Assessment

Acronym/Abbreviation	Meaning
ISC-PRIME	Industrial Source Complex-Plume Rise Model Enhancements
ISF	intake slope factor
ISL	inertial sublayer
ISO	International Standards Organization
i.v.	intravenous
IVBA	in vitro bioaccessibility
IVF	in vitro fertilization
JNK	jun N-terminal kinase
K	Kelvin (temperature); potassium; resuspension factor
K^+	potassium ion
$K_{0.5}$	concentration of free metal giving half maximal metal-dependent release
KART	Karters of American Racing Triad
K_d	dissociation constant
Kd	partition coefficient; ratio of the metal concentration in soil to that in soil solution
kDa, kD	kiloDalton
KEDI-WISC	Korean Educational Development Institute-Wechsler Intelligence Scale for Children
6-keto-PGF1α	6-keto-prostaglandin F1α (vasodilatory prostaglandin)
keV	kiloelectron volt
Ki-67	antigen, cell cycle and tumor growth marker
Kim-1	kidney injury molecule-1
Kinder-KITAP	Kinder-Testbatterie zur Aufmerksamkeitsprüfung für Kinder
K-ras	specific proto-oncogene
K-XRF	K-x-ray fluorescence method of scanning for bone Pb
Λ	lambda; resuspension rate
L	length
L, dL, mL	Liter(s) [1000 mL/L], deciliter(s) [100 mL/dL], milliliter(s) [1 mL/mL]
LA-ICP-MS	laser ablation inductively coupled plasma mass spectrometry
LC_{50}	lethal concentration (at which 50% of exposed organisms die)
LD_{50}	lethal dose (at which 50% of exposed organisms die)
LDH	lactate dehydrogenase
LDL	low-density lipoproteins
LFH-horizons	organic soil horizons located above well-drained surface soil
LF/HF	low frequency to high frequency ratio
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LINE	long interspersed nuclear element
LINE-1	long interspersed nucleotide elements-1
LLNA	local lymph node assay
ln	natural logarithm
L-NAME	L-NG-nitroarginine methyl ester
L-NOARG	L-nitroarginine
LOD	limit of detection
LOEC	lowest-observed-effect concentration
log	logarithm
LPb	low Pb
LPS	lipopolysaccharide
LSO	lateral superior olive
LTP	long-term potentiation
M	metal
M, mM, μM, nM, pM	Molar, millimolar (10^{-3} M), micromolar (10^{-6} M), nanomolar (10^{-9} M), picomolar (10^{-12} M)
m, km, cm, mm, μm, nm	meter(s), kilometer(s), centimeter(s), millimeter(s), micrometer(s) [micron(s)], nanometer(s)
MAP	mean arterial pressure
MAPK	mitogen-activated protein kinase(s), MAP kinase

Acronym/Abbreviation	Meaning
MATC	maximum acceptable toxicant concentration
max	maximum, maxima
MBP	myelin basic protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MchDMSA	mono-cyclohexyl dimercaptosuccinic acid
MCL	maximum containment level
MCP-1	monocyte chemotactic protein-1
MCV	mean corpuscular volume
MD	mean diffusivity
MDA	malondialdehyde
MDD	major depressive disorder
MDI	Mental Development Index
MDL	method detection limit
MDRD	Modification of Diet in Kidney Disease
Med, med	median
MEK1	dual specificity mitogen-activated protein kinase 1
MEK2	dual specificity mitogen-activated protein kinase 2
MENTOR	Modeling Environment for Total Risk (framework)
Mg	magnesium
Mg^{2+}	magnesium ion
MHC	major histocompatibility complex
MI	myocardial infarction, "heart attack;" myocardial ischemia
mI	myoinositol
min	minimum; minima; minute(s)
MKK1/2	MAPK kinase 1 and 2
ML	mixed layer
MMAD	mass median aerodynamic diameter
MMDD	mental retardation or developmental disabilities
MMF	mycophenolate mofetil
mmHg	millimeters of mercury
mmol, μmol, nmol	millimole(s), micromole(s), nanomole(s)
MN	micronuclei formation; mononuclear
Mn	manganese
MNE	micronucleated erythrocytes per thousand
MnO_2	manganese dioxide
Mo	molybdenum
mo	month(s)
MOA(s)	mode(s) of action
MORA	Mount Rainier National Park, Washington State
MOUDI	multi-orifice uniform deposit impactor
MPb, m-Pb	moderate Pb
MPO	myeloperoxidase
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRS	magnetic resonance spectroscopy
MS	maternal stress
MSC	mesenchymal cell
MSWI	municipal solid waste incineration
Mt	metallothionein
MTHFR	methylenetetrahydrofolate reductase
MTP	mitochondrial transmembrane pore
MW	molecular weight
MZ	marginal zinc
N	nitrogen; normal; north; number; population
n	number of observations
Na	sodium
Na^+	sodium ion
NAAQS	National Ambient Air Quality Standards
NAC	N-acetyl cysteine; nucleus accumbens
$Na_2CaEDTA$	calcium disodium ethylenediaminetetraacetic acid

Acronym/Abbreviation	Meaning
NaCl	sodium chloride
NAD	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide dehydrogenase
NADP	nicotinamide adenine dinucleotide phosphate
NADPH, NAD(P)H	reduced nicotinamide adenine dinucleotide phosphate
NAEC	no-adverse-effect concentration
NAG	N-acetyl-β-D-glucosaminidase; N-acetylglucosamine
$NaHCO_3$	sodium bicarbonate; sodium hydrogen carbonate
NANC	non-adrenergic non-cholinergic
NAS	U.S. Department of Veteran's Affair's Normative Aging Study; National Academy of Sciences
NASCAR	National Association for Stock Car Automobile Racing
NATTS	National Air Toxics Trends Station
NAWQA	National Water Quality Assessment
NCAM	neural cell adhesion molecule
NCEA	National Center for Environmental Assessment
NCore	National Core multi-pollutant monitoring network
N.D.	not detected
NDMAR	N-nitrosodimethylamine receptor
NE	norepinephrine
NECAT	New England Children's Amalgam Trial
NEI	National Emissions Inventory
NFI	non-fixed interval
NF-κB	nuclear factor kappa B
NGAL	neutrophil gelatinase-associated lipocalin
NGF	nerve growth factor
NH	non-hispanic
NHANES	National Health and Nutrition Examination Survey
NH_4Cl	ammonium chloride
NHEJ	non-homologous end joining
NHEXAS	National Human Exposure Assessment Survey
NH_4OAc	ammonium acetate
7-NI	7-nitroinidazole
Ni	nickel
NICA	non-ideal competitive absorption
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NK	natural killer
NKF-K/DOQI	National Kidney Foundation - Kidney Disease Outcomes Quality Initiative
NMDA	N-methyl-D-aspartate
NMR	nuclear magnetic resonance
nNOS	neuronal nitric oxide synthase (NOS)
NO	nitric oxide; nitric oxide radical, nitrogen monoxide
NO_2	nitrogen dioxide
No.	number
NOAA	National Oceanic and Atmospheric Administration
NOAEL	no observed adverse effect level
NOAT	Noatak National Preserve, Alaska
NOCA	North Cascades National Park, Washington State
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	nitric oxide synthase; nitric oxide systems
NO_X	nitrogen oxides, oxides of nitrogen ($NO + NO_2$)
NP	nanoparticle
NPSH	nonprotein sulfhydryl
NQO1	NAD(P)H-quinone oxidoreductase (genotype)

Acronym/Abbreviation	Meaning
NRC	National Research Council
NRCS	Natural Resources Conservation Service
Nrf2	nuclear factor erythroid 2-related factor 2
NS	not specified
NTP	National Toxicology Program
NTPDase	nucleoside triphosphate diphosphohydrolase
NW	northwest
NYC	New York City
NZ	New Zealand
O_2	molecular oxygen
O_2^-	superoxide, superoxide free radical
O_3	ozone
9-O-Ac-GD3	9-O-acetylated-GD3
OAQPS	U.S. EPA Office of Air Quality Planning and Standards, in OAR
OAR	U.S. EPA Office of Air and Radiation
OBS	observations
OC	organic carbon
OEPA	Ohio Environmental Protection Agency
OH^-	hydroxide ion
1,25-$(OH)_2$D3	1,25-dihydroxy vitamin D
O-horizon	horizon forest floor, organic soil horizon (above surface soil)
OLC	osteoblast-like cells
OLYM	Olympic National Park, Washington State
OM	organic matter
ONL	outer neuroblastic layers of the retina
$ONOO^-$	peroxynitrate ion
OR	odds ratio
ORD	U.S. EPA Office of Research and Development
OS	offspring stress
OSHA	Occupational Safety and Health Administration
OVA	ovalbumin
8-oxo-dG	8-hydroxy-2'-deoxyguanosine
P	percentile; phosphorus
P_0	parent generation
P450	cytochrome P450
p	probability value; number of paired hourly observations; statistical significance
PA	policy assessment
PAD	peripheral arterial disease
PAH(s)	polycyclic aromatic hydrocarbon(s)
Pb	lead
^{203}Pb	lead-203 radionuclide
^{204}Pb	stable isotope of lead-204
^{206}Pb	stable isotope of lead-206
^{207}Pb	stable isotope of lead-207
^{208}Pb	stable isotope of lead-208
^{210}Pb	stable isotope of lead-210
Pb^{++}	divalent Pb ion
Pb^0	elemental lead
Pb(II)	lead (II)
Pb^{2+}	lead ion
$Pb(Ac)_2$	lead acetate
PbB	blood lead concentration
PbBrCl	lead bromochloride
$Pb(C_2H_3O_2)_2$	lead (II) acetate
$PbCl^+$	lead chloride
$PbCl_2$	lead chloride
$PbCl_3$	lead (III) chloride; lead trichloride
$PbCl_4$	lead (IV) chloride; lead tetrachloride
$PbCO_3$	cerussite; lead carbonate
$Pb(CO_3)_2$	lead (IV) carbonate
$Pb(CO_3)_2(OH)_2$	hydrocerussite
$PbCrO_4$	lead (II) chromate
PbD	floor dust lead

Acronym/Abbreviation	Meaning
$PbFe_6(SO_4)_4(OH)_{12}$	plumbjarosite
PBG	porphobilinogen
$Pb(NO_3)_2$	lead(II) nitrate
Pb-NS	lead-no stress
PbO	lead oxide; litharge; massicot
PbO_2	lead dioxide
$Pb(IV)O_2$	lead dioxide
Pb_3O_4	minimum or "red Pb"
$Pb(OH)_2$	lead hydroxide
$Pb_5(PO_4)_3Cl$	pyromorphite
$Pb_5(PO_4)_3OH$	hydroxypyromorphite
PbS	galena; lead sulfide; soil lead concentration
PbSe	lead selenide
$PbSO_4$	anglesite; lead sulfate
$Pb_4SO_4(CO_3)_2(OH)_3$	macphersonite
PbxS	lead by stress
$Pb_5(VO_4)_3Cl$	vanadinite
PC12	pheochromocytoma 12 (adrenal / neuronal cell line)
PCA	principal component analysis
PCE	polychromatic erythrocyte
PCR	polymerase chain reaction
Pct	percent
PCV	packed cell volume
PD	Parkinson's disease
PDI	Psychomotor Development Index
PEC	probable effect concentration
PEL	permissible exposure limit
PER	partial exfiltration reactor
PG	prostaglandin
PGE_2, PGE2	prostaglandin E_2
PGF_2	prostaglandin F2
pH	relative acidity; Log of the reciprocal of the hydrogen ion concentration
PHA	polyhydroxyalkanoates
PHE	phenylalanine

Acronym/Abbreviation	Meaning
PIH	pregnancy induced hypertension
PIQ	performance intelligence quotient (IQ)
PIR	poverty-income ratio
PIXE	particle induced X-Ray emission; proton-induced x-ray emission
PKC	protein kinase C
PLP	proteolipid protein
PM	particulate matter
PM_X	Particulate matter of a specific size range not defined for regulatory use. Usually X refers to the 50% cut point, the aerodynamic diameter at which the sampler collects 50% of the particles and rejects 50% of the particles. The collection efficiency, given by a penetration curve, increases for particles with smaller diameters and decreases for particles with larger diameters. The definition of PMX is sometimes abbreviated as “particles with a nominal aerodynamic diameter less than or equal to X μm” although X is usually a 50% cut point.

Acronym/Abbreviation	Meaning
PM_{10}	In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 10 μm; a measurement of thoracic particles (i.e., that subset of inhalable particles thought small enough to penetrate beyond the larynx into the thoracic region of the respiratory tract). In regulatory terms, particles with an upper 50% cut-point of 10 ± 0.5 μm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix J of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53.
$PM_{2.5}$	In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 2.5 μm; a measurement of fine particles. In regulatory terms, particles with an upper 50% cut-point of 2.5 μm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix L of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53, by an equivalent method designated in accordance with 40 CFR Part 53, or by an approved regional method designated in accordance with Appendix C of 40 CFR Part 58.
$PM_{10-2.5}$	In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 10 μm and greater than a nominal 2.5 μm; a measurement of thoracic coarse particulate matter or the coarse fraction of PM10. In regulatory terms, particles with an upper 50% cut-point of 10 μm aerodynamic diameter and a lower 50% cut-point of 2.5 μm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) as measured by a reference method based on Appendix O of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53.
PM_{10C}	The PM10-2.5 concentration of PM10-2.5 measured by the 40 CFR Part 50 Appendix O reference method which consists of currently operated, co-located low-volume (16.7 Lpm) PM10 and PM2.5 reference method samplers.
p38MAPK	p38 mitogen-activated protein kinase(s)
PMN	polymorphonuclear leukocyte
P5N	pyrimidine 5'-nucleotidase
PND	post natal day
POC	particulate organic carbon
PP	polypropylene; pulse pressure
ppb	parts per billion
ppm	parts per million
PRP	post-reinforcement pause
PS	dam stress; prenatal stress; phosphatidylserine
PSA	prostate specific antigen
PSA-NCAM	polysialylated-neural cell adhesion molecule
PT	proximal tubule
PTFE	polytetrafluoroethylene
PTH	parathyroid hormone

Acronym/Abbreviation	Meaning
PTHrP	parathyroid hormone-related protein
PUFA	polyunsaturated fatty acid
PVC	polyvinyl chloride
PVD	peripheral vascular disease
Q	quantile; quartile; quintile
QRS	QRS complex in ECG
QT	QT interval in ECG
QTc	corrected QT Interval
ρ	rho; bulk density; correlation
ρS	Pearson's r correlation coefficient
R	net drainage loss out of soil depth of concern; Spearman correlation coefficient; upward resuspension flux; correlation
r	Pearson correlation coefficient
R^2	multiple regression correlation coefficient
r^2	correlation coefficient
RAAS	renin-angiotensin-aldosterone system
RAC2	gene encoding for Rac2
RBA	relative bioavailability
RBC	red blood cell
RBP	retinol binding protein
RD	radial diffusivity
REA	Risk/Exposure Assessment
Ref	reference (group)
RI-RI	concurrent random interval
RL	repeated learning
^{220}Rn	radon isotope
^{222}Rn	stable isotope of radon-222
RNA	ribonucleic acid
ROI	reactive oxygen intermediate/superoxide anion; regions of interest
ROMO	Rocky Mountain National Park, Colorado
ROS	reactive oxygen species
RR	relative risk; risk ratio
RSL	roughness sublayer (transition layer, wake layer, interfacial layer)
rtPCR	reverse transcription polymerase chain reaction
σ	sigma, standard deviation
S	south; sulfur; synthesis phase
SAB	U.S. EPA Science Advisory Board
SATs	Standard Assessment Tests
SBP	systolic blood pressure
SCE	sister chromatid exchange
Scna	α-synuclein
SD	standard deviation
SDN	sexually dimorphic nucleus
SE	standard error
Se	selenium
sec	second(s)
SEKI	Sequoia and Kings Canyon National Park, California
SEM	scanning electron microscopy; simultaneously extracted metal; standard error of the mean
SES	socioeconomic status
Sess.	Session
SFU	stacked filter unit(s)
SGA	small for gestational age
sGC	soluble guanylate cyclase
sGC-β1	soluble guanylate cyclase-beta 1
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHBG	sex hormone binding globulin
SHEDS	Stochastic Human Exposure and Dose (model)
SHM	Stockholm humic model
siRNA	small interfering RNA
SJW	silver jewelry workers
SLAMS	State and Local Air Monitoring Stations
SMC	smooth muscle cells

Acronym/Abbreviation	Meaning
SNAP-25	synaptosomal-associated protein 25
SNARE	soluble NSF attachment receptor
SNP	single-nucleotide polymorphism; sodium nitroprusside
SNS	sympathetic nervous system
SO	stratum oriens
SO_2	sulfur dioxide
So	south
SOC	superior olivary complex
SOD	superoxide dismutase
SOD1	superoxide dismutase-1
SOF	study of osteoporotic fractures
SOM	self-organizing map; soil organic matter
SP	spray painters
SP1, Sp1	specificity protein 1
SPM	suspended particulate matter
SPT	skin prick test
SREBP-2	sterol regulatory element binding protein-2
S. Rep.	Senate Report
SRIXE	synchrotron radiation induced X-ray emission
StAR	steroidogenic acute regulatory protein
STAT	signal transducer and activator of transcription
STAT3	signal transducer and activator of transcription 3
STAT5	signal transducer and activator of transcription 5
STD.	Standard
ST Interval	measured from the J point to the end of the T wave in an ECG
STN	Speciation Trends Network
Syb	synaptobrevin
Syn	synaptophysin
Syt	synaptotagmin
SZn	supplemental zinc

Acronym/Abbreviation	Meaning
T, t	time
T_3, T3	triiodothyronine
T_4, T4	thyroxine
$t_{1/2}$	half-life (-lives); time required to reduce the initial concentration by 50%
TBARS	thioBarbituric acid reactive substances; thiobarbituric acid-reactive species
T cell, T-cell	T lymphocyte
TE	trace elements
TEC	threshold effect concentrations
TEOM	tapered element oscillating microbalance, type of PM sampler
TF	ratio of the metal concentration in plant to that in soil; transferrin
TFIIIA	transcription factor IIIA
Tg	transgenic
TGF	transforming growth factor
TGF-β	β transforming growth factor
TGFβ1, TGF-β1	β1 transforming growth factor
TH	tyrosine hydroxylase
TH1, Th1	T-derived lymphocyte helper 1
TH2, Th2	T-derived lymphocyte helper 2
Th	T-helper lymphocyte
TIMP-1	tissue inhibitor of metalloproteinases-1
TIMS	thermal ionization mass spectrometry
TLC	Treatment of Lead-exposed Children (study)
T/LH	testosterone/luteinizing hormone - measure of Leydig cell function
TNF	tumor necrosis factor (e.g., TNF-α)
TNP-Ficoll	trinitrophenyl-Ficoll
TNP-OVA	trinitrophenyl-ovalbumin
TPR	total peripheral vascular resistance
TS	transferrin saturation

Acronym/Abbreviation	Meaning
TSH	thyroid stimulating hormone; total sulfhydryl
TSP	total suspended particles
TSS	total suspended solids
TXB_2	thromboxane
U	uranium
UA	urbanized area
UBL	urban boundary layer
UCL	urban canopy layer
UDDS	urban dynamometer driving schedule
UDPGT	uridine diphosphate (UDP)-glucuronosyltransferase(s)
UIUC	University of Illinois at Urbana Champaign
U.K.	United Kingdom
U.S.	United States of America
USC	U.S. Code
U.S. EPA	U.S. Environmental Protection Agency
USF	uptake slope factor
USGS	U.S. Geological Survey
USL	urban surface layer
UUDS	urban dynamic driving schedule
UV	ultraviolet radiation
UWM	Unit World Model
V	vanadium
V79	Chinese hamster lung cell line
VA	Veterans Administration
VAChAT	vesicular acetylcholine transporter
VAMP-2	vesicle-associated membrane protein-2
VA-NAS	Veterans Administration Normative Aging Study
VDAC	voltage-dependent anion channel
VDR	vitamin D receptor
VGAT	vesicular gamma aminobutyric acid (GABA) transporter
VGCC	voltage gated calcium channel(s)
VGLUT1	vesicular glutamate transporter 1
VIQ	verbal intelligence quotient (IQ)
VLPb	very low Pb
VMAT2	vesicular monoamine transporter-2
VO_4^{3-}	vanadate ion
VOC(s)	volatile organic compound(s)
vs., v.	versus
VSCC	very sharp cut cyclone
VSMC	vascular smooth muscle cells
WACAP	Western Airborne Contaminants Assessment Project
WBC	white blood cell
WCST	Wisconsin Card Sorting Test
WHAM	Windermere humic aqueous model
WHO	World Health Organization
WIAT	Wechsler Individual Achievement Test
WINS	well impactor ninety six
WISC	Wechsler Intelligence Scale for Children
WISC-R	Wechsler Intelligence Scale for Children-Revised
wk	week(s)
WML	white matter lesions
WPPSI-III	Wechsler Preschool and Primary Scales of Intelligence-III
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised
WRAT	Wide Range Achievement Test
W/S	winter/summer
WT	wild type
wt.	weight
XAFS	X-ray absorption fine structure
XANES	X-ray absorption near edge structure
XDH	xanthine dehydrogenase

Acronym/Abbreviation	Meaning
X_{ij}	observed hourly concentrations for time period i at site j
X_{ik}	observed hourly concentrations for time period i at site k
XPS	X-ray photoelectron spectroscopy
XRF	X-ray fluorescence
yr	year(s)
Zn	zinc
Zn^{2+}	zinc ion
ZPP	zirconium-potassium perchlorate; zinc protoporphyrin
Z-score	standard score

Preamble

Process of ISA Development

This preamble outlines the general process for developing an Integrated Science Assessment (ISA) including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments. The ISA provides a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the National Ambient Air Quality Standards (NAAQS). The general process for NAAQS reviews is described at http://www.epa.gov/ttn/naaqs/review.html. Figure I depicts the general NAAQS review process and information for individual NAAQS reviews is available at www.epa.gov/ttn/naaqs. This preamble is a general discussion of the basic steps and criteria used in developing an ISA; for each ISA, specific details and considerations are included in the introductory section for that assessment.

The fundamental process for developing an ISA includes:

- literature searches;
- study selection;
- evaluation and integration of the evidence; and
- development of scientific conclusions and causal judgments.

An initial step in this process is publication of a call for information in the Federal Register that invites the public to provide information relevant to the assessment, such as new or recent publications on health or welfare[1] effects of the pollutant, or from atmospheric and exposure sciences fields. The U.S. Environmental Protection Agency (EPA) maintains an ongoing literature search process for identification of relevant scientific studies published since the last review of the NAAQS. Search strategies are designed for pollutants and scientific disciplines and iteratively modified to optimize identification of pertinent publications. Papers are identified for inclusion in several additional ways: specialized searches on specific topics; independent review of tables of contents for journals in which relevant papers may be published; independent identification of relevant literature by expert scientists; review of citations in previous assessments and identification by the public and the Clean Air Scientific Advisory Committee (CASAC) during the external review process. This literature search and study

[1] Welfare effects as defined in Clean Air Act (CAA) Section 302(h) [42 U.S.C. 7602(h)] include, but are not limited to, “effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being.”

selection process is depicted in Figure II. Publications considered for inclusion in the ISA are added to the Health and Environmental Research Online (HERO) database developed by EPA (http://hero.epa.gov/); the references in the ISA include a hyperlink to the database.

Studies that have undergone scientific peer review and have been published or accepted for publication and reports that have undergone review are considered for inclusion in the ISA. Analyses conducted by EPA using publicly available data are also considered for inclusion in the ISA. All relevant epidemiologic, controlled human exposure, toxicological, and ecological and welfare effects studies published since the last review are considered, including those related to exposure-response relationships, mode(s) of action (MOA), and potentially at-risk populations and lifestages. Studies on atmospheric chemistry, environmental fate and transport, dosimetry, toxicokinetics and exposure are also considered for inclusion in the document, as well as analyses of air quality and emissions data. References that were considered for inclusion in a specific ISA can be found using the HERO website (http://hero.epa.gov).

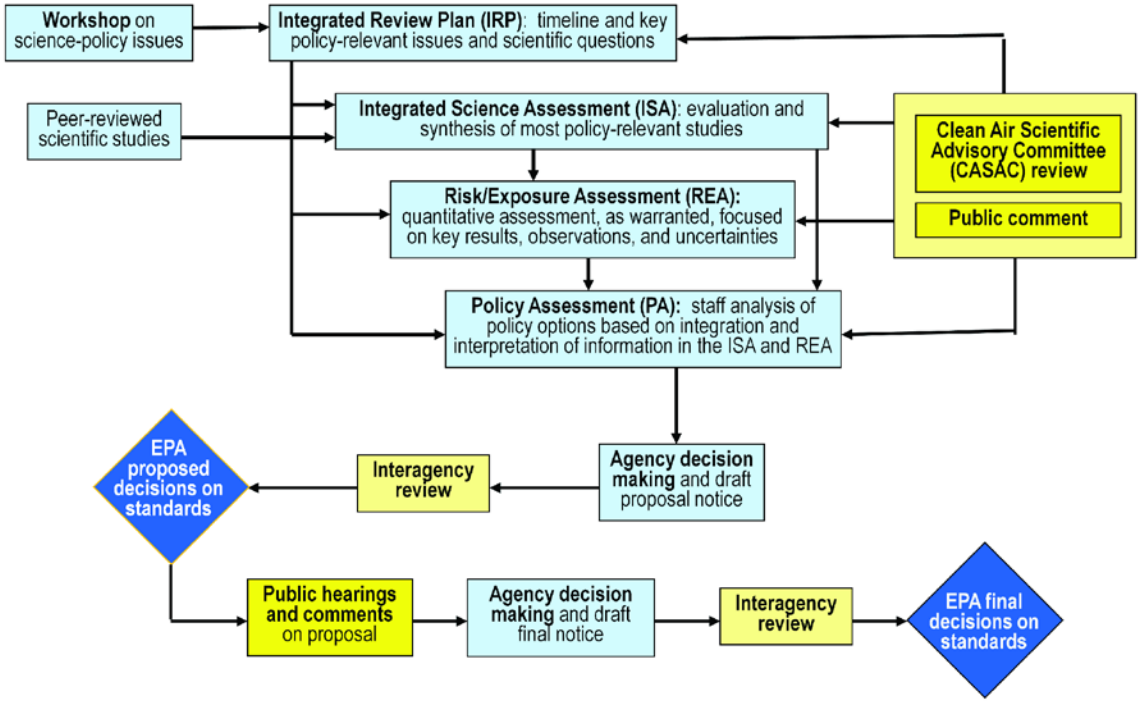


Figure I **Illustration of the key steps in the process of the review of National Ambient Air Quality Standards.**

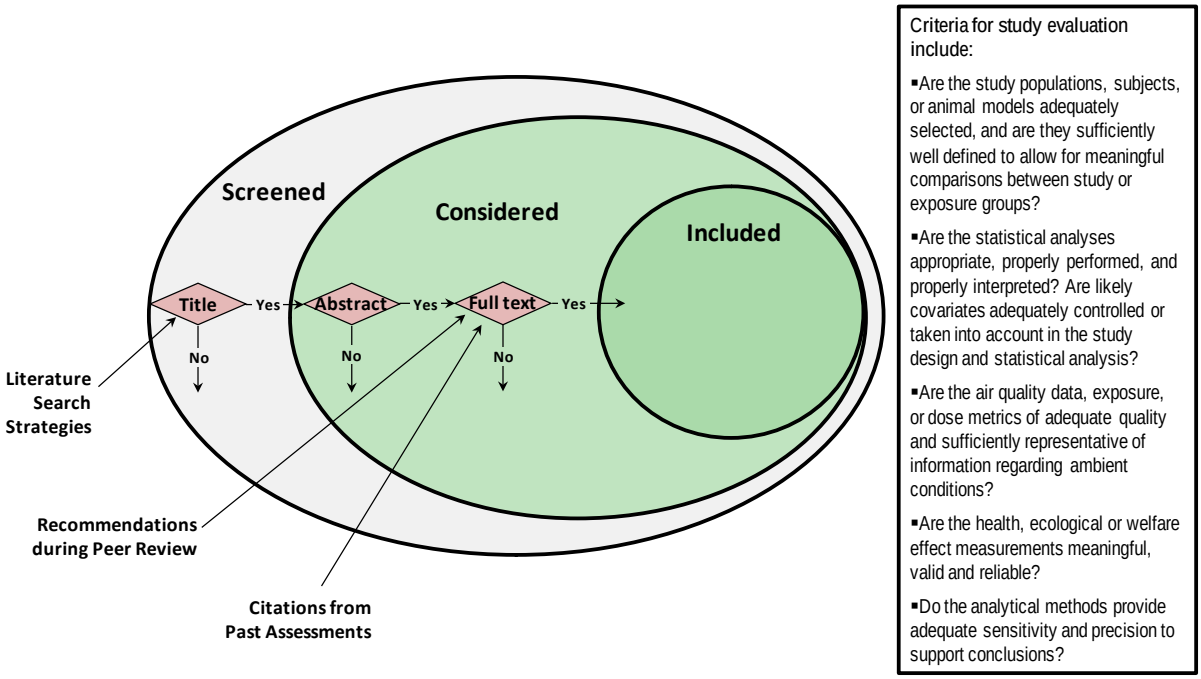


Figure II **Illustration of processes for literature search and study selection used for development of ISAs.**

Each ISA builds upon the conclusions of previous assessments for the pollutant under review. EPA focuses on peer reviewed literature published following the completion of the previous review and on any new interpretations of previous literature, integrating the results of recent scientific studies with previous findings. Important earlier studies may be discussed in detail to reinforce key concepts and conclusions or for reinterpretation in light of newer data. Earlier studies also are the primary focus in some areas of the document where research efforts have subsided, or if these earlier studies remain the definitive works available in the literature.

Selection of studies for inclusion in the ISA is based on the general scientific quality of the study, and consideration of the extent to which the study is informative and policy-relevant. Policy-relevant and informative studies include those that provide a basis for or describe the relationship between the criteria pollutant and effects, including studies that offer innovation in method or design and studies that reduce uncertainty on critical issues, such as analyses of confounding or effect modification by copollutants or other variables, analyses of concentration-response or dose-response relationships, or analyses related to time between exposure and response. Emphasis is placed on studies that examine effects associated with pollutant concentrations relevant to current population and ecosystem exposures, and particularly those pertaining to concentrations currently found in ambient

air. Other studies are included if they contain unique data, such as a previously unreported effect or MOA for an observed effect, or examine multiple concentrations to elucidate exposure-response relationships. In general, in assessing the scientific quality and relevance of health and welfare effects studies, the following considerations have been taken into account when selecting studies for inclusion in the ISA.

- Are the study populations, subjects, or animal models adequately selected, and are they sufficiently well defined to allow for meaningful comparisons between study or exposure groups?
- Are the statistical analyses appropriate, properly performed, and properly interpreted? Are likely covariates adequately controlled or taken into account in the study design and statistical analysis?
- Are the air quality data, exposure, or dose metrics of adequate quality and sufficiently representative of information regarding ambient conditions?
- Are the health, ecological or welfare effect measurements meaningful, valid and reliable?
- Do the analytical methods provide adequate sensitivity and precision to support conclusions?

Additional considerations are specific to particular disciplines. In selecting epidemiologic studies, EPA considers whether a given study: (1) presents information on associations with short- or long-term pollutant exposures at or near conditions relevant to ambient exposures; (2) addresses potential confounding by other pollutants; (3) assesses potential effect modifiers; (4) evaluates health endpoints and populations not previously extensively researched; and (5) evaluates important methodological issues related to interpretation of the health evidence (e.g., lag or time period between exposure and effects, model specifications, thresholds, mortality displacement).

Considerations for the selection of research evaluating controlled human exposure or animal toxicological studies include a focus on studies conducted using relevant pollutant exposures. For both types of studies, relevant pollutant exposures are considered to be those generally within one or two orders of magnitude of ambient concentrations. Studies in which higher doses were used may also be considered if they provide information relevant to understanding MOA or mechanisms, as noted below.

Evaluation of controlled human exposure studies focuses on those that approximated expected human exposure conditions in terms of concentration and duration. Studies should include control exposures to filtered air, as appropriate. In the selection of controlled human exposure studies, emphasis is placed on studies that: (1) investigate potentially at-risk populations and lifestages such as people with asthma or cardiovascular diseases, children or older adults; (2) address issues such as concentration-

response or time-course of responses; and (3) have sufficient statistical power to assess findings.

Review of the animal toxicological evidence focuses on studies that approximate expected human dose conditions, which vary depending on the dosimetry, toxicokinetics and biological sensitivity of the particular laboratory animal species or strains studied. Emphasis is placed on studies that: (1) investigate animal models of disease that can provide information on populations potentially at increased risk of effects; (2) address issues such as concentration-response or time-course of responses; and (3) have sufficient statistical power to assess findings. Due to resource constraints on exposure duration and numbers of animals tested, animal studies typically utilize high-concentration exposures to acquire data relating to mechanisms and assure a measurable response. Emphasis is placed on studies using doses or concentrations generally within 1-2 orders of magnitude of current levels. Studies with higher concentration exposures or doses are considered to the extent that they provide useful information to inform understanding of interspecies differences and differences between healthy and at-risk human populations. Results from in vitro studies may also be included if they provide mechanistic insight or further support for results demonstrated in vivo.

These criteria provide benchmarks for evaluating various studies and for focusing on the policy-relevant studies in assessing the body of health, ecological and welfare effects evidence. As stated initially, the intent of the ISA is to provide a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the NAAQS, not extensive summaries of all health, ecological and welfare effects studies for a pollutant. Of most relevance for inclusion of studies is whether they provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for effects associated with pollutant exposures at doses or concentrations relevant to ambient conditions that can inform decisions on whether to retain or revise the standards.

The general process for ISA development is illustrated in Figure III. In developing an ISA, EPA reviews and summarizes the evidence from: studies of atmospheric sciences; human exposure, animal toxicological, controlled human exposure and epidemiologic studies; and studies of ecological and welfare effects. In the process of developing the first draft ISA, EPA may convene a peer input meeting in which the scientific content of preliminary draft materials is reviewed to ensure that the ISA is up to date and is focused on the most policy-relevant findings, and to assist EPA with integration of evidence within and across disciplines. EPA integrates the evidence from across scientific disciplines or study types and characterizes the weight of evidence for relationships between the pollutant and various outcomes. The integration of evidence on health, and

ecological or welfare effects, involves collaboration between scientists from various disciplines. As an example, an evaluation of health effects evidence would include the integration of the results from epidemiologic, controlled human exposure, and toxicological studies, and application of the causal framework (described below) to draw conclusions. Integration of results on health or ecological effects that are logically or mechanistically connected (e.g., a spectrum of effects on the respiratory system) informs judgments of causality. Using the causal framework described in the following section, EPA scientists consider aspects such as strength, consistency, coherence, and biological plausibility of the evidence, and develop causality determinations on the nature of the relationships. Causality determinations often entail an iterative process of review and evaluation of the evidence. Two drafts of the ISA are typically released for review by the CASAC and the public, and comments received on the characterization of the science as well as the implementation of the causal framework are carefully considered in revising and completing the final ISA.

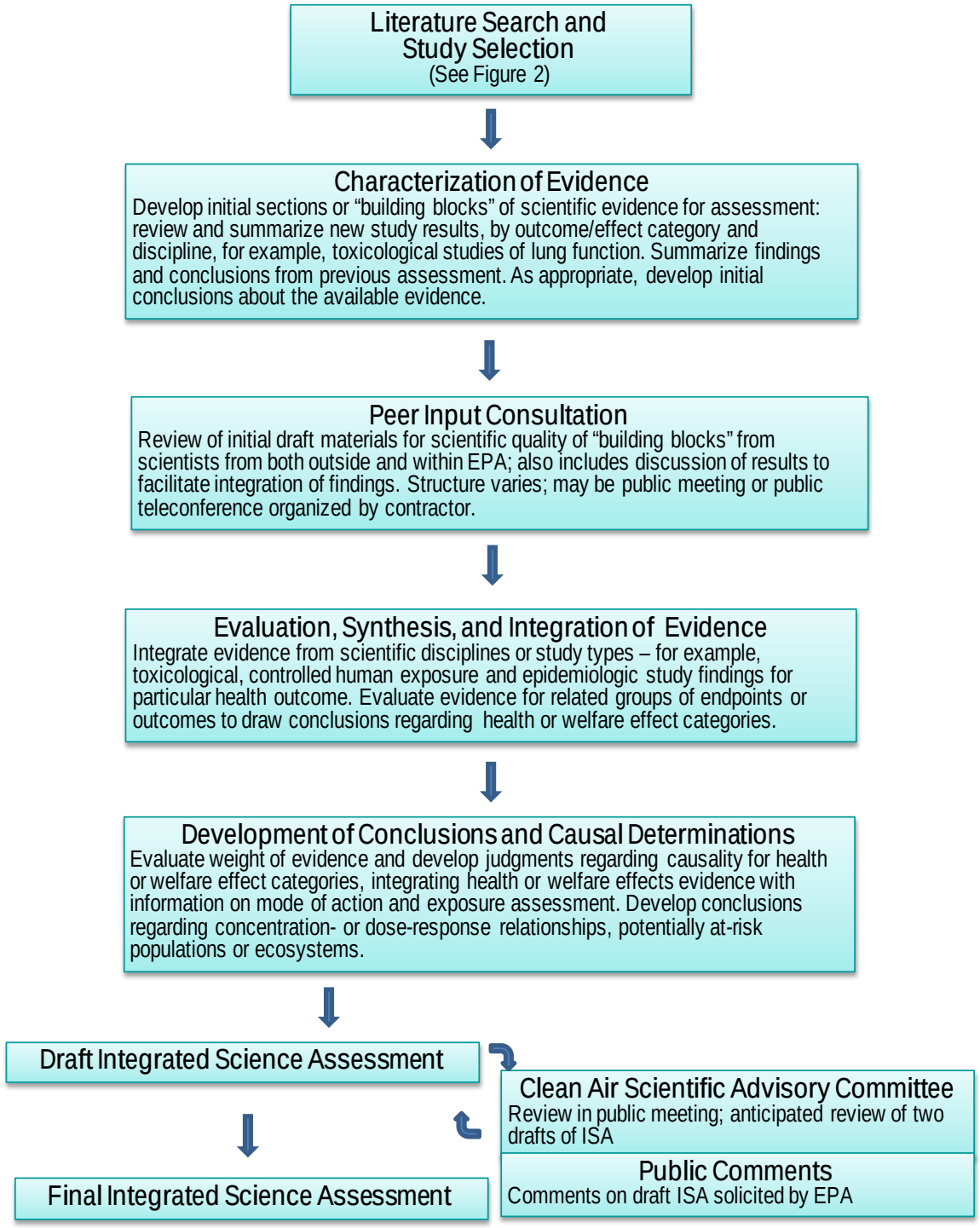


Figure III Characterization of the general process of ISA development.

EPA Framework for Causal Determination

EPA has developed a consistent and transparent basis for integration of scientific evidence and evaluation of the causal nature of air pollution-related health or welfare effects for use in developing ISAs. The framework described below establishes uniform language concerning causality and brings more specificity to the findings. This standardized language was drawn from sources across the federal government and wider scientific community, especially the National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (2008), a comprehensive report on evaluating causality. This framework:

- describes the kinds of scientific evidence used in establishing a general causal relationship between exposure and health effects;
- characterizes the process for integration and evaluation of evidence necessary to reach a conclusion about the existence of a causal relationship;
- identifies issues and approaches related to uncertainty; and
- provides a framework for classifying and characterizing the weight of evidence in support of a general causal relationship.

Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic, controlled human exposure, and animal toxicological studies) have been formulated by a number of regulatory and science agencies, including the IOM of the NAS (2008), International Agency for Research on Cancer (IARC) (2006b), U.S. EPA (2005c), and Centers for Disease Control and Prevention (CDC) (2004). Causal inference criteria have also been described for ecological effects evidence (U.S. EPA, 1998; Fox, 1991). These formalized approaches offer guidance for assessing causality. The frameworks are similar in nature, although adapted to different purposes, and have proven effective in providing a uniform structure and language for causal determinations.

Evaluating Evidence for Inferring Causation

The 1964 Surgeon General's report defined "cause" as a "significant, effectual relationship between an agent and an associated disorder or disease in the host" (HEW, 1964). More generally, a cause is defined as an agent that brings about an effect or a result. An association is the statistical relationship among variables; alone, however, it is insufficient proof of a causal relationship between an exposure and a health outcome. Unlike an association, a causal claim supports the creation of counterfactual claims, that is, a claim about what the world would have been like under different or changed circumstances [Samet and Bodurow, eds. (IOM, 2008)].

Many of the health and environmental outcomes reported in these studies have complex etiologies. Diseases such as asthma, coronary heart disease (CHD) or cancer are typically initiated by multiple agents. Outcomes depend on a variety of factors, such as age, genetic susceptibility, nutritional status, immune competence, and social factors (IOM, 2008; Gee and Payne-Sturges, 2004). Effects on ecosystems are often also multifactorial with a complex web of causation. Further, exposure to a combination of agents could cause synergistic or antagonistic effects. Thus, the observed risk may represent the net effect of many actions and counteractions.

Scientific findings incorporate uncertainty. "Uncertainty" can be defined as having limited knowledge to exactly describe an existing state or future outcome, e.g., the lack of knowledge about the correct value for a specific measure or estimate. Uncertainty analysis may be qualitative or quantitative in nature. In many cases, the analysis is qualitative, and can include professional judgment or inferences based on analogy with similar situations. Quantitative uncertainty analysis may include use of simple measures (e.g., ranges) and analytical techniques. Quantitative uncertainty analysis might progress to more complex measures and techniques, if needed for decision support. Various approaches to evaluating uncertainty include classical statistical methods, sensitivity analysis, or probabilistic uncertainty analysis, in order of increasing complexity and data requirements. However, data may not be available for all aspects of an assessment and those data that are available may be of questionable or unknown quality. Ultimately, the assessment is based on a number of assumptions with varying degrees of uncertainty. The ISA generally evaluates uncertainties qualitatively in assessing the evidence from across studies; in some situations quantitative analysis approaches, such as meta-regression, may be used.

Publication bias is a source of uncertainty regarding the magnitude of health risk estimates. It is well understood that studies reporting non-null findings are more likely to be published than reports of null findings. Publication bias can result in overestimation of effect estimate sizes (Ioannidis, 2008). For example, effect estimates from single-city epidemiologic studies have been found to be generally larger than those from multicity studies which is an indication of publication bias in that null or negative single-city results may be reported in a multicity analyses but might not be published independently (Bell et al., 2005).

Consideration of Evidence from Scientific Disciplines

Moving from association to causation involves the elimination of alternative explanations for the association. The ISA focuses on evaluation of the findings from the body of evidence, drawing upon the results of all studies determined to meet the criteria described previously. Causality determinations are based on the evaluation, integration, and synthesis of evidence from across scientific disciplines. The relative importance of different types of evidence varies by pollutant or assessment, as does the availability of different types of evidence for causality determination. Three general types of studies inform consideration of human health effects: controlled human exposure, epidemiologic and toxicological studies. Evidence on ecological or welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and numerous disciplines (e.g., community ecology, biogeochemistry and paleontological/historical reconstructions).

Direct evidence of a relationship between pollutant exposures and human health effects comes from controlled human exposure studies. Such studies experimentally evaluate the health effects of administered exposures in human volunteers under highly controlled laboratory conditions. Also referred to as human clinical studies, these experiments allow investigators to expose subjects to known concentrations of air pollutants under carefully regulated environmental conditions and activity levels. These studies provide important information on the biological plausibility of associations observed in epidemiologic studies. In some instances, controlled human exposure studies can also be used to characterize concentration-response relationships at pollutant concentrations relevant to ambient conditions. Controlled human exposures are typically conducted using a randomized crossover design, with subjects exposed both to the pollutant and a clean air control. In this way, subjects serve as their own experimental controls, effectively limiting the variance associated with many potential confounders. Considerations for evaluating controlled human study findings include the generally small sample size and short exposure time used in experimental studies, and that severe health outcomes are not assessed. By experimental design, controlled human exposure studies are structured to evaluate physiological or biomolecular outcomes in response to exposure to a specific air pollutant and/or combination of pollutants. In addition, the study design generally precludes inclusion of subjects with serious health conditions, and therefore the results often cannot be generalized to an entire population. Although some controlled human exposure studies have included health-compromised individuals such as those with respiratory or cardiovascular disease, these individuals may also be relatively healthy and may not represent the most sensitive individuals in the population. Thus, observed effects in these studies may underestimate the response in certain populations. In addition, the

study design is limited to exposures and endpoints that are not expected to result in severe health outcomes.

Epidemiologic studies provide important information on the associations between health effects and exposure of human populations to ambient air pollution. In epidemiologic or observational studies of humans, the investigator generally does not control exposures or intervene with the study population. Broadly, observational studies can describe associations between exposures and effects. These studies fall into several categories: e.g., cross-sectional, prospective cohort, panel, and time-series studies. Cross-sectional studies generally use health outcome, exposure and covariate data available at the community level (e.g., annual mortality rates and pollutant concentrations), but do not have individual-level data. Prospective cohort studies have some data collected at the individual level, generally health outcome data, and in some cases individual-level data on exposure and covariates are collected. Time-series studies evaluate the relationship for changes in a health outcome with changes in exposure indicators, such as an association between daily changes in mortality with air pollution. Panel studies include repeated measurements of health outcomes, such as respiratory symptoms or heart rhythm variability, at the individual level. “Natural experiments” offer the opportunity to investigate changes in health related to a change in exposure, such as closure of a pollution source.

In evaluating epidemiologic studies, consideration of many study design factors and issues must be taken into account to properly inform their interpretation. One key consideration is evaluation of the potential contribution of the pollutant to a health outcome when it is a component of a complex air pollutant mixture. Reported effect estimates in epidemiologic studies may reflect (1) independent effects on health outcomes; (2) effects of the pollutant acting as an indicator of a copollutant or a complex ambient air pollution mixture; and (3) effects resulting from interactions between that pollutant and copollutants.

In the evaluation of epidemiologic evidence, one important consideration is potential confounding. Confounding is “… a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)” (Rothman and Greenland, 1998). One approach to remove spurious associations due to possible confounders is to control for characteristics that may differ between exposed and unexposed persons; this is frequently termed “adjustment.” Scientific judgment is needed to evaluate likely sources and extent of confounding, together with consideration of how well the existing constellation of study designs, results, and analyses address the potential for erroneous inferences. A confounder is associated with both the exposure and the

effect; for example, confounding can occur between correlated pollutants that are associated with the same effect.

Several statistical methods are available to detect and control for potential confounders; however, none of these methods is completely satisfactory. Multivariable regression models constitute one tool for estimating the association between exposure and outcome after adjusting for characteristics of participants that might confound the results. The use of multipollutant regression models has been the prevailing approach for controlling potential confounding by copollutants in air pollution health effects studies. Finding the likely causal pollutant from multipollutant regression models is made difficult by the possibility that one or more air pollutants may be acting as a surrogate for an unmeasured or poorly measured pollutant or for a particular mixture of pollutants. In addition, pollutants may independently exert effects on the same system; for example, several pollutants may be associated with respiratory effect through either the same or different modes of action. The number and degree of diversity of covariates, as well as their relevance to the potential confounders, remain matters of scientific judgment. Despite these limitations, the use of multipollutant models is still the prevailing approach employed in most air pollution epidemiologic studies and provides some insight into the potential for confounding or interaction among pollutants.

Confidence that unmeasured confounders are not producing the findings is increased when multiple studies are conducted in various settings using different subjects or exposures, each of which might eliminate another source of confounding from consideration. For example, multicity studies can provide insight on potential confounding through the use of a consistent method to analyze data from across locations with different levels of copollutants and other covariates. Intervention studies, because of their quasi-experimental nature, can be particularly useful in characterizing causation.

Another important consideration in the evaluation of epidemiologic evidence is effect modification, which occurs when the effect differs between subgroups or strata; for example, effect estimates that vary by age group or potential risk factor. As stated by Rothman and Greenland (1998):

> "Effect-measure modification differs from confounding in several ways. The main difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure modification is a property of the effect under study … In epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-measure modification."

When a risk factor is a confounder, it is the true cause of the association observed between the exposure and the outcome; when a risk factor is an effect modifier, it changes the magnitude of the association between the exposure and the outcome in

stratified analyses. For example, the presence of a preexisting disease or indicator of low socioeconomic status may act as effect modifiers if they are associated with increased risk of effects related to air pollution exposure. It is often possible to stratify the relationship between health outcome and exposure by one or more of these potential effect modifiers. For variables that modify the association, effect estimates in each stratum will be different from one another and different from the overall estimate, indicating a different exposure-response relationship may exist in populations represented by these variables.

Exposure measurement error, which refers to the uncertainty associated with the exposure metrics used to represent exposure of an individual or population, can be an important contributor to uncertainty in air pollution epidemiologic study results. Exposure error can influence observed epidemiologic associations between ambient pollutant concentrations and health outcomes by biasing effect estimates toward or away from the null and widening confidence intervals around those estimates (Zeger et al., 2000). There are several components that contribute to exposure measurement error in air pollution epidemiologic studies, including the difference between true and measured ambient concentrations, the difference between average personal exposure to ambient pollutants and ambient concentrations at central monitoring sites, and the use of average population exposure rather than individual exposure estimates. Factors that could influence exposure estimates include nonambient sources of exposure, topography of the natural and built environment, meteorology, measurement errors, time-location-activity patterns, and the extent to which ambient pollutants penetrate indoor environments. The importance of exposure error varies with study design and is dependent on the spatial and temporal aspects of the design.

The third main type of health effects evidence, animal toxicological studies, provides information on the pollutant's biological action under controlled and monitored exposure circumstances. Taking into account physiological differences of the experimental species from humans, these studies inform characterization of health effects of concern, exposure-response relationships and MOAs. Further, animal models can inform determinations of at-risk populations. These studies evaluate the effects of exposures to a variety of pollutants in a highly controlled laboratory setting and allow exploration of toxicological pathways or mechanisms by which a pollutant may cause effects. Understanding the biological mechanisms underlying various health outcomes can prove crucial in establishing or negating causality. In the absence of human studies data, extensive, well-conducted animal toxicological studies can support determinations of causality, if the evidence base indicates that similar responses are expected in humans under ambient exposure conditions.

Interpretations of animal toxicological studies are affected by limitations associated with extrapolation between animal and human responses. The differences between humans and other species have to be taken into consideration, including metabolism, hormonal regulation, breathing pattern, and differences in lung structure and anatomy. Also, in spite of a high degree of homology and the existence of a high percentage of orthologous genes across humans and rodents (particularly mice), extrapolation of molecular alterations at the gene level is complicated by species-specific differences in transcriptional regulation. Given these differences, there are uncertainties associated with quantitative extrapolations of observed pollutant-induced pathophysiological alterations between laboratory animals and humans, as those alterations are under the control of widely varying biochemical, endocrine, and neuronal factors.

For ecological effects assessment, both laboratory and field studies (including field experiments and observational studies) can provide useful data for causality determination. Because conditions can be controlled in laboratory studies, responses may be less variable and smaller differences may be easier to detect. However, the control conditions may limit the range of responses (e.g., animals may not be able to seek alternative food sources) or incompletely reflect pollutant bioavailability, so they may not reflect responses that would occur in the natural environment. In addition, larger-scale processes are difficult to reproduce in the laboratory.

Field observational studies measure biological changes in uncontrolled situations, and describe an association between a disturbance and an ecological effect. Field data can provide important information for assessments of multiple stressors or where site-specific factors significantly influence exposure. They are also often useful for analyses of larger geographic scales and higher levels of biological organization. However, because conditions are not controlled, variability is expected to be higher and differences harder to detect. Field surveys are most useful for linking stressors with effects when stressor and effect levels are measured concurrently. The presence of confounding factors can make it difficult to attribute observed effects to specific stressors.

Some studies are considered “intermediate” and are categorized as being between laboratory and field are studies. Some use environmental media collected from the field to examine the responses in the laboratory. Others are experiments that are performed in the natural environment while controlling for some, but not all, of the environmental conditions (i.e., mesocosm studies). This type of study in manipulated natural environments can be considered a hybrid between a field experiment and laboratory study since some aspects are performed under controlled conditions but others are not. They make it possible to observe community and/or ecosystem dynamics, and provide strong

evidence for causality when combined with findings of studies that have been made under more controlled conditions.

Application of Framework for Causal Determination

In its evaluation and integration of the scientific evidence on health or welfare effects of criteria pollutants, EPA determines the weight of evidence in support of causation and characterizes the strength of any resulting causal classification. EPA also evaluates the quantitative evidence and draws scientific conclusions, to the extent possible, regarding the concentration-response relationships and the loads to ecosystems, exposures, doses or concentrations, exposure duration, and pattern of exposures at which effects are observed.

To aid judgment, various "aspects"[1] of causality have been discussed by many philosophers and scientists. The 1964 Surgeon General's report on tobacco smoking discussed criteria for the evaluation of epidemiologic studies, focusing on consistency, strength, specificity, temporal relationship, and coherence (HEW, 1964). Sir Austin Bradford Hill (Hill, 1965) articulated aspects of causality in epidemiology and public health that have been widely used (IOM, 2008; IARC, 2006b; U.S. EPA, 2005c; CDC, 2004). These aspects (Hill, 1965) have been modified (Table I) for use in causal determinations specific to health and welfare effects for pollutant exposures (U.S. EPA, 2009a).[2] Although these aspects provide a framework for assessing the evidence, they do not lend themselves to being considered in terms of simple formulas or fixed rules of evidence leading to conclusions about causality (Hill, 1965). For example, one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results and reach credible conclusions about the relative weight of the evidence and the likelihood of causality. Rather, these aspects provide a framework for systematic appraisal of the body of evidence, informed by peer and public comment and advice, which includes weighing alternative views on controversial issues. In addition, it is important to note that the aspects in Table I cannot be used as a strict checklist, but rather to determine the weight of the evidence for inferring causality. In particular, not meeting one or more of the principles does not automatically preclude a determination of causality [see discussion in (CDC, 2004)].

[1] The "aspects" described by Sir Austin Bradford Hill (Hill, 1965) have become, in the subsequent literature, more commonly described as "criteria." The original term "aspects" is used here to avoid confusion with "criteria" as it is used, with different meaning, in the Clean Air Act.

[2] The Hill aspects were developed for interpretation of epidemiologic results. They have been modified here for use with a broader array of data, i.e., epidemiologic, controlled human exposure, ecological, and animal toxicological studies, as well as in vitro data, and to be more consistent with EPA's Guidelines for Carcinogen Risk Assessment.

Table I Aspects to aid in judging causality.

Aspect	Description
Consistency of the observed association	An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
Coherence	An inference of causality from one line of evidence (e.g., epidemiologic, clinical, or animal studies) may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. Evidence on ecological or welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and subdisciplines of ecology (e.g., community ecology, biogeochemistry, and paleontological/historical reconstructions). The coherence of evidence from various fields greatly adds to the strength of an inference of causality. In addition, there may be coherence in demonstrating effects across multiple study designs or related health endpoints within one scientific line of evidence.
Biological plausibility.	An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A proposed mechanistic linking between an effect and exposure to the agent is an important source of support for causality, especially when data establishing the existence and functioning of those mechanistic links are available.
Biological gradient (exposure-response relationship)	A well-characterized exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times).
Strength of the observed association	The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. However, it is noted that a small magnitude in an effect estimate may represent a substantial effect in a population.
Experimental evidence	Strong evidence for causality can be provided through “natural experiments” when a change in exposure is found to result in a change in occurrence or frequency of health or welfare effects.
Temporal relationship of the observed association	Evidence of a temporal sequence between the introduction of an agent, and appearance of the effect, constitutes another argument in favor of causality.
Specificity of the observed association	Evidence linking a specific outcome to an exposure can provide a strong argument for causation. However, it must be recognized that rarely, if ever, does exposure to a pollutant invariably predict the occurrence of an outcome, and that a given outcome may have multiple causes.
Analogy	Structure activity relationships and information on the agent’s structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

Determination of Causality

In the ISA, EPA assesses the body of relevant literature, building upon evidence available during previous NAAQS reviews, to draw conclusions on the causal relationships between relevant pollutant exposures and health or environmental effects. ISAs use a five-level hierarchy that classifies the weight of evidence for causation[1]. In developing this hierarchy, EPA has drawn on the work of previous evaluations, most prominently the IOM's *Improving the Presumptive Disability Decision-Making Process for Veterans* [Samet and Bodurow, eds. (IOM, 2008), EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005c), and the U.S. Surgeon General's smoking report (CDC, 2004). This weight of evidence evaluation is based on integration of findings from various lines of evidence from across the health and environmental effects disciplines. These separate judgments are integrated into a qualitative statement about the overall weight of the evidence and causality. The five descriptors for causal determination are described in Table II.

Determination of causality involves the evaluation and integration of evidence for different types of health, ecological or welfare effects associated with short- and long-term exposure periods. In making determinations of causality, evidence is evaluated for major outcome categories or groups of related endpoints (e.g., respiratory effects, vegetation growth), integrating evidence from across disciplines, and evaluating the coherence of evidence across a spectrum of related endpoints to draw conclusions regarding causality. In discussing the causal determination, EPA characterizes the evidence on which the judgment is based, including strength of evidence for individual endpoints within the outcome category or group of related endpoints.

In drawing judgments regarding causality for the criteria air pollutants, the ISA focuses on evidence of effects in the range of relevant pollutant exposures or doses, and not on determination of causality at any dose. Emphasis is placed on evidence of effects at doses (e.g., blood Pb concentration) or exposures (e.g., air concentrations) that are relevant to, or somewhat above, those currently experienced by the population. The extent to which studies of higher concentrations are considered varies by pollutant and major outcome category, but generally includes those with doses or exposures in the range of one to two orders of magnitude above current or ambient conditions. Studies that use higher doses or exposures may also be considered to the extent that they provide useful information to inform understanding of mode of action, interspecies differences, or factors that may increase risk of effects for a population. Thus, a causality determination is based on

[1] The Center for Disease Control (CDC) and IOM frameworks use a four-category hierarchy for the strength of the evidence. A five-level hierarchy is used here to be consistent with the EPA Guidelines for Carcinogen Risk Assessment and to provide a more nuanced set of categories.

weight of evidence evaluation for health, ecological or welfare effects, focusing on the evidence from exposures or doses generally ranging from current levels to one or two orders of magnitude above current levels.

In addition, EPA evaluates evidence relevant to understand the quantitative relationships between pollutant exposures and health, ecological or welfare effects. This includes evaluation of the form of concentration-response or dose-response relationships and, to the extent possible, drawing conclusions on the levels at which effects are observed. The ISA also draws scientific conclusions regarding important exposure conditions for effects and populations that may be at greater risk for effects, as described in the following section.

Table II Weight of evidence for causal determination.

Causal Determination	Health Effects	Ecological and Welfare Effects
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes multiple high-quality studies	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes multiple high-quality studies.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding are minimized, but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, determination is based on multiple studies in multiple research groups.
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited. For example, (a) at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent; or (b) a well-conducted toxicological study, such as those conducted in the National Toxicology Program (NTP), shows effects in animal species,	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations, are mutually consistent in not showing an effect at any level of exposure.	Several adequate studies, examining relationships with relevant exposures, are consistent in failing to show an effect at any level of exposure.

Quantitative Relationships: Effects on Human Populations

Once a determination is made regarding the causal relationship between the pollutant and outcome category, important questions regarding quantitative relationships include:

- What is the concentration-response, exposure-response, or dose-response relationship in the human population?
- What is the interrelationship between incidence and severity of effect?
- What exposure conditions (dose or exposure, duration and pattern) are important?
- What populations and lifestages appear to be differentially affected (i.e., more at risk of experiencing effects)?

In order to address these questions, the entirety of quantitative evidence is evaluated to characterize pollutant concentrations and exposure durations at which effects were observed for exposed populations, including populations and lifestages potentially at increased risk. To accomplish this, evidence is considered from multiple and diverse types of studies, and a study or set of studies that best approximates the concentration-response relationships between health outcomes and the pollutant may be identified. Controlled human exposure studies provide the most direct and quantifiable exposure-response data on the human health effects of pollutant exposures. To the extent available, the ISA evaluates results from epidemiologic studies that characterize the form of relationships between the pollutant and health outcomes and draws conclusions on the shape of these relationships. Animal data may also inform evaluation of concentration-response relationships, particularly relative to MOAs and characteristics of at-risk populations.

An important consideration in characterizing the public health impacts associated with exposure to a pollutant is whether the concentration-response relationship is linear across the range of concentrations or if nonlinear relationships exist along any part of this range. The shape of the concentration-response curve at and below the level of the current standards is of particular interest. Various sources of variability and uncertainty, such as low data density in the lower concentration range, possible influence of exposure measurement error, and variability between individuals in susceptibility to air pollution health effects, tend to smooth and “linearize” the concentration-response function, and thus can obscure the existence of a threshold or nonlinear relationship. Since individual thresholds vary from person to person due to individual differences such as genetic level susceptibility or preexisting disease conditions (and even can vary from one time to another for a given person), it can be difficult to demonstrate that a threshold exists in a population study. These sources of variability and uncertainty may explain why the available human data at ambient concentrations for some environmental pollutants

(e.g., particulate matter [PM], O_3, lead [Pb], environmental tobacco smoke [ETS], radiation) do not exhibit thresholds for cancer or noncancer health effects, even though likely mechanisms include nonlinear processes for some key events.

Finally, identification of the population groups or lifestages that may be at greater risk of health effects from air pollutant exposures contributes to an understanding of the public health impact of pollutant exposures. In the ISA, the term "at-risk population" is used to encompass populations or lifestages that have a greater likelihood of experiencing health effects related to exposure to an air pollutant due to a variety of factors; other terms used in the literature include susceptible, vulnerable, and sensitive. These factors may be intrinsic, such as genetic or developmental factors, race, gender, lifestage, or the presence of preexisting diseases, or they may be extrinsic, such as socioeconomic status (SES), activity pattern and exercise level, reduced access to health care, low educational attainment, or increased pollutant exposures (e.g., near roadways). Epidemiologic studies can help identify populations potentially at increased risk of effects by evaluating health responses in the study population. Examples include testing for interactions or effect modification by factors such as gender, age group, or health status. Experimental studies using animal models of susceptibility or disease can also inform the extent to which health risks are likely greater in specific population groups.

Quantitative Relationships: Effects on Ecosystems or Public Welfare

Key questions for understanding the quantitative relationships between exposure (or concentration or deposition) to a pollutant and risk to ecosystems or the public welfare include:

- What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations, functions, etc.) appear to be affected, or are more sensitive to effects? Are there differences between locations or materials in welfare effects responses, such as impaired visibility or materials damage?
- Under what exposure conditions (amount deposited or concentration, duration and pattern) are effects seen?
- What is the shape of the concentration-response or exposure-response relationship?

Evaluations of causality generally consider the probability of quantitative changes in ecological and welfare effects in response to exposure. A challenge to the quantification of exposure-response relationships for ecological effects is the great regional and local spatial variability, as well as temporal variability, in ecosystems. Thus, exposure-response relationships are often determined for a specific ecological system and scale,

rather than at the national or even regional scale. Quantitative relationships therefore are estimated site by site and may differ greatly between ecosystems.

Concepts in Evaluating Adversity of Health Effects

In evaluating health evidence, a number of factors can be considered in delineating between adverse and nonadverse health effects resulting from exposure to air pollution. Some health outcomes, such as hospitalization for respiratory or cardiovascular diseases, are clearly considered adverse. It is more difficult to determine the extent of change that constitutes adversity in more subtle health measures. These include a wide variety of responses, such as alterations in markers of inflammation or oxidative stress, changes in pulmonary function or heart rate variability, or alterations in neurocognitive function measures. The challenge is determining the magnitude of change in these measures when there is no clear point at which a change becomes adverse. The extent to which a change in health measure constitutes an adverse health effect may vary between populations. Some changes that may not be considered adverse in healthy individuals would be potentially adverse in more at-risk individuals.

The extent to which changes in lung function are adverse has been discussed by the American Thoracic Society (ATS) in an official statement titled *What Constitutes an Adverse Health Effect of Air Pollution?* (ATS, 2000). An air pollution-induced shift in the population distribution of a given risk factor for a health outcome was viewed as adverse, even though it may not increase the risk of any one individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no identifiable individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution such that no identifiable individual experiences clinically relevant effects. This shift toward decreased lung function, however, would be considered adverse because individuals within the population would have diminished reserve function and therefore would be at increased risk to further environmental insult. The committee also observed that elevations of biomarkers, such as cell number and types, cytokines and reactive oxygen species, may signal risk for ongoing injury and clinical effects or may simply indicate transient responses that can provide insights into mechanisms of injury, thus illustrating the lack of clear boundaries that separate adverse from nonadverse effects.

The more subtle health outcomes may be connected mechanistically to health events that are clearly adverse. For example, air pollution may affect markers of transient myocardial ischemia such as ST-segment abnormalities or onset of exertional angina. These effects may not be apparent to the individual, yet may still increase the risk of a number of cardiac events, including myocardial infarction and sudden death. Thus, small changes in

physiological measures may not appear to be clearly adverse when considered alone, but may be a part of a coherent and biologically plausible chain of related health outcomes that range up to responses that are very clearly adverse, such as hospitalization or mortality.

Concepts in Evaluating Adversity of Ecological Effects

Adversity of ecological effects can be understood in terms ranging in biological level of organization; from the cellular level to the individual organism and to the population, community, and ecosystem levels. In the context of ecology, a population is a group of individuals of the same species, and a community is an assemblage of populations of different species interacting with one another that inhabit an area. An ecosystem is the interactive system formed from all living organisms and their abiotic (physical and chemical) environment within a given area (IPCC, 2007). The boundaries of what could be called an ecosystem are somewhat arbitrary, depending on the focus of interest or study. Thus, the extent of an ecosystem may range from very small spatial scales to, ultimately, the entire Earth (IPCC, 2007).

Effects on an individual organism are generally not considered to be adverse to public welfare. However if effects occur to enough individuals within a population, then communities and ecosystems may be disrupted. Changes to populations, communities, and ecosystems can in turn result in an alteration of ecosystem processes. Ecosystem processes are defined as the metabolic functions of ecosystems including energy flow, elemental cycling, and the production, consumption and decomposition of organic matter (U.S. EPA, 2002a). Growth, reproduction, and mortality are species-level endpoints that can be clearly linked to community and ecosystem effects and are considered to be adverse when negatively affected. Other endpoints such as changes in behavior and physiological stress can decrease ecological fitness of an organism, but are harder to link unequivocally to effects at the population, community, and ecosystem level. The degree to which pollutant exposure is considered adverse may also depend on the location and its intended use (i.e., city park, commercial, and cropland). Support for consideration of adversity beyond the species level by making explicit the linkages between stress-related effects at the species and effects at the ecosystem level is found in *A Framework for Assessing and Reporting on Ecological Condition: an SAB report* (U.S. EPA, 2002a). Additionally, the National Acid Precipitation Assessment Program (NAPAP, 1991) uses the following working definition of “adverse ecological effects” in the preparation of reports to Congress mandated by the Clean Air Act: “any injury (i.e., loss of chemical or physical quality or viability) to any ecological or ecosystem component, up to and including at the regional level, over both long and short terms.”

On a broader scale, ecosystem services may provide indicators for ecological impacts. Ecosystem services are the benefits that people obtain from ecosystems (UNEP, 2003). According to the Millennium Ecosystem Assessment, ecosystem services include: "provisioning services such as food and water; regulating services such as regulation of floods, drought, land degradation, and disease; supporting services such as soil formation and nutrient cycling; and cultural services such as recreational, spiritual, religious, and other nonmaterial benefits." For example, a more subtle ecological effect of pollution exposure may result in a clearly adverse impact on ecosystem services if it results in a population decline in a species that is recreationally or culturally important.

References for Preamble

ATS (American Thoracic Society). (2000). What constitutes an adverse health effect of air pollution? This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 161: 665-673.

Bell, ML; Dominici, F; Samet, JM. (2005). A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology 16: 436-445. http://dx.doi.org/10.1097/01.ede.0000165817.40152.85

CDC (Centers for Disease Control and Prevention). (2004). The health consequences of smoking: A report of the Surgeon General. Washington, DC: U.S. Department of Health and Human Services. http://www.surgeongeneral.gov/library/smokingconsequences/

Fox, GA. (1991). Practical causal inference for ecoepidemiologists. J Toxicol Environ Health A 33: 359-373. http://dx.doi.org/10.1080/15287399109531535

Gee, GC; Payne-Sturges, DC. (2004). Environmental health disparities: A framework integrating psychosocial and environmental concepts [Review]. Environ Health Perspect 112: 1645-1653. http://dx.doi.org/10.1289/ehp.7074

HEW (U.S. Department of Health, Education and Welfare). (1964). Smoking and health: Report of the advisory committee to the surgeon general of the public health service. Washington, DC: U.S. Department of Health, Education, and Welfare. http://profiles.nlm.nih.gov/ps/retrieve/ResourceMetadata/NNBBMQ

Hill, AB. (1965). The environment and disease: Association or causation? Proc R Soc Med 58: 295-300.

IARC (International Agency for Research on Cancer). (2006b). Preamble to the IARC monographs. Lyon, France. http://monographs.iarc.fr/ENG/Preamble/

Ioannidis, JPA. (2008). Why most discovered true associations are inflated [Review]. Epidemiology 19: 640-648. http://dx.doi.org/10.1097/EDE.0b013e31818131e7

IOM (Institute of Medicine). (2008). Improving the presumptive disability decision-making process for veterans. In JM Samet; CC Bodurow (Eds.). Washington, DC: National Academies Press. http://www.nap.edu/openbook.php?record_id=11908

IPCC (Intergovernmental Panel on Climate Change). (2007). Climate change 2007: Impacts, adaptation and vulnerability. Cambridge, UK: Cambridge University Press.

NAPAP (National Acid Precipitation Assessment Program). (1991). The experience and legacy of NAPAP: Report of the Oversight Review Board of the National Acid Precipitation Assessment Program. Washington, DC.

Rothman, KJ; Greenland, S. (1998). Modern epidemiology (2nd ed.). Philadelphia, PA: Lippincott, Williams, & Wilkins.

U.S. EPA (U.S. Environmental Protection Agency). (1998). Guidelines for ecological risk assessment [EPA Report]. (EPA/630/R-95/002F). Washington, DC. http://www.epa.gov/raf/publications/guidelines-ecological-risk-assessment.htm

U.S. EPA (U.S. Environmental Protection Agency). (2002a). A framework for assessing and reporting on ecological condition: An SAB report [EPA Report]. (EPA-SAB-EPEC-02-009). Washington, DC. http://www.ntis.gov/search/product.aspx?ABBR=PB2004100741

U.S. EPA (U.S. Environmental Protection Agency). (2005c). Guidelines for carcinogen risk assessment [EPA Report]. (EPA/630/P-03/001F). Washington, DC. http://www.epa.gov/cancerguidelines/

U.S. EPA (U.S. Environmental Protection Agency). (2009a). Integrated science assessment for particulate matter [EPA Report]. (EPA/600/R-08/139F). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546

UNEP (United Nations Environment Programme). (2003). Ecosystems and human well-being: A framework for assessment. Washington, DC: Island Press.

Zeger, SL; Thomas, D; Dominici, F; Samet, JM; Schwartz, J; Dockery, D; Cohen, A. (2000). Exposure measurement error in time-series studies of air pollution: Concepts and consequences. Environ Health Perspect 108: 419-426.

Legislative and Historical Background

Legislative Requirements for the NAAQS Review

Two sections of the Clean Air Act (CAA) govern the establishment and revision of the NAAQS. Section 108 (42:U.S.C.:7408) directs the Administrator to identify and list certain air pollutants and then to issue air quality criteria for those pollutants. The Administrator is to list those air pollutants that in her "… judgment, cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare; …" and, "… the presence of which in the ambient air results from numerous or diverse mobile or stationary sources;" and, "… for which … [the Administrator] plans to issue air quality criteria…." Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in the ambient air …" (42:U.S.C.:7408([b]). Section 109 (42:U.S.C.:7409) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants for which air quality criteria are issued. Section 109(b)(1) defines a primary standard as one "…the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health." The legislative history of Section 109 indicates that a primary standard is to be set at "… the maximum permissible ambient air level … which will protect the health of any [sensitive] group of the population," and that for this purpose "… reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group…" (S. Rep. No. 91:1196, 91st Cong., 2d Sess. 10 [1970]). A secondary standard, as defined in Section 109(b)(2), must "… specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air." Welfare effects (as defined in Section 302(h); 42:U.S.C.:7602[h]) include, but are not limited to, "… effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

The requirement that primary standards provide an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified (*Lead Industries Association v. EPA,* 647:F.2d:1130-1154 [D.C.Cir 1980]; *American Petroleum*

Institute v. Costle, 665:F.2d:1176-1186 [D.C.Cir. 1981]; *American Farm Bureau Federation v. EPA*, 559:F.3d:512-533 [D.C. Cir. 2009]; *Association of Battery Recyclers v. EPA*, 604:F.3d:613, 617-618 [D.C. Cir. 2010]). Both kinds of uncertainties are components of the risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that provide an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree. The CAA does not require the Administrator to establish a primary NAAQS at a zero-risk level or at background concentration levels (*Lead Industries v. EPA*, [647:F.2d:at 1156 n.51]), but rather at a level that reduces risk sufficiently so as to protect public health with an adequate margin of safety.

In addressing the requirement for an adequate margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of sensitive population(s) at risk, and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment (*Lead Industries Association v. EPA*, [647:F.2d:1161-1162]; *Whitman v. American Trucking Associations*, [531:U.S.:457-495 (2001)]).

In setting standards that are "requisite" to protect public health and welfare as provided in Section 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, EPA may not consider the costs of implementing the standards (see generally, *Whitman v. American Trucking Associations*, [531:U.S.:457, 465-472, 475-476 (2001)]). Likewise, "… [a]ttainability and technological feasibility are not relevant considerations in the promulgation of national ambient air quality standards." (*American Petroleum Institute v. Costle*, [665:F.2d:1185]).

Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the Administrator shall complete a thorough review of the criteria published under Section 108 and the national ambient air quality standards … and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate … ." Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria … and the national primary and secondary ambient air quality standards … and shall recommend to the Administrator any new … standards and revisions of existing criteria and standards as may be appropriate … ." Since the early 1980's, this independent review function has been performed by the Clean Air Scientific Advisory Committee (CASAC).

History of the NAAQS for Pb

Unlike pollutants such as PM and carbon monoxide (CO), air quality criteria had not been issued for Pb as of the enactment of the Clean Air Act of 1970, which first set forth the requirement to set national ambient air quality standards for criteria pollutants. EPA did not intend to issue air quality criteria for lead, and accordingly had not listed lead under Section 108. EPA had determined to control lead air pollution through regulations to phase-out use of lead additives in gasoline and EPA viewed those controls, and possibly additional federal controls, as the best approach to controlling lead emissions (See 41 FR 14921 (April 8, 1976). However, the decision not to list lead under Section 108 was challenged by environmental and public health groups and the U.S. District Court for the Southern District of New York concluded that EPA was required to list lead under Section 108. (*Natural Resources Defense Council v. EPA*, 411 F. Supp. 864 [S.D. N.Y. 1976], aff'd, 545 F.2d 320 [2d Cir. 1978]).

Accordingly, on April 8, 1976, EPA published a notice that Pb had been listed under Section 108 as a criteria pollutant (41 FR 14921) and on October 5, 1978, EPA promulgated primary and secondary NAAQS for Pb under Section 109 of the Act (43 FR 46246). Both primary and secondary standards were set at a level of 1.5 micrograms per cubic meter ($\mu g/m^3$), measured as Pb in total suspended particles (Pb-TSP), not to be exceeded by the maximum arithmetic mean concentration averaged over a calendar quarter. These standards were based on the 1977 Pb Air Quality Criteria for Lead Document (AQCD) (U.S. EPA, 1977).

The first review of the Pb standards was initiated in the mid-1980s. The scientific assessment for that review is described in the 1986 Pb AQCD (U.S. EPA, 1986a), the associated Addendum (U.S. EPA, 1986c) and the 1990 Supplement (U.S. EPA, 1990a). As part of the review, the Agency designed and performed human exposure and health risk analyses (U.S. EPA, 1989), the results of which were presented in a 1990 Staff Paper

(U.S. EPA, 1990c). Based on the scientific assessment and the human exposure and health risk analyses, the 1990 Staff Paper presented recommendations for consideration by the Administrator (U.S. EPA, 1990c). After consideration of the documents developed during the review and the significantly changed circumstances since Pb was listed in 1976, the Agency did not propose any revisions to the 1978 Pb NAAQS. In a parallel effort, the Agency developed the broad, multi-program, multimedia, integrated U.S. Strategy for Reducing Lead Exposure (U.S. EPA, 1991). As part of implementing this strategy, the Agency focused efforts primarily on regulatory and remedial clean-up actions aimed at reducing Pb exposures from a variety of non-air sources judged to pose more extensive public health risks to U.S. populations, as well as on actions to reduce Pb emissions to air, such as bringing more areas into compliance with the existing Pb NAAQS (U.S. EPA, 1991).

The most recent review of the Pb air quality criteria and standards was initiated in November, 2004 (69 FR 64926) and the Agency's plans for preparation of the *Air Quality Criteria Document* (AQCD) and conduct of the NAAQS review were contained in two documents: *Project Work Plan for Revised Air Quality Criteria for Lead* (U.S. EPA, 2005e); and *Plan for Review of the National Ambient Air Quality Standards for Lead* (U.S. EPA, 2006f). The schedule for completion of this review was governed by a judicial order in *Missouri Coalition for the Environment v. EPA* (No. 4:04CV00660 ERW, Sept. 14, 2005; and amended on April 29, 2008 and July 1, 2008), which specified a schedule for the review of duration substantially shorter than five years.

The scientific assessment for the review is described in the 2006 *Air Quality Criteria for Lead* [2006 Pb AQCD; (U.S. EPA, 2006b)], multiple drafts of which received review by CASAC and the public. EPA also conducted human exposure and health risk assessments and a pilot ecological risk assessment for the review, after consultation with CASAC and receiving public comment on a draft analysis plan (U.S. EPA, 2006d). Drafts of these quantitative assessments were reviewed by CASAC and the public. The pilot ecological risk assessment was released in December 2006 (ICF, 2006) and the final health risk assessment report was released in November 2007 (U.S. EPA, 2007g). The policy assessment based on both of these assessments, air quality analyses and key evidence from the AQCD was presented in the Staff Paper (U.S. EPA, 2006g), a draft of which also received CASAC and public review. The final Staff Paper presented OAQPS staff's evaluation of the public health and welfare policy implications of the key studies and scientific information contained in the 2006 Pb AQCD and presented and interpreted results from the quantitative risk/exposure analyses conducted for this review. Based on this evaluation, the Staff Paper presented OAQPS staff recommendations that the Administrator give consideration to substantially revising the primary and secondary standards to a range of levels at or below 0.2 $\mu g/m^3$.

Immediately subsequent to completion of the Staff Paper, EPA issued an advance notice of proposed rulemaking (ANPR) that was signed by the Administrator on December 5, 2007 (72 FR 71488).[1] CASAC provided advice and recommendations to the Administrator with regard to the Pb NAAQS based on its review of the ANPR and the previously released final Staff Paper and risk assessment reports. The proposed decision on revisions to the Pb NAAQS was signed on May 1, 2008 and published in the Federal Register on May 20, 2008 (73 FR 29184). Members of the public provided both written and, at two public hearings, oral comments and the CASAC Pb Panel also provided advice and recommendations to the Administrator based on its review of the proposal notice. The final decision on revisions to the Pb NAAQS was signed on October 15, 2008 and published in the Federal Register on November 12, 2008 (73 FR 66964).

The November 2008 notice described EPA's decision to revise the primary and secondary NAAQS for Pb from a level of 1.5 $\mu g/m^3$ to a level of 0.15 $\mu g/m^3$. EPA's decision on the level for the primary standard was based on the much-expanded health effects evidence on neurocognitive effects of Pb in children. The level of 0.15 $\mu g/m^3$ was established to protect against air Pb-related health effects, including intelligence quotient (IQ) decrements in the most highly exposed children, those exposed at the level of the standard. Results of the quantitative risk assessment were judged supportive of the evidence-based framework estimates. The averaging time was revised to a rolling three-month period with a maximum (not-to-be-exceeded) form, evaluated over a three-year period. As compared to the previous averaging time of calendar quarter, this revision was considered to be more scientifically appropriate and more health protective. The rolling average gives equal weight to all three-month periods, and the new calculation method gives equal weight to each month within each three-month period. Further, the rolling average yields 12 three-month averages each year to be compared to the NAAQS versus four averages in each year for the block calendar quarters pertaining to the previous standard. The indicator of Pb-TSP was retained, reflecting the evidence that Pb particles of all sizes pose health risks. The secondary standard was revised to be identical in all respects to the revised primary standards.[2]

Revisions to the NAAQS were accompanied by revisions to the data handling procedures, the treatment of exceptional events, and the ambient air monitoring and

[1] The ANPR was one of the features of the revised NAAQS review process that EPA instituted in 2006. In 2009, this component of the process was replaced by reinstatement of the OAQPS policy assessment (previously termed the Staff Paper).
[2] The 2008 NAAQS for Pb are specified at 40 CFR 50.16.

reporting requirements, as well as emissions inventory reporting requirements.[1] One aspect of the new data handling requirements is the allowance for the use of Pb-PM_{10} monitoring for Pb NAAQS attainment purposes in certain limited circumstances at non-source-oriented sites. The monitoring network requirements resulted in a substantial number of new monitors being required as of January 2010, Subsequent to the 2008 rulemaking, additional revisions were made to the monitoring network requirements, which required additional monitors as of December 2011; the complete current requirements are described in Section 2.4.

On February 26, 2010 (75 FR 8934), EPA formally initiated its current review of the air quality criteria for Pb, requesting the submission of recent scientific information on specified topics. Soon after, a science policy workshop was held to identify key policy issues and questions to frame the review of the Pb NAAQS (75 FR 20843). Drawing from the workshop discussions, a draft IRP [*Integrated Review Plan for the National Ambient Air Quality Standards for Lead* (U.S. EPA, 2011d)], was developed and made available in late March, 2011 for public comment and consultation with CASAC and was discussed by the CASAC via a publicly accessible teleconference consultation on May 5, 2011 (76 FR 20347, 76 FR 21346). The final IRP (U.S. EPA, 2011c) was released in November, 2011 (76 FR 76972).

As part of the science assessment phase of the current review, EPA held a workshop in December 2010 (75 FR 69078) to discuss, with invited scientific experts, preliminary draft materials prepared during the ongoing development of the Pb ISA. The first external review draft *ISA for Lead* was released on May 6, 2011 (U.S. EPA, 2011e). The CASAC Pb Review Panel met at a public meeting on July 20, 2011 to review the draft ISA (76 FR 36120). Subsequently, on December 9, 2011, the CASAC panel provided a consensus letter for their review to the Administrator of the EPA (Frey and Samet, 2011). The second external review draft *ISA for Lead*, (U.S. EPA, 2012a) was discussed at a public meeting of the CASAC Pb Review Panel on April 10, 2012 (77 FR 14783). Subsequently, the CASAC panel provided a consensus letter for their review to the Administrator of the EPA(Frey, 2012). The third external review draft ISA for Lead was released on November 27, 2012(U.S. EPA, 2012b). The CASAC panel met at a public meeting on February 5, 2013, to review the draft ISA (78 FR 938). Subsequently, on June 4, 2013, the CASAC provided a consensus letter for their review to the Administrator of the EPA (Frey, 2013).

[1] The 2008 federal regulatory measurement methods for Pb are specified in 40 CFR 50, Appendix G and 40 CFR part 53. Consideration of ambient air measurements with regard to judging attainment of the standards is specified in 40 CFR 50, Appendix R. The Pb monitoring network requirements are specified in 40 CFR 58, Appendix D, Section 4.5. Guidance on the approach for implementation of the new standards was described in the Federal Register notices for the proposed and final rules (73 FR 29184; 73 FR 66964).

References for Legislative and Historical Background

Frey, C; Samet, JM. (2011). CASAC review of the EPA's integrated science assessment for lead (first external review draft- May 2011). (EPA-CASAC-12-002). Washington, DC: U.S. Environmental Protection Agency, Clean Air Scientific Advisory Committee.

Frey, C. (2012). CASAC review of the EPA's integrated science assessment for lead (second external review draft- February 2012). (EPA-CASAC-12-005). Washington, D.C.: U.S. Environmental Protection Agency, Clean Air Scientific Advisory Committee.

Frey, C. (2013). CASAC review of the EPA's integrated science assessment for lead (third external review draft- November 2012). (EPA-CASAC-13-004). Washington, D.C.: U.S. Environmental Protection Agency, Clean Air Scientific Advisory Committee.

ICF (ICF International). (2006). Lead human exposure and health risk assessments and ecological risk assessment for selected areas: Pilot phase: External review draft technical report. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards.

U.S. EPA (U.S. Environmental Protection Agency). (1977). Air quality criteria for lead [EPA Report]. (EPA-600/8-77-017). Washington, DC. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=20013GWR.txt

U.S. EPA (U.S. Environmental Protection Agency). (1986a). Air quality criteria for lead [EPA Report]. (EPA/600/8-83/028aF-dF). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=32647

U.S. EPA (U.S. Environmental Protection Agency). (1986c). Lead effects on cardiovascular function, early development, and stature: An addendum to U.S. EPA Air Quality Criteria for Lead (1986) [EPA Report]. (EPA-600/8-83/028aF). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (1989). Review of the national ambient air quality standards for lead: Exposure analysis methodology and validation: OAQPS staff report [EPA Report]. (EPA-450/2-89-011). Research Triangle Park, NC.

U.S. EPA (U.S. Environmental Protection Agency). (1990a). Air quality criteria for lead: Supplement to the 1986 addendum [EPA Report]. (EPA/600/8-89/049F). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (1990c). Review of the national ambient air quality standards for lead: Assessment of scientific and technical information: OAQPS staff paper [EPA Report]. (EPA-450/2-89-022). Research Triangle Park, NC.

U.S. EPA (U.S. Environmental Protection Agency). (1991). Strategy for reducing lead exposures [EPA Report]. Washington, DC. http://www.epa.gov/ttn/naaqs/standards/pb/data/leadstrategy1991.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2005e). Project work plan for revised air quality criteria for lead [EPA Report]. (NCEA-R-1465). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=113963

U.S. EPA (U.S. Environmental Protection Agency). (2006b). Air quality criteria for lead: Volume I of II [EPA Report]. (EPA/600/R-05/144aF). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/CFM/recordisplay.cfm?deid=158823

U.S. EPA (U.S. Environmental Protection Agency). (2006d). Analysis plan for human health and ecological risk assessment for the review of the lead national ambient air quality standards (draft) [EPA Report]. Research Triangle Park, NC. http://www.epa.gov/ttn/naaqs/standards/pb/s_pb_cr_pd.html

U.S. EPA (U.S. Environmental Protection Agency). (2006f). Plan for review of the national ambient air quality standards for lead [EPA Report]. Research Triangle Park, NC. http://www.epa.gov/ttn/naaqs/standards/pb/s_pb_cr_pd.html

U.S. EPA (U.S. Environmental Protection Agency). (2006g). Review of the national ambient air quality standards for lead: Policy assessment of scientific and technical information: OAQPS staff paper - first draft [EPA Report]. (EPA-452/P-06-002). Research Triangle Park, NC.

U.S. EPA (U.S. Environmental Protection Agency). (2007g). Lead: Human exposure and health risk assessments for selected case studies: Volume 1: Human exposure and health risk assessments - full-scale [EPA Report]. (EPA-452/R-07-014a). Research Triangle Park, NC. http://www.ntis.gov/search/product.aspx?ABBR=PB2008102573

U.S. EPA (U.S. Environmental Protection Agency). (2011c). Integrated review plan for the national ambient air quality standards for lead [EPA Report]. (EPA-452/R-11-008). Research Triangle Park, NC.

U.S. EPA (U.S. Environmental Protection Agency). (2011d). Integrated review plan for the national ambient air quality standards for lead: External review draft [EPA Report]. (EPA-452/D-11-001). Research Triangle Park, NC.

U.S. EPA (U.S. Environmental Protection Agency). (2011e). Integrated science assessment for lead (first external review draft) [EPA Report]. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=226323

U.S. EPA (U.S. Environmental Protection Agency). (2012a). Integrated science assessment for lead (2nd external review draft) [EPA Report]. (EPA/600/R-10/075B). RTP, NC.

U.S. EPA (U.S. Environmental Protection Agency). (2012b). Integrated science assessment for lead (3rd external review draft) [EPA Report]. (EPA/600/R-10/075C). Research Triangle Park, NC.

Executive Summary

Introduction

This Integrated Science Assessment (ISA) is a synthesis and evaluation of the most policy-relevant science that forms the scientific foundation for the review of the primary (health-based) and secondary (welfare-based)[1] national ambient air quality standard (NAAQS) for Lead (Pb). In 2008, the levels of the primary and secondary NAAQS for Pb were lowered ten-fold, from the 1978 level of 1.5 $\mu g/m^3$, to a level of 0.15 $\mu g/m^3$. The averaging time was revised to a rolling three-month period with a maximum (not-to-be-exceeded) form, evaluated over a three-year period. EPA's decision on the level for the revised primary standard in 2008 was based on the substantially expanded body of health effects evidence available at that time, including that on cognitive effects of Pb in children. The revised standard was established to protect against air Pb-related human health effects, including intelligence quotient (IQ) loss, in the most highly exposed children.

The Preamble discusses the general framework for conducting the science assessment and developing an ISA, including criteria for selecting studies for inclusion in the ISA, evaluating and integrating the scientific evidence and developing scientific conclusions regarding the causal association of air pollution with health and environmental effects.

As described in Table II of the Preamble, the ISA uses a five-level hierarchy that classifies the weight of evidence for causation:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

Studies most relevant to the review of the NAAQS are highlighted in the ISA. In drawing judgments regarding causality for the criteria air pollutants, evidence of health and environmental effects in the range of relevant pollutant exposures or biomarker concentrations is considered. Considerations that are specific to the causal determinations drawn for the health and ecological effects of Pb are described in more detail in

[1] Welfare effects as defined in Clean Air Act (CAA) Section 302(h) [42 U.S.C. 7602(h)] include, but are not limited to, "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

Section 1.1. Briefly, both long and short-term Pb exposures were considered. Evidence from experimental animal studies observing effects of exposures resulting in blood Pb levels within an order of magnitude of those currently experienced by the U.S. general population was emphasized. With regard to the epidemiologic evidence, population-based studies using Pb biomarkers (i.e., blood or bone Pb concentrations) were emphasized over occupational studies. Relevant concentrations for drawing causality judgments for the welfare effects of Pb were determined considering Pb concentrations generally within one or two orders of magnitude above those which have been observed in the environment and the available evidence for concentrations at which effects were observed in plants, invertebrates, and vertebrates. Once conclusions are drawn, evidence relevant to quantifying the health or environmental risks is assessed.

Sources, Fate and Transport of Lead in the Environment, and the Resulting Human Exposure and Dose

Emissions of Pb to ambient air declined by more than two orders of magnitude over the period 1970 to 2008 following the ban on alkyl-Pb additives for on-road gasoline and tightened industrial emission standards. Air emissions in the U.S. were estimated to be 950 tons in 2008, a small fraction of the Pb processed in U.S. Pb-related industries. More than half of these emissions were from piston-engine aircraft. Other important sources of ambient air Pb, beginning with the next largest, include metals processing, fossil fuel combustion, other industrial sources, and roadway-related sources.

During the same period that saw the dramatic decrease in Pb emissions, ambient air Pb concentrations[1] also declined. The median value (across monitoring sites) for the maximum 3-month average concentration in 2010, 0.03 micrograms per cubic meter ($\mu g/m^3$), was approximately thirty times lower than it was in 1980. The sharpest drop in Pb concentration occurred from 1980-1990; concentrations continued to decline up to 2010. Specific levels near Pb sources as well as away from Pb sources have also shown a sharp decrease (Section 1.2.2).

The history of atmospheric deposition has led to measurable Pb concentrations in rain, snowpack, soil, surface waters, sediments, agricultural plants, livestock, and wildlife across the world, with the highest concentrations near Pb sources, such as smelters. After

[1] The original indicator for the Pb NAAQS is the mass of the Pb portion of total suspended particles (Pb-TSP). The Pb-TSP indicator was retained in 2008 in recognition of the role of all particulate matter (PM) sizes in ambient air Pb exposures (Section 1.2.2). The Federal Reference Method (FRM) Pb-TSP sampler's size-selective performance is known to be affected by wind speed and direction, and collection efficiency has been demonstrated to decline with particle size. Under certain conditions regulatory Pb monitoring can also be performed for ambient Pb sampled using the FRM for Pb sampled in particles with an upper 50% cut-point of 10 ± 0.5 micrometer (μm) aerodynamic diameter (Pb-PM_{10}). Pb-PM_{10} is allowed in certain instances where the expected Pb concentration does not approach the NAAQS and no sources of ultracoarse Pb particles are nearby.

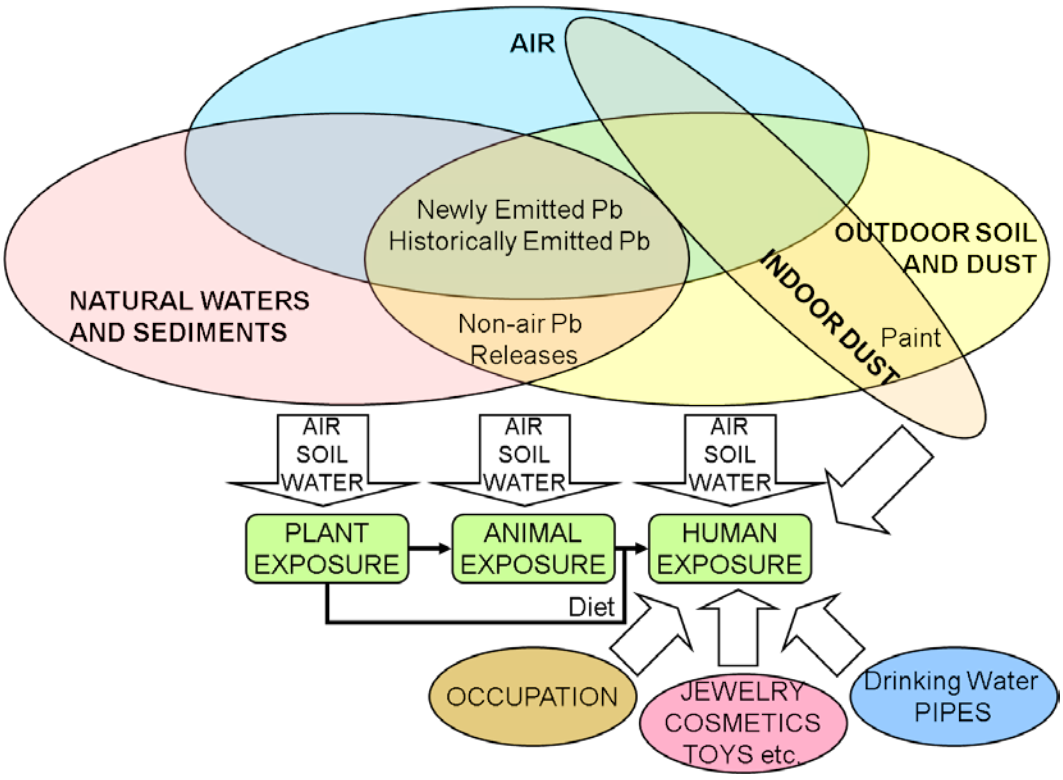
the phase-out of Pb from on-road gasoline and declining industrial emissions in the U.S., Pb concentrations have decreased considerably in rain, snowpack, and surface waters. Pb is retained in soils and sediments, where it provides a historical record of deposition and associated concentrations. The national average Pb concentration in soil in non-urban locations was 18.9 milligrams of Pb per kilogram (mg Pb/kg), measured in over 1,300 non-urban, generally vegetated sampling locations from 1961 through 1997. The national median fresh surface water dissolved Pb concentration (1991-2003) was 0.5 micrograms per liter (µg/L) (Section 1.2.3). In remote lakes, sediment profiles indicate higher Pb concentrations in near surface sediment as compared to pre-industrial era sediment from greater depth; sediment profiles indicate peak Pb concentrations between 1960 and 1980 (when industrial and mobile source Pb emissions in the U.S. were at their peak).

The size distribution of Pb-bearing particulate matter (PM), (i.e., PM having Pb as one of its components) depends on whether there are contributions from industrial sources or near-road environments (Section 1.2.2). Airborne particles containing Pb (Pb bearing PM[1]) tend to be small (much of the distribution <10 µm) compared with soil or dust particles containing Pb (~50 µm to several hundred µm). Coarse Pb-bearing PM (i.e., approximately 2.5 – 10 µm) deposits to a great extent near its source, contributing to local soil Pb contamination, while fine Pb-bearing PM (i.e., smaller than approximately 2.5 µm) can be transported long distances and possibly deposit in remote areas. Depending on local conditions, deposited particles may be resuspended and redeposited multiple times before further transport becomes unlikely.

There are multiple sources of Pb in the environment, and human exposure to Pb involves multiple pathways. Figure ES-1 shows how Pb can move through multiple environmental media. The “air/soil/water” arrows of the figure depict Pb exposures to plants, animals, and/or humans through contact with Pb-containing media. Air-related pathways of ambient Pb exposure are the focus of this assessment. Pathways of exposure to Pb from ambient air include both inhalation of Pb and ingestion of Pb in dust or soil that originated in the ambient air. For example, dietary Pb exposure may be air-related if ambient air Pb deposits on plant materials or in water that becomes available for human consumption. Dust and soil particles containing Pb are typically in the size range that is ingested rather than inhaled. However, soil can act as a reservoir for deposited Pb emissions, and exposure to soil contaminated with deposited Pb can occur through resuspended PM as well as hand-to-mouth contact, which is the main pathway of childhood exposure to Pb. The primary contribution of ambient air Pb to young children’s blood Pb concentrations is generally due to ingestion of Pb following its deposition in soils and dusts rather than inhalation of ambient air (Section 3.1.1.2). Non-ambient, non-

[1] Pb-bearing PM larger than 10 µm have a sharp concentration gradient with distance from the source, because larger particles have greater settling velocities.

air-related exposures include hand-to-mouth contact with Pb-containing consumer goods, hand-to-mouth contact with dust or chips of peeling Pb-containing paint, or ingestion of Pb in drinking water conveyed through Pb pipes. As a result of the multitude of possible exposure pathways, the contribution from specific pathways (e.g., consumer products, diet, soil, ambient air) to blood Pb concentrations is situation specific.



Note: This Venn diagram illustrates the passage of Pb through multiple environmental media compartments through which plant, animal, and human exposures can occur.

Figure ES-1 Conceptual model of multimedia Pb exposure.

The majority of Pb in the body is stored in bone (roughly 90% in adults, 70% in children). Much of the remaining Pb is found in soft tissues; only about 1% of Pb is found in the blood. Pb in blood is primarily (~99%) bound to red blood cells [RBCs]). The small fraction of Pb in blood plasma (<1% of Pb in blood) may be the more biologically labile and toxicologically active fraction of the circulating Pb. Both Pb uptake to and elimination from soft tissues are much faster than they are in bone. Pb accumulates in bone regions undergoing the most active calcification at the time of

exposure. Pb in bone becomes distributed in trabecular (e.g., patella [knee cap]) and the more dense cortical bones (e.g., tibia [shin bone]).

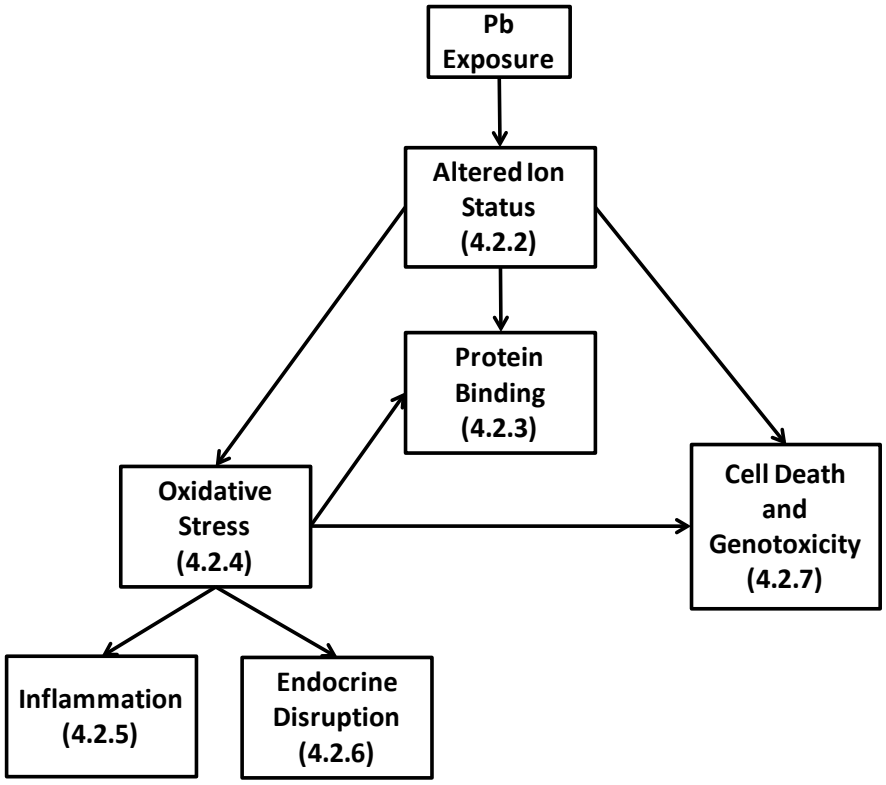
Blood Pb is the most common index of Pb exposure in epidemiologic studies of Pb health effects. Overall, blood Pb levels have been decreasing among U.S. children and adults for the past thirty-five years. The median blood Pb level for the U.S. population is 1.1 micrograms per deciliter (μg/dL), with a 95th percentile blood Pb level of 3.3 μg/dL based on the 2009–2010 National Health and Nutrition Examination Survey (NHANES) data. Among children aged 1-5 years, the median and 95th percentiles are slightly higher at 1.2 μg/dL and 3.4 μg/dL, respectively. Other common Pb exposure metrics used in epidemiologic studies are Pb in bone, which generally reflects cumulative exposure over long periods (months to years), and Pb in cord blood, which is an indicator of prenatal and neonatal blood Pb concentration.

Blood Pb is dependent on both the recent exposure history of the individual, as well as the long-term exposure history that determines total body burden and the amount of Pb stored in the bone. The contribution of bone Pb to blood Pb changes throughout an individual's life time, and depends on the duration and intensity of the exposure, age, and various other physiological stressors (e.g., nutritional status, pregnancy, menopause, extended bed rest, hyperparathyroidism) that may affect bone remodeling, which normally and continuously occurs. In children, largely due to faster exchange of Pb to and from bone, blood Pb is both an index of recent exposure and potentially an index of body burden. Generally, bone Pb is an index of cumulative exposure and body burden. Pb is sequestered in two types of bone compartments; Pb in trabecular bone exchanges more rapidly with the blood than Pb in denser cortical bone. Therefore, Pb in cortical bone is a better marker of cumulative exposure, and Pb in trabecular bone is more likely to be correlated with blood Pb concentration. During pregnancy, Pb is transferred from the mother to the fetus. Transplacental transfer of Pb may be facilitated by an increase in the plasma/blood Pb concentration ratio during pregnancy. Maternal-to-fetal transfer of Pb appears to be related partly to the mobilization of Pb from the maternal skeleton.

Integrative Overview of Health and Ecological Effects

There is substantial overlap between the ecological and human health endpoints related to Pb exposure, which can be mediated through multiple, interconnected modes of action (MOAs). The cellular/subcellular effect constituting the principal MOA for human health and ecological endpoints is altered ion status. Other related MOAs include protein binding, oxidative stress, inflammation, endocrine disruption, and cell death and genotoxicity (Figure ES-2). Since the mechanisms of Pb toxicity in some organ systems are the same or similar across species, many of the downstream health and ecological

effects are similar across species from invertebrates to vertebrates, including humans (Section 1.8.1).



Note: The subsections where these MOAs are discussed are indicated in parentheses. (Section 4.2.2; Section 4.2.3; Section 4.2.4; Section 4.2.5; Section 4.2.6; and Section 4.2.7).

Figure ES-2 Schematic representation of the relationships between the various MOAs by which Pb exerts its effects.

Health Effects of Pb

Evidence from epidemiologic and toxicological studies was considered in combination with the evidence from other disciplines such as toxicokinetics in determining the causal relationships for the health endpoints discussed in this assessment. Detailed discussions of the evidence relating to conclusions regarding the health effects of Pb are in Section 1.6 and Chapter 4. The major conclusions regarding health effects from Pb exposure in children and adults are presented in Table ES-1 and summarized below.

Table ES-1 Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Nervous System Effects (Section 1.6.1)	
Children – Nervous System Effects (Section 1.6.1.1)	
Cognitive Function Decrements	Causal Relationship (Table 4-17)
Clear evidence of cognitive function decrements (as measured by Full Scale IQ, academic performance, and executive function) in young children (4 to 11 years old) with mean or group blood Pb levels measured at various lifestages and time periods between 2 and 8 µg/dL. Clear support from animal toxicological studies that demonstrate decrements in learning, memory, and executive function with dietary exposures resulting in relevant blood Pb levels of 10-25 µg/dL. Plausible MOAs are demonstrated.	
Externalizing Behaviors: Attention, Impulsivity and Hyperactivity[b,d, e]	Causal Relationship (Table 4-17)
Clear evidence of attention decrements, impulsivity and hyperactivity (assessed using objective neuropsychological tests and parent and teacher ratings) in children 7-17 years and young adults ages 19-20 years. The strongest evidence for blood Pb-associated increases in these behaviors was found in prospective studies examining prenatal (maternal or cord), age 3-60 months, age 6 years, or lifetime average (to age 11-13 years) mean blood Pb levels of 7 to 14 µg/dL and groups with early childhood (age 30 months) blood Pb levels >10 µg/dL. Biological plausibility is provided by animal toxicological studies demonstrating impulsivity or impaired response inhibition with relevant prenatal, lactational, post-lactational and lifetime Pb exposures. Plausible MOAs are demonstrated.	
Externalizing Behaviors: Conduct Disorders in Children and Young Adults[c, d]	Likely Causal Relationship (Table 4-17)
Prospective epidemiologic studies find that early childhood (age 30 months, 6 years) or lifetime average (to age 11-13 years) blood Pb levels or tooth Pb levels (from ages 6-8 years) are associated with criminal offenses in young adults ages 19-24 years and with higher parent and teacher ratings of behaviors related to conduct disorders in children ages 8-17 years. Pb-associated increases in conduct disorders were found in populations with mean blood Pb levels 7 to14 µg/dL; associations with lower blood Pb levels as observed in cross-sectional studies were likely to be influenced by higher earlier Pb exposures. There is coherence in epidemiologic findings among related measures of conduct disorders. Evidence of Pb induced aggression in animals was mixed, with increases in aggression found in some studies of adult animals with gestational plus lifetime Pb exposure but not juvenile animals. The lack of clear biological plausibility produces some uncertainty.	
Internalizing Behaviors	Likely Causal Relationship (Table 4-17)
Prospective epidemiologic studies find associations of higher lifetime average blood (mean: ~14 µg/dL) or childhood tooth (from ages 6-8 years) Pb levels with higher parent and teacher ratings of internalizing behaviors such as symptoms of depression or anxiety, and withdrawn behavior in children ages 8-13 years. Consideration of potential confounding by parental caregiving was not consistent and findings from cross-sectional studies in populations ages 5 and 7 years with mean blood Pb levels of 5 µg/dL were mixed. Animal toxicological studies demonstrate depression-like behaviors and increases in emotionality with relevant lactational exposures. Plausible MOAs are demonstrated.	
Auditory Function Decrements	Likely Causal Relationship (Table 4-17)
A prospective epidemiologic study and large cross-sectional studies indicate associations between blood Pb levels and increased hearing thresholds at ages 4-19 years. Across studies, associations were found with blood Pb levels measured at various time periods, including prenatal maternal, neonatal (10 day, mean 4.8 µg/dL), lifetime average, and concurrent (ages 4-19 years) blood Pb levels (median 8 µg/dL). Plausible MOAs are demonstrated. The lack of biological plausibility in animals with relevant exposures produces some uncertainty.	

Table ES-1 (Continued): Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Visual Function Decrements	Inadequate to Infer a Causal Relationship (Table 4-17)
The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.	
Motor Function Decrements	Likely Causal Relationship (Table 4-17)
Prospective epidemiologic studies provide evidence of associations of fine and gross motor function decrements in children ages 4-17 years with lifetime average blood Pb levels and with blood Pb levels measured at various time periods with means generally ranging from 4.8 to 12 µg/dL. Results were inconsistent in cross sectional studies with concurrent blood Pb level means 2-5 µg/dL. Limited evidence in animal toxicological studies with relevant Pb exposures.	
Adults – Nervous System Effects (Section 1.6.1.2)	
Cognitive Function Decrements	Likely Causal Relationship (Table 4-17)
Prospective studies indicate associations of higher baseline bone Pb levels with declines in cognitive function (executive function, visuospatial skills, learning and memory) in adults (>age 50 years) over 2- to 4-year periods. Cross-sectional studies provide additional support. Uncertainties remain regarding the timing, frequency, duration and level of the Pb exposures contributing to the effects observed and residual confounding by age. Biological plausibility is provided by findings that relevant lifetime Pb exposures from gestation, birth, or after weaning induce learning impairments in adult animals and by evidence demonstrating plausible MOAs.	
Psychopathological Effects	Likely Causal Relationship (Table 4-17)
Cross-sectional studies in a few populations demonstrate associations of higher concurrent blood or tibia Pb levels with self-reported symptoms of depression and anxiety in adults. Uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the observed associations and residual confounding by age. Observations of depression-like behavior in animals with dietary lactational Pb exposure, with some evidence at relevant blood Pb levels, and evidence demonstrating plausible MOAs in experimental animals provides support.	
Auditory Function Decrements	Suggestive of a Causal Relationship (Table 4-17)
A high-quality prospective epidemiologic study finds associations of higher tibia Pb level with a greater rate of elevations in hearing threshold over 20 years. Some evidence indicates effects on relevant MOAs but important uncertainties remain related to effects on auditory function in animals with relevant Pb exposures.	
Visual Function Decrements	Inadequate to Infer a Causal Relationship (Table 4-17)
The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.	
Neurodegenerative Diseases	Inadequate to Infer a Causal Relationship (Table 4-17)
The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.	
Cardiovascular Effects (Section 1.6.2)	
Hypertension	Causal Relationship (Table 4-24)
Prospective epidemiologic studies with adjustment for multiple potential confounders consistently find associations of blood and bone Pb levels with hypertension incidence and increased blood pressure (BP) in adults. Cross-sectional studies provide supporting evidence. Meta-analyses underscore the consistency and reproducibility of the Pb associated increase in blood pressure and hypertension (a doubling of concurrent blood Pb level (between 1 and 40 µg/dL) is associated with a 1 mmHg increase in systolic BP); however, uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies. Experimental animal studies demonstrate effects on BP after long-term Pb exposure resulting in mean blood Pb levels of 10 µg/dL or greater. Plausible MOAs are demonstrated.	
Subclinical Atherosclerosis	Suggestive of a Causal Relationship (Table 4-24)
Cross-sectional analyses of NHANES data find associations of blood Pb level with peripheral artery disease (PAD) in adults. Animal toxicological evidence is limited to studies of MOA (oxidative stress, inflammation, endothelial cell dysfunction) that demonstrate biologically plausible mechanisms through which Pb exposure may initiate atherosclerotic vessel disease.	

Table ES-1 (Continued): Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Coronary Heart Disease	Causal Relationship (Table 4-24)
Prospective epidemiologic studies consistently find associations of Pb biomarkers with cardiovascular mortality and morbidity, specifically myocardial infarction (MI), ischemic heart disease (IHD), or HRV; however, uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies. Thrombus formation was observed in animals after relevant long term exposure and MOAs (hypertension, decreased HRV, increased corrected QT (QTc) interval, and corrected QRS complex (QRSc) duration in electrocardiogram [ECG]) are demonstrated in humans and animals.	
Cerebrovascular Disease	Inadequate to Infer a Causal Relationship (Table 4-24)
The available epidemiologic and toxicological evidence is of insufficient, quantity, quality, and/or consistency. Plausible MOAs, which are shared with hypertension and atherosclerosis, are demonstrated.	
Renal Effects (Section 1.6.3)	
Reduced Kidney Function	Suggestive of a Causal Relationship (Table 4-31)
Multiple high quality epidemiologic studies provide evidence that Pb exposure is associated with reduced kidney function; however, uncertainty remains regarding the potential for reverse causality to explain findings in humans. Further, inconsistencies and limitations in occupational studies, epidemiologic studies of children and clinical trials of chelation of CKD patient preclude strong inferences to be drawn based on their results. Although longitudinal studies found Pb-associated decrements in renal function in populations with mean blood Pb levels of 7 and 9 µg/dL, the contributions of higher past Pb exposures cannot be excluded. Animal toxicological studies demonstrate Pb-induced kidney dysfunction at blood Pb levels greater than 30 µg/dL; however, evidence in animals with blood Pb levels < 20 µg/dL is generally not available. At blood Pb levels between 20 and 30 µg/dL studies provide some evidence for dysfunction in kidney function measures (e.g., decreased creatinine clearance, increased serum creatinine, increased BUN). Plausible MOAs (Pb induced hypertension, renal oxidative stress and inflammation, morphological changes, and increased uric acid) are demonstrated.	
Immune System Effects (Section 1.6.4)	
Atopic and Inflammatory Responses	Likely Causal Relationship (Table 4-34)
Prospective studies of children ages 1-5 years indicate associations of prenatal cord and childhood blood Pb levels with asthma and allergy. This evidence is supported by cross-sectional associations between higher concurrent blood Pb levels (>10 µg/dL) in children and higher IgE. Uncertainties related to potential confounding by SES, smoking or allergen exposure are reduced through consideration of the evidence from experimental animal studies. The biological plausibility for the effects of Pb on IgE is provided by consistent findings in animals with gestational or gestational-lactational Pb exposures, with some evidence at blood Pb levels relevant to humans. Strong evidence of Pb-induced increases in Th2 cytokine production and inflammation in animals demonstrates MOA.	
Decreased Host Resistance	Likely Causal Relationship (Table 4-34)
Animal toxicological studies provide the majority of the evidence for Pb-induced decreased host resistance. Dietary Pb exposure producing relevant blood Pb levels (7-25 µg/dL) results in increased susceptibility to bacterial infection and suppressed delayed type hypersensitivity. Further, evidence demonstrating plausible MOA, including suppressed production of Th1 cytokines and decreased macrophage function in animals, provides coherence.	
Autoimmunity	Inadequate to Infer a Causal Relationship (Table 4-34)
The available toxicological and epidemiologic studies do not sufficiently inform Pb-induced generation of auto-antibodies with relevant Pb exposures.	

Table ES-1 (Continued): Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Hematologic Effects (Section 1.6.5)	
Decreased Red Blood Cell (RBC) Survival and Function	Causal Relationship (Table 4-35)
Animal toxicological studies demonstrate that exposures resulting in blood Pb levels relevant to humans (2-7 µg/dL) alter several hematological parameters (Hemoglobin [Hb], Hematocrit [Hct], and mean corpuscular volume [MCV]),increase measures of oxidative stress and increase cytotoxicity in red blood cell (RBC) precursor cells. Limited body of epidemiologic studies provides additional support for the association of Pb exposure with these endpoints. Plausible MOAs are demonstrated in experimental animals.	
Altered Heme Synthesis	Causal Relationship (Table 4-35)
Consistent findings from studies in experimental adult animal studies report that relevant exposures (e.g. blood Pb levels of 6.5 µg/dL) cause decreased ALAD and ferrochelatase activities. Additional support is garnered from a larger body of ecotoxicological studies demonstrating decreased ALAD activity across a wide range of species and a limited body of epidemiologic studies. Plausible MOAs are demonstrated in experimental animals.	
Reproductive and Developmental Effects (Section 1.6.6)	
Development	Causal Relationship (Table 4-48)
Multiple cross-sectional epidemiologic studies report associations between concurrent blood Pb levels and delayed pubertal onset for girls (6-18 years) and boys (8-15 years). These associations are consistently observed in populations with concurrent blood Pb levels 1.2-9.5 µg/dL. Few studies consider confounding by nutrition. Uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies of older children. Experimental animal studies demonstrate delayed onset of puberty in female pups with blood Pb levels of 1.3-13 µg/dL and delayed male sexual maturity at blood Pb levels of 34 µg/dL.	
Birth Outcomes (e.g., low birth weight, spontaneous abortion)	Suggestive of Causal Relationship (Table 4-48)
Some well-conducted epidemiologic studies report associations of maternal Pb biomarkers or cord blood Pb with preterm birth and low birth weight/fetal growth; however, the epidemiologic evidence is inconsistent overall and findings from experimental animal studies are mixed.	
Male Reproductive Function	Causal Relationship (Table 4-48)
Key evidence is provided by toxicological studies in rodents, non-human primates, and rabbits showing detrimental effects on semen quality, sperm and fecundity/fertility with supporting evidence in epidemiologic studies. Toxicological studies with relevant Pb exposure routes leading to blood Pb concentrations ranging from 5-43 µg/dL reported effects on sperm quality and sperm production rate, sperm DNA damage, and histological or ultrastructural damage to the male reproductive organs. Consistent associations in studies of occupational populations with concurrent blood Pb levels of 25 µg/dL and greater, report detrimental effects of Pb on sperm; however, uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies.	
Female Reproductive Function	Suggestive of Causal Relationship (Table 4-48)
Although findings are mixed overall, the body of evidence include some high-quality epidemiologic and toxicological studies, suggesting that Pb may affect some aspects of female reproductive function (hormone level, placental pathology).	

Table ES-1 (Continued): Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Cancer (Section 1.6.7)	
Cancer	Likely Causal Relationship (Table 4-50)
The animal toxicological literature provides the strong evidence for long-term exposure (i.e., 18 months or 2 years) to high concentrations of Pb (> 2,600 ppm) inducing tumor development; findings from epidemiologic studies inconsistent. Plausible MOAs are demonstrated.	

[a] In drawing conclusions regarding the causal relationship between Pb exposure and human health effects, evidence in the range of relevant pollutant exposures or biomarker levels was considered. Specifically, population-based epidemiology studies were emphasized with the recognition that many of the U.S populations studied included individuals with higher past than recent Pb exposures. Evidence from toxicological studies of effects observed in experimental animals at biomarker levels (e.g. blood Pb) comparable to those currently experienced by the U.S. general population were emphasized. Generally, studies with dietary exposures resulting in blood Pb levels within one order of magnitude above the upper end of the distribution of U.S. blood Pb levels were considered in forming concusions, with the majority of studies reporting blood Pb levels below 30 µg/dL. Studies with higher blood Pb levels were considered if they informed the evaluation of MOA, mechanisms, or kinetics. (Preamble, Section 1.1).

[b] Within the attention deficit hyperactivity disorder domain of externalizing behaviors, studies of Pb exposure have focused primarily on attention, impulsivity, and hyperactivity. Because the studies of ADHD were limited in terms of their design and did not adequately consider potential confounding by factors such as SES, parental education, or parental caregiving quality, they were not a major consideration in drawing conclusions about the relationship between Pb exposure and attention, impulsivity, and hyperactivity.

[c] Two domains of conduct disorders,(i.e., undersocialized aggressive conduct disorder and socialized aggressive conduct disorder), are combined for the purpose of this assessment because it is difficult to differentiate between these two domains in the available epidemiologic studies, which examine multiple endpoints such as delinquent behavior, aggression, antisocial behavior. Criminal offenses are included in the evaluation because they can be predicted by earlier conduct disorders (Section 4.3.3.2).

[d] There was limited evaluation of potential confounding by parental psychopathology, which is a strong risk factor for externalizing behaviors, in the majority of the epidemiologic studies; however, evidence of an association of between psychopathology in parents and Pb exposure in their children is not available (Section 4.3.3).

[e] Strong evidence from experimental animal studies reduces uncertainty related to confounding generally.

Effects of Pb Exposure in Children

Multiple epidemiologic studies conducted in diverse populations of children consistently demonstrate the harmful effects of Pb exposure on cognitive function (as measured by IQ decrements, decreased academic performance and poorer performance on tests of executive function). Blood Pb-associated effects on cognitive function were found in populations of children (ages 4-10) with mean or group blood Pb levels measured concurrently or earlier in the range of 2-8 µg/dL[1]. Evidence suggests that some Pb-related cognitive effects may be irreversible and that the neurodevelopmental effects of Pb exposure may persist into adulthood (Section 1.9.4). Epidemiologic studies also demonstrate that Pb exposure is associated with decreased attention, and increased impulsivity and hyperactivity in children (externalizing behaviors). This is supported by findings in animal studies demonstrating both analogous effects and biological plausibility at relevant exposure levels. Pb exposure can also exert harmful effects on blood cells and blood producing organs, and is likely to cause an increased risk of symptoms of depression and anxiety and withdrawn behavior (internalizing behaviors),

[1] The age range and blood Pb levels are based on studies described in detail in Section 4.3.2.

decreases in auditory and motor function, asthma and allergy, as well as conduct disorders in children and young adults. There is some uncertainty about the Pb exposures contributing to the effects and blood Pb levels observed in epidemiologic studies; however, these uncertainties are greater in studies of older children and adults than in studies of young children (Section 1.9.5). Despite these uncertainties, it is clear that Pb exposure in childhood presents a risk; further, there is no evidence of a threshold below which there are no harmful effects on cognition from Pb exposure.

Effects of Pb Exposure in Adults

A large body of evidence from both epidemiologic studies of adults and experimental studies in animals demonstrates the effect of long-term Pb exposure on increased blood pressure (BP) and hypertension (Section 1.6.2). In addition to its effect on BP, Pb exposure can also lead to coronary heart disease and death from cardiovascular causes and is associated with cognitive function decrements, symptoms of depression and anxiety, and immune effects in adult humans. The extent to which the effects of Pb on the cardiovascular system are reversible is not well-characterized. Additionally, the frequency, timing, level, and duration of Pb exposure causing the effects observed in adults has not been pinpointed, and higher past exposures may contribute to the development of health effects measured later in life. It is clear however, that Pb exposure can result in harm to the cardiovascular system that is evident in adulthood and may also affect a broad array of organ systems.

Ecological Effects of Pb

Ecological effects of Pb are summarized for terrestrial, freshwater and saltwater ecosystems, and the ISA discusses endpoints common to plants, invertebrates and vertebrates along with considerations of uncertainties in relating atmospheric Pb concentrations to ecosystem effects. Effects of Pb in ecosystems are primarily associated with Pb deposition onto soil and water, subsequent transport, and exposure through environmental media (soil, water, sediment, biota). The 2006 Pb Air Quality Criteria Document (AQCD) (U.S. EPA, 2006b) and previous EPA assessments reported effects of Pb exposure on both terrestrial and aquatic organisms that included reduced survival, reproduction and growth as well as effects on behavior, development, and heme production. Studies reviewed in this ISA generally support the ecological findings of previous Pb assessments with some effects observed in additional species and at lower concentrations. Reproduction, growth, and survival are endpoints commonly used in ecological risk assessment because they can lead to effects at the population, community,

and ecosystem levels of biological organization. Impacts on hematological, neurobehavioral and physiological stress endpoints may increase susceptibility to other stressors and affect the fitness of individual organisms. Increasing exposures generally result in increasing responses in laboratory and field experiments but the relationship of exposure and responses is difficult to characterize quantitatively in natural systems because of the influence of multiple environmental variables on both Pb bioavailability and toxicity, and substantial species and lifestage differences in Pb sensitivity.

A brief discussion of the conclusions from this assessment and earlier Pb AQCDs regarding Pb effects on reproduction, growth, and survival is provided below and summarized in Table ES-2 along with effects of Pb on neurobehavior, hematological, and stress endpoints. Causal determinations for ecological effects were based on integration of information on biogeochemistry, bioavailability, biological effects, and exposure-response relationships of Pb in terrestrial, freshwater, and saltwater environments. In general, the number of studies available for assessing causality is greater for freshwater organisms than for marine environments. A detailed discussion for all relevant welfare effects (i.e., ecological effects) is provided in Section 1.7 and Chapter 6.

Table ES-2 Summary of causal determinations for the relationship between Pb exposure and effect on plants, invertebrates, and vertebrates.

Level		Effect	Terrestrial[a]	Freshwater[a]	Saltwater[a]
Community- and Ecosystem		Community and Ecosystem Effects (Section 1.7.3.7)	Likely Causal	Likely Causal	Inadequate
Population–Level Endpoints	**Organism–Level Responses**	Reproductive and Developmental Effects-Plants (Section 1.7.3.1)	Inadequate	Inadequate	Inadequate
		Reproductive and Developmental Effects-Invertebrates (Section 1.7.3.1)	Causal	Causal	Suggestive
		Reproductive and Developmental Effects-Vertebrates (Section 1.7.3.1)	Causal	Causal	Inadequate
		Growth-Plants (Section 1.7.3.2)	Causal	Likely Causal	Inadequate
		Growth-Invertebrates (Section 1.7.3.2)	Likely Causal	Causal	Inadequate
		Growth-Vertebrates (Section 1.7.3.2)	Inadequate	Inadequate	Inadequate
		Survival-Plants (Section 1.7.3.3)	Inadequate	Inadequate	Inadequate
		Survival- Invertebrates (Section 1.7.3.3)	Causal	Causal	Inadequate
		Survival- Vertebrates (Section 1.7.3.3)	Likely Causal	Causal	Inadequate
		Neurobehavioral Effects-Invertebrates (Section 1.7.3.4)	Likely Causal	Likely Causal	Inadequate
		Neurobehavioral Effects-Vertebrates (Section 1.7.3.4)	Likely Causal	Likely Causal	Inadequate
	Sub-organismal Responses	Hematological Effects-Invertebrates (Section 1.7.3.5)	Inadequate	Likely Causal	Suggestive
		Hematological Effects-Vertebrates (Section 1.7.3.5)	Causal	Causal	Inadequate
		Physiological Stress-Plants (Section 1.7.3.6)	Causal	Likely Causal	Inadequate
		Physiological Stress-Invertebrates (Section 1.7.3.6)	Likely Causal	Likely Causal	Suggestive
		Physiological Stress-Vertebrates (Section 1.7.3.6)	Likely Causal	Likely Causal	Inadequate

[a]Conclusions are based on the weight of evidence for causal determination in Table II of the ISA Preamble. Ecological effects observed at or near ambient Pb concentrations measured in soil, sediment and water in the most recent available studies (Table 1-1). were emphasized and studies generally within one to two orders of magnitude above the reported range of these values were considered in the body of evidence for terrestrial (Section 6.3.12), freshwater (Section 6.4.12) and saltwater (Section 6.4.21) ecosystems.

Effects on Development and Reproduction

Reduced reproduction at the level of individual organisms can result in lowered population numbers or extermination, decreased species diversity, and a decline in relative or absolute population numbers at the community level. Effects of Pb on various development, fertility, and hormone maintenance endpoints have been documented in multiple species of terrestrial and freshwater organisms. In plants, only a few studies have addressed reproductive effects of Pb exposure. Among the animal species tested, freshwater invertebrates were the most sensitive to Pb with respect to reproduction (Section 1.7.3.1).

Effects on Growth

Effects on growth observed at the species level can translate into effects at the ecosystem level. Exposure to Pb has been shown to have effects on growth in plants and in some species of invertebrates and vertebrates. Evidence for effects of Pb on growth is strongest in terrestrial plants. These effects are typically found in laboratory studies with high Pb exposure concentrations or in field studies near stationary sources such as metal industries or mines where concentrations of multiple metals are elevated relative to non-polluted locations. Many of those laboratory and field studies evaluate the effects of increasing levels of Pb exposure, and find that effects on plant growth increase with increasing exposure ("biological gradients"). Evidence for Pb effects on growth in invertebrates has been observed most extensively in freshwater species, with growth inhibition in a few sensitive species occurring in the range of Pb concentration values available for U.S. surface waters. In general, juvenile organisms are more sensitive than adults. There are only limited data on growth effects in vertebrates (Section 1.7.3.2).

Effects on Survival

Decreased survival of individuals within a population can have ecosystem-level impacts. Pb is generally not toxic to aquatic or terrestrial plants at concentrations found in the environment away from stationary sources, probably due to the fact that plants often sequester large amounts of Pb in roots, with little translocation to other parts of the plant. Aquatic invertebrates are generally more sensitive to Pb exposure than other types of organisms, with survival reduced in laboratory studies of a few species at concentrations occurring near Pb sources, as well as at concentrations occasionally encountered in the general environment (that is, far from major Pb sources). Many terrestrial invertebrates tolerate higher concentrations of Pb. Limited studies with vertebrates showed adverse effects of Pb on survival at concentrations higher than typical ambient Pb levels in the

environment, although juvenile organisms are usually more sensitive than adults (Section 1.7.3.3).

Neurobehavioral Effects

Historical and recent evidence from Pb-exposed animals indicates that Pb affects behaviors, such as food consumption, avoidance and escape from predators, behavioral regulation of body temperature, and prey capture. Alterations to these behaviors can decrease the overall fitness of the organism. Evidence from laboratory studies has shown effects of Pb exposure on nervous system endpoints in both terrestrial and freshwater animal taxa (Section 1.7.3.4).

Hematological Effects

Changes in hematological characteristics including ALAD (delta-aminolevulinic acid dehydratase, an important rate-limiting enzyme needed for heme production) activity, blood cell counts, and serum profiles are associated with Pb exposure in both aquatic and terrestrial animals. It is commonly recognized that ALAD is an indicator of Pb exposure across a wide range of animals as shown in both field and laboratory studies. Studies conducted over the last two decades have shown that hematological responses are associated with Pb in the environment (Section 1.7.3.5).

Effects on Physiological Stress

Increased levels of antioxidant enzymes (in response to oxidative stress or altered cell signaling) and increased lipid peroxidation (the process by which free radicals induce the oxidation of fatty acids, leading to cell membrane damage) are considered to be reliable biomarkers of stress. Alterations in these biomarkers are associated with Pb exposure in plants, invertebrates and vertebrates, and they may be indicative of increased susceptibility to other stressors, as well as reduction in individual fitness. Markers of oxidative damage and antioxidant activity have been observed in field studies in a wide range of species in terrestrial and aquatic environments when Pb is present (along with other chemicals), and also following laboratory exposures (Section 1.7.3.6).

Community and Ecosystem Effects

The effects of Pb on growth, reproduction, and survival at the level of individual organisms, especially when considered cumulatively, are likely to result in effects on population, community and ecosystem structure and function. Effects at those higher

levels of biological organization are confirmed by both laboratory and field experiments. In these experiments decreases in abundance, reduced species diversity, shifts in soil microbial and plant community composition (in terrestrial ecosystems), and sediment-associated and aquatic plant community composition (in freshwater ecosystems) have been observed following Pb exposure. However, such ecosystem-wide effects can only be tested directly in a few of the cases where individual organism effects are found. Quantitative characterization of exposure-response relationships is difficult at the community and ecosystem levels because potential confounders such as the presence of other metals, physico-chemical variables and other stressors cannot be controlled and their effects are incompletely characterized (Section 1.7.3.7).

Policy Relevant Considerations

Public Health Significance

The 2006 Pb AQCD (U.S. EPA, 2006b) concluded that neurodevelopmental effects in children and cardiovascular effects in adults were of the greatest public health concern because the evidence indicated that these effects occurred at the lowest blood Pb levels, compared to other health effects. The evidence reviewed in the current assessment supports and builds upon this conclusion. Small shifts in the population mean IQ can be highly significant from a public health perspective because such shifts could translate into a larger proportion of the population functioning at the low end of the IQ distribution (Section 1.9.1), as well as a smaller proportion of population functioning at the high end of the distribution[1]. Additionally, small Pb-associated increases in the population mean blood pressure could result in an increase in the proportion of the population with hypertension that is significant from a public health perspective.

Air Lead(Pb)-to-Blood Lead(Pb) Relationships

A limited number of epidemiologic studies evaluated relationships between air Pb and blood Pb (Section 1.9.2). Regression models are typically used to produce slopes that estimate the change in blood Pb per change in air Pb concentration (µg/dL per µg Pb/m^3). The larger the slope, the larger is the estimated contribution of air Pb to the blood Pb level in exposed populations.

The range of air-to-blood slope estimates is 4 to 9 µg/dL per µg/m^3 in studies of children. The differences in the estimates across studies, at least in part, reflect the choice of model

[1] This statement follows from the conceptual model described by Weiss et al. (1988), which assumes that the incremental concentration-response between Pb exposure and IQ is similar across the full range of IQ and is not based on actual data.

(e.g., some models predict an increase in the blood Pb-air Pb slope with decreasing air Pb concentration while other models predict a constant blood Pb-air Pb slope across all air Pb concentrations). In addition, differences in the estimates across studies may reflect the different terms that are included in the model (e.g., soil Pb); these terms may account for some of the variation in blood Pb that is attributable to air Pb. Other factors that may explain the variation in the derived blood Pb-air Pb slope include differences in the populations examined and Pb sources (e.g., leaded gasoline or smelter).

Concentration-Response Relationships for Health Effects

Previous assessments found that progressively lower blood Pb levels were associated with cognitive deficits in children, and newly available evidence is generally consistent with findings of the previous review (Section 1.9.3). Compelling evidence for a larger incremental effect of Pb on children's IQ at lower blood Pb levels compared to higher blood Pb levels was presented in the 2006 Pb AQCD based on the international pooled analysis of seven prospective cohort studies, as well as several individual studies. This was supported by a subsequent reanalysis of the pooled data focusing on the shape of the concentration-response function. Several recent studies also support the findings of the original pooled analysis. The majority of the epidemiologic evidence from stratified analyses comparing the lower and the higher ends of the blood Pb distributions also indicates larger effect of Pb on IQ at lower blood Pb levels. The shape of concentration-response relationships is not well characterized for association of health effects with blood or bone Pb concentrations in adults (Section 1.9.3).

Pb Exposure and Neurodevelopmental Deficits in Children

Information about the patterns of exposure that contribute to the blood Pb levels and effects observed in epidemiologic studies is generally lacking. Although, blood Pb may reflect both recent exposures as well as past exposures because Pb is both taken up by and released from the bone, uncertainty regarding the role of recent exposure is greater in adults and older children than in young children who do not have lengthy exposure histories. Several lines of evidence inform the interpretation of epidemiologic studies of young children with regard to the exposures that contribute to observed health effects (Section 1.9.4). Epidemiologic studies find associations of cognitive function with several different blood Pb metrics that represent blood Pb during lifestages or time periods from the prenatal period through adolescence. This epidemiologic evidence is supported by studies of rodents and monkeys indicating that Pb exposures during multiple lifestages and time periods, including prenatal only, prenatal plus lactational, postnatal only, and lifetime are observed to induce impairments in learning. These

findings are consistent with the fact that the nervous system continues to develop throughout childhood.

Potentially At-Risk Populations

The NAAQS are intended to protect public health with an adequate margin of safety. In so doing, protection is provided for both the population as a whole and those groups at increased risk for health effects in response to the air pollutant for which each NAAQS is set. Children are at increased risk for the effects of Pb exposure. Among children, the youngest age groups were observed to be most at risk of elevated blood Pb levels, with levels decreasing with increasing age of the children. Evidence related to childhood and other at-risk factors is described in Section 1.9.6.

Pb Concentrations Corresponding to Ecological Effects

There is limited evidence to relate ambient air concentrations of Pb to levels of deposition onto terrestrial and aquatic ecosystems and to subsequent movement of atmospherically-deposited Pb through environmental compartments (e.g., soil, sediment, water, and biota) (Section 1.9.7). The contribution of atmospheric Pb to specific sites is not clear, and the connection between air concentration of Pb and ecosystem exposure continues to be poorly characterized. Furthermore, the level at which Pb elicits a specific effect is difficult to establish in terrestrial and aquatic systems, due to the influence of other environmental variables (e.g., pH, organic matter) on both Pb bioavailability and toxicity, and also to substantial species differences in Pb sensitivity. Current evidence indicates that Pb is bioaccumulated in biota; however, the sources of Pb in biota have only been identified in a few studies, and the relative contribution of Pb from all sources is usually not known.

Summary

Overall, the evidence evaluated for the current review expands upon findings of the 2006 Pb AQCD and previous assessments, which concluded that there was a strong body of evidence substantiating the health effects from Pb exposure as well as strong evidence of the effects from Pb exposure on some ecological endpoints.

Pb exposure exerts harmful effects on a broad array of organ systems. Cognitive function decrements in children are the effects that are best substantiated as occurring at the lowest blood Pb concentrations (Section 1.6.1.1). There is also a strong body of evidence demonstrating that Pb exposure can cause cardiovascular effects; this evidence strongly suggests that long-term Pb exposure plays a role. Since Pb exposures were generally

higher in the past than they are today, uncertainties exist regarding the relative importance of recent versus past exposure in the development of the Pb-related health effects in the adult populations studied.

With regard to the ecological effects of Pb, uptake of Pb into fauna and subsequent effects on reproduction, growth and survival are established and are further supported by more recent evidence. These may lead to effects at the population, community, and ecosystem level of biological organization. In both terrestrial and aquatic organisms, gradients in response are observed with increasing concentration of Pb and some studies report effects within the range of Pb detected in environmental media over the past several decades. Specifically, effects on reproduction, growth, and survival in sensitive freshwater invertebrates are well-characterized from controlled studies at concentrations at or near Pb concentrations occasionally encountered in U.S. fresh surface waters. Hematological and stress related responses in some terrestrial and aquatic species were also associated with elevated Pb levels in polluted areas. However, in natural environments, modifying factors affect Pb bioavailability and toxicity and there are considerable uncertainties associated with generalizing effects observed in controlled studies to effects at higher levels of biological organization. Furthermore, available studies on community and ecosystem-level effects are usually from contaminated areas where Pb concentrations are much higher than typically encountered in the environment. The contribution of atmospheric Pb to specific sites is not clear and the connection between air concentration of Pb and ecosystem exposure continues to be poorly characterized. Furthermore, the level at which Pb elicits a specific effect is difficult to establish in terrestrial and aquatic systems, due to the influence of other environmental variables (e.g., pH, organic matter) on both Pb bioavailability and toxicity, and also to substantial species differences in Pb sensitivity.

References for Executive Summary

U.S. EPA (U.S. Environmental Protection Agency). (2006b). Air quality criteria for lead: Volume I of II [EPA Report]. (EPA/600/R-05/144aF). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/CFM/recordisplay.cfm?deid=158823

CHAPTER 1 INTEGRATIVE SUMMARY

1.1 ISA Development and Scope

This chapter summarizes and synthesizes the recently available scientific evidence and is intended to provide a concise synopsis of the ISA conclusions and findings that best inform the review of the current NAAQS for lead (Pb). *The Integrated Review Plan (IRP) for the National Ambient Air Quality Standards for Lead* (U.S. EPA, 2011c) identifies a series of policy-relevant questions (in Chapter 3 of the plan) that provide the framework for this assessment. These questions also frame the entire review of the NAAQS for Pb, and thus are informed by both science and policy considerations.

The ISA organizes, presents, and integrates the scientific evidence, which is considered, along with findings from risk analyses and policy considerations, to help the U.S. Environmental Protection Agency (EPA) address these questions during the NAAQS review for Pb. The ISA includes:

- An integration of the evidence on the human health effects associated with Pb exposure, a discussion of important uncertainties identified in the interpretation of the scientific evidence, and an integration across different scientific disciplines and across individual endpoints within major outcome categories.
- An integration of the evidence on the welfare effects[1] of Pb in terrestrial, freshwater and saltwater ecosystems, discussion of endpoints common to plants, invertebrates and vertebrates and consideration of uncertainties in relating atmospheric Pb concentrations to welfare effects.
- An integration of the effects associated with exposure to Pb across the scientific disciplines for health and ecology, focusing on common modes of action.
- Discussion of policy relevant considerations, such as potentially at-risk populations and concentration-response relationships.

EPA has a systematic process for evaluating the scientific evidence and for drawing conclusions and judgments regarding the causal association of air pollution with health and environmental effects. The ISA process includes literature search strategies, criteria for selecting and evaluating studies, approaches for evaluating weight of the evidence, and a framework for making causality determinations. As part of this process, the ISA is reviewed by the public and peer reviewed by a formal panel of scientific experts (the Clean Air Scientific Advisory Committee [CASAC]). The process and causality

[1] Welfare effects as defined in Clean Air Act (CAA) Section 302(h) [42 U.S.C. 7602(h)] include, but are not limited to, "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

framework are described in more detail in the Preamble to the ISA. This section provides a brief overview of the process for development of this ISA.

EPA initiated the current review of the Pb NAAQS in February 2010 with a call for information from the public (75 FR 8934). In addition, literature searches were conducted routinely to identify studies published since the last review, focusing on studies published from 2006 (close of the previous scientific assessment) through September 2011. References that were considered for inclusion or actually cited in this ISA can be found at http://hero.epa.gov/lead.

This ISA evaluates relevant epidemiologic, animal toxicological, and welfare effects studies, including those related to concentration-response relationships, mode(s) of action (MOA), and susceptible populations. Additionally, air quality and emissions data, studies on environmental fate and transport, and issues related to Pb toxicokinetics and exposure were considered for inclusion in the document. Previous AQCDs (U.S. EPA, 2006b, 1986b, 1977) have included an extensive body of evidence on these topics. In this ISA, the conclusions and key findings from previous reviews are summarized at the beginning of each section, to provide the foundation for consideration of evidence from recent studies. Results of key studies from previous reviews are included in discussions or tables and figures, as appropriate, and conclusions are drawn based on the synthesis of evidence from recent studies with the extensive literature summarized in previous reviews.

The Preamble discusses the general framework for conducting the science assessment and developing an ISA, including criteria for selecting studies for inclusion in the ISA evaluating and integrating the scientific evidence and developing scientific conclusions. In selecting the studies for inclusion in the Pb ISA, particular emphasis is placed on those studies most relevant to the review of the NAAQS.

In drawing judgments regarding causality for the criteria air pollutants, evidence of health effects in the range of relevant pollutant exposures or doses is considered. Evidence from experimental animal studies observing effects at biomarker levels comparable to, or somewhat above, those currently experienced by the U.S. general population were emphasized. Generally studies with dietary exposures resulting in blood Pb levels within one order of magnitude above the upper end of the distribution of U.S. blood Pb levels were considered in forming conclusions[1] with the majority of studies reporting blood Pb levels below 30 µg/dL. Studies with higher blood Pb levels were considered if they informed the evaluation of modes of action, mechanisms, or kinetics. For toxicological studies where blood Pb levels were not measured, judgments regarding how to

[1] For example, the 95th percentile of the NHANES (2009-2010) distribution of blood Pb level in children 1-5 years old is 3.4 µg/m^3 (CDC, 2013); however, the proportion of individuals with blood Pb levels that exceed this concentration varies depending on factors including age and sex (Section 3.4).

distinguish high from the more relevant low doses were made considering the range of doses across the available body of evidence and emphasizing studies at the lower end of the range.

With respect to the epidemiologic evidence, population-based studies using Pb biomarkers (i.e. blood or bone Pb concentrations) were emphasized with the recognition that many of the U.S populations studied included individuals with higher past than recent Pb exposures. For example, in U.S. population studies during years past (1968-1980) when air concentrations in the U.S. were much higher than they are today, the population geometric mean blood Pb levels were roughly an order of magnitude above current population geometric mean blood Pb levels (Sections 3.4, 5.1, and 4.4.1). Recent occupational studies of populations with relatively high mean blood Pb levels were considered insofar as they addressed a topic area that was of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

Relevant concentrations for drawing causality judgments for the welfare effects of Pb were determined considering the range of Pb concentrations in the environment and the available evidence for concentrations at which effects were observed in plants, invertebrates, and vertebrates. Effects observed at or near ambient Pb concentrations measured in soil, sediment and water in the most recent available studies (Table 1-1) were emphasized and studies generally within one to two orders of magnitude above the reported range of these values were considered in the body of evidence for terrestrial, freshwater and saltwater ecosystems. Studies at higher concentrations were used to the extent that they informed modes of action and illustrated the wide range of sensitivity to Pb across taxa.

The causal determinations for terrestrial, freshwater, and saltwater effects are divided into two categories. The first category includes endpoints that are commonly used in ecological risk assessment (reproduction, growth, and survival). Impacts on these endpoints have the potential to lead to population-level (e.g., abundance, production, extirpation), community-level (e.g., taxa richness, relative abundance) and ecosystem-level effects (Ankley et al., 2010; Suter et al., 2005). The second category includes organism- and sub-organism-level responses such as physiological stress, hematological effects, and neurobehavioral effects. As recognized in EPA's Framework for Ecological Risk Assessment (U.S. EPA, 1992), and in the adverse outcome pathway (AOP) framework (Ankley et al., 2010) endpoints that are measured at one level of biological organization may be related to an endpoint at a higher level. The AOP conceptual framework was proposed to link mechanistic data from initiating events at the molecular level through a series of higher order biological responses to growth, survival and

reproductive endpoints that can be used in ecological risk assessment, i.e., at the population level and higher. In the case of Pb, sub-organismal responses (i.e., physiological stress, hematological effects) and organism-level responses (neurobehavioral alterations) may decrease the overall fitness of an organism, even though their connection to effects at higher levels of biological organization may not have been characterized. Furthermore, the effects of Pb on ecosystems necessarily begin with some initial effects at the molecular level of specific organisms within the ecosystem (U.S. EPA, 1986b). There are many different molecular and cellular level effects, and toxicity of Pb in ecosystems may be attained through multiple modes of action.

The ISA considers evidence of health effects for both short- and long-term pollutant exposures. Since biomarkers are typically used as an index of exposure or dose in epidemiologic studies, there is uncertainty regarding the timing, frequency, level, and duration of the exposure(s) associated with the observed effects and blood Pb (or other biomarker) levels measured in these studies. Some animal toxicological studies provide evidence to inform the exposure patterns that can induce effects in animals and these studies are drawn upon to interpret the human health effects evidence. Exposure regimens used in toxicological studies typically include chronic exposure (i.e., over 10% of the lifespan of the animal), long-term exposure (e.g., greater than 4 weeks in rodents) and acute or short-term exposure (e.g., less than 4 weeks in rodents). For the purpose of this assessment, short-term human exposures are generally defined to include exposures of months (e.g., <one year) while long-term human exposures include those greater than one year in duration. Information including the age of the population studied, study period and study location is also used to aid in the interpretation of findings from epidemiologic studies because Pb exposures have declined over time and exposures vary depending on proximity to Pb sources.

As described in the Preamble (Table II), this ISA uses a five-level hierarchy that classifies the weight of evidence for causation:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

Briefly, evidence is judged sufficient to conclude that there is a *causal* relationship with relevant Pb exposures when chance, bias and confounding can be ruled out with reasonable confidence. The weight of evidence may be judged “likely to be a causal relationship” or “suggestive of a causal relationship” when important uncertainties

remain. A conclusion of "*likely causal*" may be appropriate if evidence is available from multiple studies or several lines of evidence including cases where the weight of the health effects evidence is largely derived from multiple animal toxicological studies. A conclusion that the evidence is *suggestive* of a causal relationship reflects generally limited evidence, but may include "at least one high-quality epidemiology study" or "a well conducted toxicological study". Evidence is *inadequate* to determine whether a causal relationship exists when the available studies are of insufficient quantity, quality, consistency, or statistical power. If several adequate studies, covering the full range of exposure levels that human beings are known to encounter, considering at-risk populations, are mutually consistent in not showing an effect, the relationship may be judged *not likely to be causal*.

Beyond judgments regarding causality are questions relevant to quantifying health or environmental risks based on the understanding of the quantitative relationships between pollutant exposures and health or welfare effects. Once a determination is made regarding the causal relationship between the pollutant and outcome category, important questions regarding quantitative relationships include:

- What is the concentration-response, exposure-response, or dose-response relationship in the human population?
- What exposure conditions (dose or exposure, exposure pathways, duration and pattern) are important?
- What populations and lifestages appear to be differentially affected i.e., at greater risk of Pb-related health effects?
- What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations, functions, etc.) appear to be affected or are more sensitive to effects?

This ISA is composed of a Preamble, a Legislative and Historical Background, an Executive Summary, and six chapters. Chapter 1 presents an Integrative Summary. Chapter 2 highlights key concepts or issues relevant to understanding the sources, ambient concentrations, and fate and transport of Pb in the environment. Chapter 3 summarizes key concepts and recent findings on Pb exposures, toxicokinetics, and biomarkers reflecting Pb exposure and body burden. Chapter 4 presents a discussion of the MOA of Pb and evaluates and integrates epidemiologic and animal toxicological information on health effects related to Pb exposure. Chapter 5 summarizes the evidence on potentially at-risk populations. Chapter 6 evaluates welfare effects evidence that is relevant to the review of the secondary NAAQS for Pb.

This chapter summarizes and integrates the newly available scientific evidence that best informs consideration of the policy-relevant questions that frame this assessment. The organization of this chapter generally follows the organization of the document as a

whole, with several additional sections including: a discussion of the assessment development and scope (Section 1.1); an integration of the evidence across the disciplines of health and ecology (Section 1.8); a discussion of policy-relevant considerations (Section 1.9); and, an overall summary (Section 1.10).

1.2 Ambient Pb: Source to Concentration

1.2.1 Sources, Fate and Transport of Ambient Pb

The findings of this review build upon those from the 2006 Pb AQCD (U.S. EPA, 2006b), which documented the decline in ambient air Pb emissions following the phase out of alkyl-Pb additives for on-road gasoline and reductions in industrial facility emissions of Pb. Pb emissions declined by 98% from 1970 to 1995 and then by an additional 77% from 1995 to 2008. The 2008 National Emissions Inventory (NEI) reported ambient air Pb emissions of 950 tons. Air Pb emissions represent just a small fraction (by weight) of the Pb processed in U.S. Pb-related industries.

As at the time of the last review, the 2008 NEI (U.S. EPA, 2011a), indicates that piston-engine aircraft emissions comprise the largest share (58%) of total atmospheric Pb emissions in the U.S. Other sources of ambient air Pb, beginning with the next largest, include metal working and mining, fossil fuel combustion, other industrial sources, and miscellaneous sources. On a site-specific basis, emissions are greatest at metal industry sites. Over the period 1991-2010, the amount of Pb used in secondary Pb processing increased by 37%. Exports of Pb increased by 103%, with 2010 exports sent to Mexico as refined Pb; to Canada, China, and Japan in spent Pb-acid batteries; and, to the Republic of Korea as Pb in concentrate (USGS, 2012).

Global atmospheric Pb deposition peaked in the 1970s, followed by a decline (Section 2.2). Pb deposition is greater near Pb emission sources. Both wet and dry deposition are important mechanisms for removing Pb from the atmosphere, and the atmosphere is the main environmental transport media for Pb which is deposited onto surface water and soil. Wet deposition is more important for the fine fraction while the coarse fraction is usually removed by dry deposition. Pb associated with coarse PM deposits to a great extent near local industrial sources, contributing to soil Pb concentrations in those locations, while fine Pb-bearing PM can be transported long distances, contributing Pb contamination in remote areas. Depending on local conditions, once they are deposited, particles may be resuspended and redeposited before reaching a site where further transport is unlikely, especially for dry deposition (Section 2.3). Surface waters act as an important reservoir, with Pb lifetimes in the water column

largely controlled by deposition and resuspension of Pb in sediments. Substantial amounts of Pb may be input to surface waters and sediments by wastewater discharges and through transport of Pb from vehicle wear and building materials in runoff waters without having become airborne. Pb containing sediment particles can be remobilized into the water column (Section 2.3).

1.2.2 Monitoring and Concentrations of Ambient Air Pb

The indicator for the Pb NAAQS is Pb in total suspended particles (Pb-TSP). The Federal Reference Method (FRM) for Pb-TSP specifies that ambient air is drawn through a high-volume TSP sampler onto a glass fiber filter. The Pb-TSP sampler's size selective performance is known to be affected by wind speed and direction, and collection efficiency has been demonstrated to decline with increasing particle size with an uncertain upper size limit (Wedding et al., 1977). There have been only a few studies since the publication of the 2006 Pb AQCD with regard to sampling error in the Pb-TSP FRM or alternatives to the existing Pb-TSP sampling technology. In addition to monitors used historically for sampling Pb-PM, several single stage and multi-stage impactors and inlets used for sampling PM concentrations are also potential options for Pb-PM monitoring when the majority of particles are smaller than 15 μm. Ambient air Pb monitoring requirements have undergone several changes since publication of the 2006 Pb AQCD. The current Pb monitoring network design requirements include two types of FRM monitoring sites: source-oriented and non-source-oriented (Section 2.4). For the purpose of analyzing data for the ISA, monitors reporting to the U.S. EPA Air Quality System (AQS) database were considered to be source-oriented if they were designated in AQS as source-oriented, or if they were located within 1 mile of a 0.5 ton per year or greater source, identified using emissions estimates in the 2005 or 2008 NEI (U.S. EPA, 2008a) (U.S. EPA, 2011a). Source-oriented FRM Pb-TSP monitoring sites are required near sources of air Pb emissions which are expected to or have been shown to contribute to ambient air Pb concentrations in excess of the NAAQS.
Non-source-oriented FRM (Pb-TSP or Pb-PM_{10}) monitoring is also required at national core multipollutant monitoring network (NCore) sites in Core Based Statistical Areas (CBSA) with a population of at least 500,000. In addition to FRM monitoring, Pb is also routinely measured in smaller particle fractions in the chemical speciation network (CSN), interagency monitoring of protected visual environment (IMPROVE), and the national air toxics trends station (NATTS) networks. While monitoring in multiple networks provides extensive geographic coverage, measurements between networks are not directly comparable in all cases because there are differences in the methods,

including the different particle size ranges sampled in the different networks. Depending on monitoring network, Pb is monitored in TSP, PM_{10}, or $PM_{2.5}$.

Ambient air Pb concentrations have declined drastically over the period 1980-2010 (Section 2.5). The median value (across monitoring sties) for the maximum 3-month average concentration within a year has dropped by 97% from 0.87 $\mu g/m^3$ in 1980 to 0.03 $\mu g/m^3$ in 2010. The mean of maximum 3-month average Pb concentrations at source-oriented sites was skewed toward the 75th percentile of the data distribution and exceeded the level of the NAAQS, suggesting that ambient air Pb concentrations are high near a subset of industrial sources of airborne Pb. Studies in the peer-reviewed literature have shown slightly elevated Pb concentrations downwind of industrial sources and airports. Estimates for the natural background Pb concentrations from sources including volcanoes, sea-salt spray, and biogenic sources are ~0.00002 to 0.001 $\mu g/m^3$.

The size distribution of Pb-bearing PM has changed over time and varies by site (Section 2.5.3). Recent study results indicate that the size distribution has generally shifted upward since the 1980s, with the mode of the size distribution of Pb-PM particles now falling between 2.5 μm and 10 μm (Cho et al., 2011). The Pb-PM size distribution depends on whether there are contributions from industrial sources or near-road environments. In contrast to Cho et al. (2011), analysis of the distributional properties of the Pb-PM measured by the AQS monitors, which are often sited near sources, suggests that the largest proportion of particles is still below 2.5 μm in diameter.

1.2.3 Ambient Pb Concentrations in Non-Air Media and Biota

Releases of Pb to the atmosphere have contributed to measurable increases in Pb in rain, snowpack, soil, surface waters, sediments, agricultural plants, livestock, and wildlife across the world, with highest concentrations near Pb sources, such as smelters. After the phase-out of Pb from on-road gasoline and with reductions in industrial emissions, Pb concentrations have decreased considerably in rain, snowpack, and surface waters.

Declining Pb concentrations in tree foliage, trunk sections, and grasses, as well as surface sediments and soils, have also been observed (U.S. EPA, 2006b).

Often, Pb is retained in soils and sediments, where it provides a historical record of deposition. In remote lakes, sediment profiles indicate higher Pb concentrations in near surface sediment as compared to pre-industrial era sediment from greater depth and indicate peak concentrations between 1960 and 1980 (when leaded on-road gasoline was at peak use). Concentrations of Pb in moss, lichens, peat, and aquatic bivalves have been used to understand spatial and temporal distribution patterns of air Pb concentrations.

Ingestion and water intake are the major routes of Pb exposure for aquatic organisms, and food, drinking water, and inhalation are major routes of exposure for livestock and terrestrial wildlife.

Overall, Pb concentrations have decreased substantially in media through which Pb is rapidly transported, such as air and water. Substantial Pb remains in soil and sediment sinks. In areas less affected by major local sources, the highest concentrations are below the surface layers and reflect the phase-out of Pb from on-road gasoline and emission reductions from other sources.

Information on ambient Pb concentrations in non-air media and biota is reported in Section 2.6, and concentrations considered in the interpretation of the ecological evidence are tabulated in Table 1-1. As noted in the Preamble, the ecological causal determinations focus on studies where effects of Pb exposure are observed at or near ambient levels of Pb and studies generally within the range of one to two orders of magnitude above current or ambient conditions were also considered in the body of evidence.

Table 1-1 Pb concentrations in non-air media and biota considered for ecological assessment.

Media	Pb Concentration	Years Data Obtained	References
Soil (non-urban)	Contiguous U.S. Median: 15 mg Pb/kg (dry weight) Contiguous U.S. 95th Percentile: 50 mg Pb/kg (dry weight)	1961-1976	Shaklette (1984)
	National Average: 18.9 mg Pb/kg (dry weight) Range of state averages: 5-38.6 mg Pb/kg (dry weight)	1961-1997	U.S. EPA (2007d, 2006b, 2003b)
Freshwater Sediment	Median: 73 mg Pb/kg (dry weight)	1996-2001	Mahler et al. (2006)
	Median: 28 mg Pb/kg[b] (dry weight)	1991-2003	U.S. EPA (2006b)
Saltwater Sediment	Range: 0.6 to 1,050 mg Pb/kg[a]	Dates not available	Sadiq (1992)
Fresh Surface Water (Dissolved Pb)[b]	Median: 0.50 µg Pb/L[b]; Max: 30 µg Pb/L, 95th percentile 1.1 µg Pb/L	1991-2003	U.S. EPA (2006b)
	Range: 0.0003-0.075 µg Pb/L (Set of National Parks in western U.S.)	2002-2007	Field and Sherrell (2003), U.S. National Park Service (2011)
Saltwater[c]	Range: 0.01–27 µg Pb/L	Dates not available	Sadiq (1992)
Vegetation	Lichens: 0.3-5 mg Pb/kg (dry weight) (Set of National Parks in western U.S.)	2002-2007	U.S. National Park Service (2011)
	Grasses: Geometric Mean: 0.31 kg Pb/kg (dry weight)	1980s-2000s	Vandenhove et al. (2009)
Vertebrates	Fish: Geometric Mean: 0.59 mg Pb/kg (dry weight) (whole fish) Geometric Mean: 0.15 mg Pb/kg (dry weight) (liver) Range: 0.08-22.6 mg Pb/kg (dry weight) (whole fish) Range: 0.01-12.7 mg Pb/kg (dry weight) (liver)	1991-2003	U.S. EPA (2006b)
	Fish (from a set of national parks in western U.S.): 0.0033 (fillet) to 0.97 (liver) mg Pb/kg (dry weight) Moose[d,e]: 0.008-0.029 mg Pb/kg (dry weight) (meat) Moose[d,e]: 0.012-0.023 mg Pb/kg (dry weight) (liver)	2002-2007	U.S. National Park Service (2011)

[a]No information available regarding wet or dry weight

[b]Based on synthesis of National Water-Quality Assessment (NAWQA) data reported in 2006 Pb AQCD (U.S. EPA, 2006b)

[c]Data from a combination of brackish and marine saltwater samples. In general, Pb in seawater is higher in coastal areas and estuaries since these locations are closer to sources of Pb contamination and loading from terrestrial systems.

[d] The reference cited and its source citations show that observations date from studies published in 1977-1990, indicating that the data were obtained no later than those years. Further, these measurements seem to be for non-U.S. locations, including the max, which is well above other reported values in these refs.

[e]Three moose in one Alaskan park

1.3 Exposure to Ambient Pb

Human Pb exposure is difficult to assess because Pb has multiple sources in the environment and passes through various media (Section 3.1). Air-related pathways of Pb exposure are the focus of this assessment. In addition to inhalation of Pb in ambient air, air-related Pb exposure pathways include inhalation and ingestion of Pb in indoor dust and/or outdoor soil that originated from recent or historic ambient air (e.g., air Pb that has penetrated into the residence either via the air or tracking of soil), ingestion of Pb in drinking water drawn from surface water contaminated from atmospheric deposition or contaminated from surface runoff of deposited Pb, and ingestion of Pb in dietary sources after uptake by plants or grazing animals. Soil can act as a reservoir for deposited Pb emissions. Exposure to soil contaminated with deposited Pb can occur through resuspended PM as well as hand-to-mouth contact, which is the main pathway of childhood air-related exposure to Pb. The primary contribution of ambient air Pb to young children's blood Pb concentrations is generally due to ingestion of Pb following its deposition in soils and dusts rather than inhalation of ambient air (Section 3.1.1.2). Non-ambient air-related exposures include hand-to-mouth contact with dust or chips of peeling Pb-containing paint, or ingestion of Pb in drinking water conveyed through Pb pipes. Several study results indicate that Pb-containing paint in the home and home age (often a surrogate for the presence of Pb paint) are important residential factors that increase risk of elevated blood Pb (Sections 1.9.6 and 5.2.6). Most Pb biomarker studies do not indicate species or isotopic signature. As a consequence, non-air exposures are reviewed in this section, because they can also contribute to Pb body burden.

A number of monitoring and modeling techniques have been employed for ambient Pb exposure assessment. Environmental Pb concentration data can be collected from ambient air Pb monitors, soil Pb samples, dust Pb samples, and dietary Pb samples to estimate human exposure. Exposure estimation error depends in part on the collection efficiency of these methods; collection efficiency for ambient air Pb FRM samplers is described in Section 2.4. Models, such as the Integrated Exposure Uptake Biokinetic (IEUBK) model, simulate human exposure to Pb from multiple sources and through various routes including inhalation and ingestion. IEUBK model inputs include soil-Pb concentration, air-Pb concentration, dietary-Pb intake including drinking water, Pb-dust ingestion, human activity, and biokinetic factors. The relative contribution from specific exposure pathways (e.g., water, diet, soil, ambient air) to blood Pb concentrations is situation specific. Measurements and/or assumptions can be utilized when formulating the model inputs; errors in measurements and assumptions thus have the potential to propagate through exposure models.

The size distribution of dust particles containing Pb differs from the size distribution of inhalable ambient Pb-bearing PM (Sections 2.5 and 3.1). Airborne particles containing Pb tend to be small (much of the distribution <10 µm) compared with soil or dust particles containing Pb (~50 µm to several hundred µm). Ingestion through hand-to-mouth contact is the predominant exposure pathway for the larger particles in soil and dust containing Pb.

1.4 Toxicokinetics

The majority of Pb in the body is found in bone (roughly 90% in adults, 70% in children); only about 1% of Pb is found in the blood. Pb in blood is primarily (~99%) bound to red blood cells (RBCs). It has been suggested that the small fraction of Pb in plasma (<1%) may be the more biologically labile and toxicologically active fraction of the circulating Pb. The relationship between Pb in blood and plasma is pseudo-linear at relatively low daily Pb intakes (i.e., <10 µg/kg per day) and at blood Pb concentrations <25 µg/dL, and becomes curvilinear at higher blood Pb concentrations due to saturable binding to RBC proteins. As blood Pb level increases and the higher affinity binding sites for Pb in RBCs become saturated, a larger fraction of the blood Pb is available in plasma to distribute to brain and other Pb-responsive tissues. See Section 3.2 for additional details.

The burden of Pb in the body may be viewed as divided between a dominant slow (i.e., uptake and elimination) compartment (bone) and smaller fast compartment(s) (soft tissues). Pb uptake to and elimination from soft tissues is much faster than in bone. Pb accumulates in bone regions undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone (e.g., patella); whereas, in adulthood, calcification occurs at sites of remodeling in cortical (e.g., tibia) and trabecular bone (Aufderheide and Wittmers, 1992). A high bone formation rate in early childhood results in the rapid uptake of circulating Pb into mineralizing bone; however, in early childhood bone Pb is also recycled to other tissue compartments or excreted in accordance with a high bone resorption rate (O'Flaherty, 1995). Thus, much of the Pb acquired early in life is not permanently fixed in the bone.

The exchange of Pb from plasma to the bone surface is a relatively rapid process. Pb in bone becomes distributed in trabecular and the more dense cortical bone. The proportion of cortical to trabecular bone in the human body varies by age, but on average is about 80% cortical to 20% trabecular. Of the bone types, trabecular bone is more reflective of recent exposures than is cortical bone due to the slow turnover rate and lower blood perfusion of cortical bone. Some Pb diffuses to kinetically deeper bone regions where it is relatively inert, particularly in adults. These bone compartments are much more labile

in infants and children than in adults as reflected by half-times for movement of Pb from bone into the plasma (e.g., cortical half-time = 0.23 years at birth, 3.7 years at 15 years of age, and 23 years in adults; trabecular half-time = 0.23 years at birth, 2.0 years at 15 years of age, and 3.8 years in adults) (Leggett, 1993). See Section 3.2 for additional details.

Evidence for maternal-to-fetal transfer of Pb in humans is derived from cord blood to maternal blood Pb ratios (i.e., cord blood Pb concentration divided by mother's blood Pb). Group mean ratios range from about 0.7 to 1.0 at the time of delivery for mean maternal blood Pb levels ranging from 1.7 to 8.6 µg/dL. Transplacental transfer of Pb may be facilitated by an increase in the plasma/blood Pb concentration ratio during pregnancy. Maternal-to-fetal transfer of Pb appears to be related partly to the mobilization of Pb from the maternal skeleton. See Section 3.2.2.4 for additional details.

The dominant elimination phase of Pb kinetics in the blood, exhibited shortly after a change in exposure occurs, has a half-life of ~20-30 days. An abrupt change in Pb uptake gives rise to a relatively rapid change in blood Pb, to a new quasi-steady state, achieved in ~75-100 days (i.e., 3-4 times the blood elimination half-life). A slower phase of Pb clearance from the blood may become evident with longer observation periods following a decrease in exposure due to the gradual redistribution of Pb among bone and other compartments. See Section 3.3 for additional details.

1.5 Pb Biomarkers

Overall, blood Pb levels have been decreasing among U.S. children and adults over the past 35 years (Section 3.4). The median blood Pb level for the entire U.S. population is 1.1 µg/dL and the 95th percentile blood Pb level is 3.3 µg/dL, based on the 2009-2010 National Health and Nutrition Examination Survey (NHANES) data (CDC, 2013). Among children aged 1-5 years, the median and 95th percentiles were slightly higher, at 1.2 µg/dL and 3.4 µg/dL, respectively.

Blood Pb is dependent on both the recent exposure history of the individual, as well as the long-term exposure history that determines body burden and Pb in bone. The contribution of bone Pb to blood Pb changes, depending on the duration and intensity of the exposure, age, and various other physiological stressors (e.g., nutritional status, pregnancy, menopause, extended bed rest, hyperparathyroidism) that may affect bone remodeling, which normally and continuously occurs. In children, largely due to faster exchange of Pb to and from bone, blood Pb is both an index of recent exposure and potentially an index of body burden. In adults and children whose exposure to Pb has effectively ceased or greatly decreased, there is a rapid decline in blood Pb over the first

few months followed by a more gradual, slow decline in blood Pb concentrations over the period of years due to the gradual release of Pb from bone. Bone Pb is an index of cumulative exposure and body burden. Even bone compartments should be recognized as reflective of differing exposure periods with Pb in trabecular bone exchanging more rapidly than Pb in cortical bone with the blood. Consequently, Pb in cortical bone is a better marker of cumulative exposure, while Pb in trabecular bone is more likely to be correlated with blood Pb, even in adults. See Section 3.3 for additional details.

Sampling frequency is an important consideration when evaluating blood Pb and bone Pb levels in epidemiologic studies, particularly when the exposure is not well characterized. It is difficult to determine what blood Pb is reflecting in cross-sectional studies that sample blood Pb once, whether recent exposure or movement of Pb from bone into blood from historical exposures. In contrast, cross-sectional studies of bone Pb and longitudinal samples of blood Pb concentrations over time provide more of an index of cumulative exposure and are more reflective of average Pb body burdens over time. The degree to which repeated sampling will reflect the actual long-term time-weighted average blood Pb concentration depends on the sampling frequency in relation to variability in exposure. High variability in Pb exposures can produce episodic (or periodic) oscillations in blood Pb concentration that may not be captured with low sampling frequencies. Furthermore, similar blood Pb concentrations in two individuals (or populations), regardless of their age, do not necessarily translate to similar body burdens or similar exposure histories.

The concentration of Pb in urine follows blood Pb concentration. There is added complexity with Pb in urine because concentration is also dependent upon urine flow rate, which requires timed urine samples that is often not feasible in epidemiologic studies. Other biomarkers have been utilized to a lesser extent (e.g., Pb in teeth). See Section 3.3.

1.6 Health Effects

This section summarizes and evaluates the evidence from toxicological and epidemiologic studies of the health effects associated with Pb exposure and integrates that evidence across these disciplines. The coherence of the findings from experimental animal and epidemiologic studies, including evidence for potential MOA, is evaluated to establish biological plausibility and address uncertainties in the epidemiologic evidence due to biases from factors such as reverse causality and confounding. Both short- and long-term Pb exposures are considered (Section 1.1); information on the frequency, timing, level and duration of exposure in animal toxicological studies is used to inform

the interpretation of epidemiologic studies regarding the relevant patterns of exposure that are likely to be associated with the health effects.

The health evidence is organized into groups of related endpoints (e.g., cognitive function, externalizing behaviors, neurodegenerative diseases). This evidence is considered in combination with the evidence from other fields (e.g., toxicokinetics) and weighed against the attributes described in the framework for causal determination (Table II of the Preamble) to draw conclusions regarding the causal relationship between Pb exposure and the health effects evaluated in this assessment. A more detailed discussion of the underlying evidence used to formulate each causal determination can be found in Chapter 5 of this document. Table 1-2 summarizes the conclusions formed regarding the causal relationships between Pb exposure and health effects.

Table 1-2 Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Nervous System Effects (Section 4.3.15)	
Children – Nervous System Effects	
Cognitive Function Decrements	Causal Relationship (Table 4-17)
Clear evidence of cognitive function decrements (as measured by Full Scale IQ, academic performance, and executive function) in young children (4 to 11 years old) with mean or group blood Pb levels measured at various lifestages and time periods between 2 and 8 µg/dL. Clear support from animal toxicological studies that demonstrate decrements in learning, memory, and executive function with dietary exposures resulting in relevant blood Pb levels of 10-25 µg/dL. Plausible MOAs are demonstrated.	
Externalizing Behaviors: Attention, Impulsivity and Hyperactivity[b,d, e]	Causal Relationship (Table 4-17)
Clear evidence of attention decrements, impulsivity and hyperactivity (assessed using objective neuropsychological tests and parent and teacher ratings) in children 7-17 years and young adults ages 19-20 years. The strongest evidence for blood Pb-associated increases in these behaviors was found in prospective studies examining prenatal (maternal or cord), age 3-60 months, age 6 years, or lifetime average (to age 11-13 years) mean blood Pb levels of 7 to 14 µg/dL and groups with early childhood (age 30 months) blood Pb levels >10 µg/dL. Biological plausibility is provided by animal toxicological studies demonstrating impulsivity or impaired response inhibition with relevant prenatal, lactational, post-lactational and lifetime Pb exposures. Plausible MOAs are demonstrated.	

Table 1-2 (Continued): Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Externalizing Behaviors: Conduct Disorders in Children and Young Adults[c, d]	Likely Causal Relationship (Table 4-17)
Prospective epidemiologic studies find that early childhood (age 30 months, 6 years) or lifetime average (to age 11-13 years) blood Pb levels or tooth Pb levels (from ages 6-8 years) are associated with criminal offenses in young adults ages 19-24 years and with higher parent and teacher ratings of behaviors related to conduct disorders in children ages 8-17 years. Pb-associated increases in conduct disorders were found in populations with mean blood Pb levels 7 to14 µg/dL; associations with lower blood Pb levels as observed in cross-sectional studies were likely to be influenced by higher earlier Pb exposures. There is coherence in epidemiologic findings among related measures of conduct disorders. Evidence of Pb induced aggression in animals was mixed, with increases in aggression found in some studies of adult animals with gestational plus lifetime Pb exposure but not juvenile animals. The lack of clear biological plausibility produces some uncertainty.	
Internalizing Behaviors	Likely Causal Relationship (Table 4-17)
Prospective epidemiologic studies find associations of higher lifetime average blood (mean: ~14 µg/dL) or childhood tooth (from ages 6-8 years) Pb levels with higher parent and teacher ratings of internalizing behaviors such as symptoms of depression or anxiety, and withdrawn behavior in children ages 8-13 years. Consideration of potential confounding by parental caregiving was not consistent and findings from cross-sectional studies in populations ages 5 and 7 years with mean blood Pb levels of 5 µg/dL were mixed. Animal toxicological studies demonstrate depression-like behaviors and increases in emotionality with relevant lactational exposures. Plausible MOAs are demonstrated.	
Auditory Function Decrements	Likely Causal Relationship (Table 4-17)
A prospective epidemiologic study and large cross-sectional studies indicate associations between blood Pb levels and increased hearing thresholds at ages 4-19 years. Across studies, associations were found with blood Pb levels measured at various time periods, including prenatal maternal, neonatal (10 day, mean 4.8 µg/dL), lifetime average, and concurrent (ages 4-19 years) blood Pb levels (median 8 µg/dL). Plausible MOAs are demonstrated. The lack of biological plausibility in animals with relevant exposures produces some uncertainty.	
Visual Function Decrements	Inadequate to Infer a Causal Relationship (Table 4-17)
The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.	
Motor Function Decrements	Likely Causal Relationship (Table 4-17)
Prospective epidemiologic studies provide evidence of associations of fine and gross motor function decrements in children ages 4-17 years with lifetime average blood Pb levels and with blood Pb levels measured at various time periods with means generally ranging from 4.8 to 12 µg/dL. Results were inconsistent in cross sectional studies with concurrent blood Pb level means 2-5 µg/dL. Limited evidence in animal toxicological studies with relevant Pb exposures.	
Adults – Nervous System Effects	
Cognitive Function Decrements	Likely Causal Relationship (Table 4-17)
Prospective studies indicate associations of higher baseline bone Pb levels with declines in cognitive function (executive function, visuospatial skills, learning and memory) in adults (>age 50 years) over 2- to 4-year periods. Cross-sectional studies provide additional support. Uncertainties remain regarding the timing, frequency, duration and level of the Pb exposures contributing to the effects observed and residual confounding by age. Biological plausibility is provided by findings that relevant lifetime Pb exposures from gestation, birth, or after weaning induce learning impairments in adult animals and by evidence demonstrating plausible MOAs.	
Psychopathological Effects	Likely Causal Relationship (Table 4-17)
Cross-sectional studies in a few populations demonstrate associations of higher concurrent blood or tibia Pb levels with self-reported symptoms of depression and anxiety in adults. Uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the observed associations and residual confounding by age. Observations of depression-like behavior in animals with dietary lactational Pb exposure, with some evidence at relevant blood Pb levels, and evidence demonstrating plausible MOAs in experimental animals provides support.	

Table 1-2 (Continued): Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Auditory Function Decrements	Suggestive of a Causal Relationship (Table 4-17)
A high-quality prospective epidemiologic study finds associations of higher tibia Pb level with a greater rate of elevations in hearing threshold over 20 years. Some evidence indicates effects on relevant MOAs but important uncertainties remain related to effects on auditory function in animals with relevant Pb exposures.	
Visual Function Decrements	Inadequate to Infer a Causal Relationship (Table 4-17)
The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.	
Neurodegenerative Diseases	Inadequate to Infer a Causal Relationship (Table 4-17)
The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.	
Cardiovascular Effects (Section 4.4.7)	
Hypertension	Causal Relationship (Table 4-24)
Prospective epidemiologic studies with adjustment for multiple potential confounders consistently find associations of blood and bone Pb levels with hypertension incidence and increased blood pressure (BP) in adults. Cross-sectional studies provide supporting evidence. Meta-analyses underscore the consistency and reproducibility of the Pb associated increase in blood pressure and hypertension (a doubling of concurrent blood Pb level (between 1 and 40 µg/dL) is associated with a 1 mmHg increase in systolic BP); however, uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies. Experimental animal studies demonstrate effects on BP after long-term Pb exposure resulting in mean blood Pb levels of 10 µg/dL or greater. Plausible MOAs are demonstrated.	
Subclinical Atherosclerosis	Suggestive of a Causal Relationship (Table 4-24)
Cross-sectional analyses of NHANES data find associations of blood Pb level with peripheral artery disease (PAD) in adults. Animal toxicological evidence is limited to studies of MOA (oxidative stress, inflammation, endothelial cell dysfunction) that demonstrate biologically plausible mechanisms through which Pb exposure may initiate atherosclerotic vessel disease.	
Coronary Heart Disease	Causal Relationship (Table 4-24)
Prospective epidemiologic studies consistently find associations of Pb biomarkers with cardiovascular mortality and morbidity, specifically myocardial infarction (MI), ischemic heart disease (IHD), or HRV; however, uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies. Thrombus formation was observed in animals after relevant long term exposure and MOAs (hypertension, decreased HRV, increased corrected QT (QTc) interval, and corrected QRS complex (QRSc) duration in electrocardiogram [ECG]) are demonstrated in humans and animals.	
Cerebrovascular Disease	Inadequate to Infer a Causal Relationship (Table 4-24)
The available epidemiologic and toxicological evidence is of insufficient, quantity, quality, and/or consistency. Plausible MOAs, which are shared with hypertension and atherosclerosis, are demonstrated.	
Renal Effects (Section 4.5.5)	
Reduced Kidney Function	Suggestive of a Causal Relationship (Table 4-31)
Multiple high quality epidemiologic studies provide evidence that Pb exposure is associated with reduced kidney function; however, uncertainty remains regarding the potential for reverse causality to explain findings in humans. Further, inconsistencies and limitations in occupational studies, epidemiologic studies of children and clinical trials of chelation of CKD patient preclude strong inferences to be drawn based on their results. Although longitudinal studies found Pb-associated decrements in renal function in populations with mean blood Pb levels of 7 and 9 µg/dL, the contributions of higher past Pb exposures cannot be excluded. Animal toxicological studies demonstrate Pb-induced kidney dysfunction at blood Pb levels greater than 30 µg/dL; however, evidence in animals with blood Pb levels < 20 µg/dL is generally not available. At blood Pb levels between 20 and 30 µg/dL studies provide some evidence for dysfunction in kidney function measures (e.g., decreased creatinine clearance, increased serum creatinine, increased BUN). Plausible MOAs (Pb induced hypertension, renal oxidative stress and inflammation, morphological changes, and increased uric acid) are demonstrated.	

Table 1-2 (Continued): Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Immune System Effects (Section 4.6.8)	
Atopic and Inflammatory Responses	Likely Causal Relationship (Table 4-34)
Prospective studies of children ages 1-5 years indicate associations of prenatal cord and childhood blood Pb levels with asthma and allergy. This evidence is supported by cross-sectional associations between higher concurrent blood Pb levels (>10 µg/dL) in children and higher IgE. Uncertainties related to potential confounding by SES, smoking or allergen exposure are reduced through consideration of the evidence from experimental animal studies. The biological plausibility for the effects of Pb on IgE is provided by consistent findings in animals with gestational or gestational-lactational Pb exposures, with some evidence at blood Pb levels relevant to humans. Strong evidence of Pb-induced increases in Th2 cytokine production and inflammation in animals demonstrates MOA.	
Decreased Host Resistance	Likely Causal Relationship (Table 4-34)
Animal toxicological studies provide the majority of the evidence for Pb-induced decreased host resistance. Dietary Pb exposure producing relevant blood Pb levels (7-25 µg/dL) results in increased susceptibility to bacterial infection and suppressed delayed type hypersensitivity. Further, evidence demonstrating plausible MOA, including suppressed production of Th1 cytokines and decreased macrophage function in animals, provides coherence.	
Autoimmunity	Inadequate to Infer a Causal Relationship (Table 4-34)
The available toxicological and epidemiologic studies do not sufficiently inform Pb-induced generation of auto-antibodies with relevant Pb exposures.	
Hematologic Effects (Section 4.7.4)	
Decreased Red Blood Cell (RBC) Survival and Function	Causal Relationship (Table 4-35)
Animal toxicological studies demonstrate that exposures resulting in blood Pb levels relevant to humans (2-7 µg/dL) alter several hematological parameters (Hemoglobin [Hb], Hematocrit [Hct], and mean corpuscular volume [MCV]),increase measures of oxidative stress and increase cytotoxicity in red blood cell (RBC) precursor cells. Limited body of epidemiologic studies provides additional support for the association of Pb exposure with these endpoints. Plausible MOAs are demonstrated in experimental animals.	
Altered Heme Synthesis	Causal Relationship (Table 4-35)
Consistent findings from studies in experimental adult animal studies report that relevant exposures (e.g. blood Pb levels of 6.5 µg/dL) cause decreased ALAD and ferrochelatase activities. Additional support is garnered from a larger body of ecotoxicological studies demonstrating decreased ALAD activity across a wide range of species and a limited body of epidemiologic studies. Plausible MOAs are demonstrated in experimental animals.	
Reproductive and Developmental Effects (Section 4.8.5)	
Development	Causal Relationship (Table 4-48)
Multiple cross-sectional epidemiologic studies report associations between concurrent blood Pb levels and delayed pubertal onset for girls (6-18 years) and boys (8-15 years). These associations are consistently observed in populations with concurrent blood Pb levels 1.2-9.5 µg/dL. Few studies consider confounding by nutrition. Uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies of older children.Experimental animal studies demonstrate delayed onset of puberty in female pups with blood Pb levels of 1.3-13 µg/dL and delayed male sexual maturity at blood Pb levels of 34 µg/dL.	
Birth Outcomes (e.g., low birth weight, spontaneous abortion)	Suggestive of Causal Relationship (Table 4-48)
Some well-conducted epidemiologic studies report associations of maternal Pb biomarkers or cord blood Pb with preterm birth and low birth weight/fetal growth; however, the epidemiologic evidence is inconsistent overall and findings from experimental animal studies are mixed.	

Table 1-2 (Continued): Summary of causal determinations for the relationship between exposure to Pb and health effects.

Health Outcome	Causality Determination[a] (Table with Key Evidence)
Male Reproductive Function	Causal Relationship (Table 4-48)
Key evidence is provided by toxicological studies in rodents, non-human primates, and rabbits showing detrimental effects on semen quality, sperm and fecundity/fertility with supporting evidence in epidemiologic studies. Toxicological studies with relevant Pb exposure routes leading to blood Pb concentrations ranging from 5-43 µg/dL reported effects on sperm quality and sperm production rate, sperm DNA damage, and histological or ultrastructural damage to the male reproductive organs. Consistent associations in studies of occupational populations with concurrent blood Pb levels of 25 µg/dL and greater, report detrimental effects of Pb on sperm; however, uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies.	
Female Reproductive Function	Suggestive of Causal Relationship (Table 4-48)
Although findings are mixed overall, the body of evidence include some high-quality epidemiologic and toxicological studies, suggesting that Pb may affect some aspects of female reproductive function (hormone level, placental pathology).	
Cancer (Section 4.10.5)	
Cancer	Likely Causal Relationship (Table 4-50)
The animal toxicological literature provides the strong evidence for long-term exposure (i.e., 18 months or 2 years) to high concentrations of Pb (> 2,600 ppm) inducing tumor development; findings from epidemiologic studies inconsistent. Plausible MOAs are demonstrated.	

[a] In drawing conclusions regarding the causal relationship between Pb exposure and human health effects, evidence in the range of relevant pollutant exposures or biomarker levels was considered. Specifically, population-based epidemiology studies were emphasized with the recognition that many of the U.S populations studied included individuals with higher past than recent Pb exposures. Evidence from toxicological studies of effects observed in experimental animals at biomarker levels (e.g. blood Pb) comparable to those currently experienced by the U.S. general population were emphasized. Generally, studies with dietary exposures resulting in blood Pb levels within one order of magnitude above the upper end of the distribution of U.S. blood Pb levels were considered in forming concusions, with the majority of studies reporting blood Pb levels below 30 µg/dL. Studies with higher blood Pb levels were considered if they informed the evaluation of MOA, mechanisms, or kinetics. (Preamble, Section 1.1).

[b] Within the attention deficit hyperactivity disorder domain of externalizing behaviors, studies of Pb exposure have focused primarily on attention, impulsivity, and hyperactivity. Because the studies of ADHD were limited in terms of their design and did not adequately consider potential confounding by factors such as SES, parental education, or parental caregiving quality, they were not a major consideration in drawing conclusions about the relationship between Pb exposure and attention, impulsivity, and hyperactivity.

[c] Two domains of conduct disorders,(i.e., undersocialized aggressive conduct disorder and socialized aggressive conduct disorder), are combined for the purpose of this assessment because it is difficult to differentiate between these two domains in the available epidemiologic studies, which examine multiple endpoints such as delinquent behavior, aggression, antisocial behavior. Criminal offenses are included in the evaluation because they can be predicted by earlier conduct disorders (Section 4.3.3.2).

[d] There was limited evaluation of potential confounding by parental psychopathology, which is a strong risk factor for externalizing behaviors, in the majority of the epidemiologic studies; however, evidence of an association of between psychopathology in parents and Pb exposure in their children is not available (Section 4.3.3).

[e] Strong evidence from experimental animal studies reduces uncertainty related to confounding generally.

1.6.1 Nervous System Effects

The collective body of epidemiologic and toxicological evidence integrated across that reviewed in the 2006 Pb AQCD (U.S. EPA, 2006b) coupled with recently available data demonstrates the effects of Pb exposure on a range of nervous system effects. In children, these effects include cognitive function (Sections 4.3.2.1, 4.3.2.2, 4.3.2.3, 4.3.2.4, 4.3.2.5), externalizing behaviors (Section 4.3.3), internalizing behaviors (Section 4.3.4), auditory function (Section 4.3.6.1), visual function (Section 4.3.6.2), and motor function (Section 4.3.7). In adults, nervous system effects examined in relation to Pb exposure include cognitive function (Section 4.3.2.7), psychopathological effects (Section 4.3.5), auditory function (Section 4.3.6.1), visual function (Section 4.3.6.2), and neurodegenerative diseases (Section 4.3.9).

1.6.1.1 Children

Cognitive Function Decrements

Multiple prospective studies conducted in diverse populations consistently demonstrate associations of higher blood and tooth Pb levels with lower full scale IQ (FSIQ), executive function, and academic performance and achievement. Most studies examined representative populations and had moderate to high follow-up participation without indication of selective participation among children with higher blood Pb levels and lower cognitive function. Associations between blood Pb level and cognitive function decrements were found with adjustment for several potential confounding factors, most commonly, socioeconomic status (SES), parental IQ, parental education, and parental caregiving quality. In children ages 4-11 years, associations were found with prenatal, early childhood, childhood average, and concurrent blood Pb levels in populations with mean or group blood Pb levels in the range 2-8 µg/dL (Section 4.3.2). Neither epidemiologic nor toxicological evidence has identified an individual critical lifestage or duration of Pb exposure within childhood that is associated with cognitive function decrements. Several epidemiologic studies found a supralinear concentration-response relationship. A threshold for cognitive function decrements is not discernable from the available evidence (i.e., examination of early childhood blood Pb or concurrent [with peak <10 µg/dL] blood Pb in the range of < 1 to 10 µg/dL). Evidence in children was clearly supported by observations of Pb-induced impairments in learning, memory, and executive function in juvenile animals. Several studies in animals indicated learning impairments with prenatal, lactational, post-lactational and lifetime (with or without

prenatal) Pb exposures that resulted in blood Pb levels of 10-25 µg/dL. The mode of action for Pb-associated cognitive function decrements is supported by observations of Pb-induced impairments in neurogenesis, synaptogenesis and synaptic pruning, long term potentiation, and neurotransmitter function in the hippocampus, prefrontal cortex, and nucleus accumbens. The associations consistently found for FSIQ and other measures of cognitive function in prospective studies of children with adjustment for SES, parental education, and parental caregiving quality and the biological plausibility provided by evidence in animals for impairments in learning, memory, and executive function with relevant Pb exposures and evidence describing modes of action is sufficient to conclude that there is a causal relationship between Pb exposure and decrements in cognitive function in children.

Externalizing Behaviors

There are three domains of externalizing behaviors (Section 4.3.3). These domains are attention deficit hyperactivity disorder, undersocialized aggressive conduct disorder, and socialized aggressive conduct disorder. Studies of the effect of Pb exposure on the domain of attention deficit hyperactivity disorder have focused primarily on attention, impulsivity, and hyperactivity not diagnosis of ADHD. For the purpose of this assessment, the two domains of conduct disorders are combined because it is difficult to differentiate between these two domains based on the available epidemiologic studies of Pb exposure, which examine multiple endpoints such as delinquent behavior, aggression, and antisocial behavior. Criminal offenses are included within domain because they can be predicted by earlier conduct disorders.

Attention, Impulsivity and Hyperactivity

Although examined less extensively than cognitive function, several prospective studies demonstrated associations of blood or tooth Pb levels measured years before outcomes with attention decrements and hyperactivity in children 7-17 years and young adults ages 19-20 years as assessed using objective neuropsychological tests and rated by parents and teachers. Most of these prospective studies examined representative populations without indication of participation conditional on blood Pb levels and behavior. The results from prospective studies were adjusted for potential confounding by SES as well as parental education and caregiving quality, with some studies also considering parental cognitive function, birth outcomes, substance abuse, and nutritional factors. In prospective studies, blood Pb-associated attention decrements and hyperactivity were found in populations with prenatal (maternal or cord), age 3-60 month average, age 6 year, or lifetime average (to age 11-13 years) mean blood Pb levels of 7 to 14 µg/dL and groups with age 30 month blood Pb levels >10 µg/dL. Most well-conducted cross-sectional studies that

examined several potential confounding factors found associations of attention decrements, impulsivity, and hyperactivity in children ages 5-7.5 years with concurrent blood Pb levels with means of 5-5.4 µg/dL but cannot establish temporality or exclude the influence of higher blood Pb levels earlier in childhood. Biological plausibility for observations in children is provided by several findings in animals for increases in impulsivity or impaired response inhibition with relevant post-weaning and lifetime Pb exposures that resulted in blood Pb levels of 11 to 30 µg/dL. The mode of action for Pb-associated attention decrements, impulsivity, and hyperactivity is supported by observations of Pb-induced impairments in neurogenesis, synaptic pruning, and dopamine transmission in the prefrontal cerebral cortex, cerebellum, and hippocampus. The consistency of epidemiologic evidence for attention decrements and hyperactivity from prospective studies and the biological plausibility provided by evidence for Pb-induced impulsivity in animals and for underlying modes of action is sufficient to conclude that there is a causal relationship between Pb exposure and effects on attention, impulsivity, and hyperactivity in children.

Conduct Disorders in Children and Young Adults

Prospective studies consistently indicate that earlier childhood (e.g., age 30 months, 6 years) or lifetime average (to age 11-13 years) blood Pb levels or tooth (from ages 6-8 years) Pb levels are associated with criminal offenses in young adults ages 19-24 years and with higher parent and teacher ratings of behaviors related to conduct disorders in children ages 7-17 years. Pb-associated increases in conduct disorders were found in populations with mean blood Pb levels 7-14 µg/dL. Associations with lower blood Pb levels that are not influenced by higher earlier Pb exposures are not well characterized. These associations were found without indication of strong selection bias and with adjustment for SES, parental education and IQ, parental caregiving quality, family functioning, smoking, and substance abuse. Supporting evidence is provided by cross-sectional evidence of children participating in NHANES and a meta-analysis of prospective and cross-sectional studies. Additionally, there is coherence in epidemiologic findings among related measures of conduct disorders. Evidence for Pb-induced aggression in animals is mixed with increases in aggression found in some studies of adult animals with gestational plus lifetime Pb exposure but not juvenile animals. The consistent epidemiologic evidence from prospective and cross-sectional studies for criminal offenses and ratings of behaviors related to conduct disorders but uncertainty due to lack of clear evidence for aggression in animals is sufficient to conclude that a causal relationship is likely to exist between Pb exposure and conduct disorders in children and young adults.

Internalizing Behaviors

Prospective studies in a few populations demonstrate associations of higher lifetime average blood (mean: ~14 µg/dL) or childhood tooth (from ages 6-8 years) Pb levels with higher parent and teacher ratings of internalizing behaviors such withdrawn behavior and symptoms of depression and anxiety in children ages 8-13 years. The lack of selective participation by blood Pb level and associations found with parental and teacher ratings do not provide strong indication of biased reporting of behaviors for children with higher blood Pb levels. The few cross-sectional associations in populations with mean concurrent blood Pb levels of 5 µg/dL were inconsistent. Pb-associated increases in internalizing behaviors were found with adjustment for maternal education and SES-related variables. Consideration for potential confounding by parental caregiving quality was inconsistent. Despite some uncertainty in the epidemiologic evidence, the biological plausibility for the effects of Pb on internalizing behaviors is provided by a few findings in animals with dietary lactational Pb exposure, with some evidence at blood Pb levels relevant to humans. Additional toxicological evidence supports modes of action, including Pb-induced changes in the HPA axis and dopaminergic and GABAergic systems. The evidence from prospective studies in a few populations of children and the coherence with evidence from a few animal studies with relevant Pb exposures and mode of action but some uncertainty related to potential confounding by parental caregiving quality in studies of children is sufficient to conclude that a causal relationship is likely to exist between Pb exposure and internalizing behaviors in children.

Auditory Function Decrements

Evidence from a prospective study and cross-sectional studies in a few U.S. populations of children indicates associations of higher blood Pb level with increases in hearing thresholds and decreases auditory processing or auditory evoked potentials with adjustment for potential confounding by SES in most studies and by child health and nutritional factors in some studies. The high participation rates, particularly in the prospective study with follow-up from birth, reduce the likelihood of biased participation by children with higher blood Pb levels. Across studies, associations were found with blood Pb levels measured at various time periods, including prenatal maternal, neonatal (10 day, mean 4.8 µg/dL), lifetime average (to age 5 years), and concurrent (ages 4-19 years) blood Pb levels (median 8 µg/dL). Evidence for Pb-associated increases in hearing thresholds or latencies of auditory evoked potentials was found in adult monkeys with lifetime dietary Pb exposure. However, these effects in adult animals were found with higher peak or concurrent blood Pb levels (i.e., 33-150 µg/dL) than those relevant to this ISA; thus, the biological plausibility for epidemiologic observations is unclear. The evidence in children, particularly that from a prospective study and observations of

decreased auditory evoked potentials in animals indicating a possible mode of action, but uncertainties related to effects on auditory function in juvenile animals with relevant Pb exposures, is sufficient to conclude that a causal relationship is likely to exist between Pb exposure and decrements in auditory function in children.

Visual Function Decrements

A study in children and a few studies in animals show Pb-associated increases in supernormal electroretinograms, the biological relevance of which is unclear. Because the available epidemiologic and toxicological evidence is of insufficient quantity, quality, and consistency, the evidence is inadequate to determine that a causal relationship exists between Pb exposure and visual function in children.

Motor Function Decrements

Evidence from prospective studies in a few populations indicates associations of decrements in fine and gross motor function with higher neonatal, concurrent, and lifetime average blood Pb levels in children ages 4.5-6 years and with higher earlier childhood (ages 0-5 year average, age 78 months) blood Pb levels in children ages 15-17 years. The means for these blood Pb metrics ranged from 4.8 to 12 µg/dL. These associations were found with adjustment for several potential confounding factors, including SES, parental caregiving quality, and child health and without indication of substantial selection bias. Evidence from cross-sectional studies was less consistent. The biological plausibility for associations observed in children is provided by a study that found poorer balance in male mice with relevant gestational to early postnatal (PND10) Pb exposures. The limited available evidence in a few prospective cohorts of children, but uncertainty because of the limited available findings in mice with relevant exposures is sufficient to conclude that a causal relationship is likely to exist between Pb exposure and decrements in motor function in children.

1.6.1.2 Adults

Cognitive Function

In adults without occupational exposure, recent prospective studies in the NAS and BMS cohorts indicate associations of higher baseline tibia (means 19, 20 µg/g) or patella (mean 25 µg/g) Pb levels with declines in cognitive function in adults (>age 50 years) over 2- to 4-year periods. While the specific covariates differed between studies, these bone

Pb-associated cognitive function decrements were found with adjustment for potential confounding factors such as age, education, SES, current alcohol use, and current smoking. Supporting evidence is provided by cross-sectional analyses of the NAS, BMS, and the Nurses' Health Study, which found stronger associations with bone Pb level than concurrent blood Pb level. Cross-sectional studies also considered more potential confounding factors, including dietary factors, physical activity, medication use, and comorbid conditions. The multiple exposures and health outcomes examined in many studies reduces the likelihood of biased participation specifically by adults with higher Pb exposure and lower cognitive function. The collective evidence indicates associations in cohorts of white men and women and a cohort of more ethnically diverse men and women. The specific timing, frequency, duration, and magnitude of Pb exposures contributing to the associations observed with bone Pb levels are not discernable from the evidence. Also, there is potential for residual confounding by age. The effects of recent Pb exposures on cognitive function decrements in adults were indicated in Pb-exposed workers by associations found with blood Pb levels, although these studies did not consider potential confounding by other workplace exposures. The biological plausibility for the effects of Pb exposure on cognitive function decrements in adults is provided by findings that relevant lifetime Pb exposures from gestation, birth, or after weaning induce learning impairments in adult animals and by evidence for the effects of Pb altering neurotransmitter function in hippocampus, prefrontal cortex, and nucleus accumbens. The associations between bone Pb level and cognitive function decrements consistently found in the few prospective and cross-sectional studies of adults without occupational Pb exposure, the coherence with animal findings, and toxicological evidence supporting modes of action but uncertainties related to potential residual confounding by age in epidemiologic studies are sufficient to conclude that a causal relationship is likely to exist between long-term cumulative Pb exposure and cognitive function decrements in adults.

Psychopathological Effects

Cross-sectional studies in a few populations demonstrate associations of higher concurrent blood or tibia Pb levels with self-reported symptoms of depression and anxiety in adults. The examination of multiple exposures and outcomes in the available studies does not provide strong indication of biased reporting of psychopathological effects specifically by adults with higher Pb exposures. In adults, Pb-associated increases in depression and anxiety were found with adjustment for age, SES, and in the NAS, daily alcohol intake. The biological plausibility for epidemiologic evidence is provided by observations of depression-like behavior in animals with dietary lactational Pb exposure, with some evidence at relevant blood Pb levels and by toxicological evidence supporting modes of action, including Pb-induced changes in the HPA axis and

dopaminergic and GABAergic systems. The associations of blood and bone Pb level with self-reported psychopathological effects found in the few studies of adults without occupational Pb exposure, the biological plausibility provided by the coherence with findings from a few animal studies and evidence for underlying modes of action, but uncertainties related to residual confounding of bone Pb results by age in epidemiologic studies are sufficient to conclude that a causal relationship is likely to exist between Pb exposure and psychopathological effects in adults.

Auditory Function Decrements

The the evidence provided by the analysis of NAS men for associations of higher tibia Pb level with a higher rate of elevations in hearing threshold over 20 years and observations of decreased auditory evoked potentials in animals indicating a possible mode of action but uncertainties related to effects on auditory function in adult animals with relevant Pb exposures, is suggestive of a causal relationship between Pb exposure and auditory function decrements in adults.

Visual Function Decrements

Studies in adult animals show differential effects on ERGs, depending on the timing and concentration of exposure. A case control study finds higher Pb in retinal tissue from macular degeneration cases but lacks rigorous statistical analysis and examination of potential confounding. Because the available epidemiologic and toxicological evidence is of insufficient quantity, quality, and consistency, the evidence is inadequate to determine that a causal relationship exists between Pb exposure and visual function in adults.

Neurodegenerative Disease

While evidence is inconclusive for Amyotrophic Lateral Sclerosis (ALS)and Alzheimer's disease, a few case-control studies each found higher blood Pb levels in adults with essential tremor and higher bone Pb levels in adults with Parkinson's disease. Because of the inconclusive evidence for some diseases and limitations such as reverse causation for essential tremor and the lack of consideration for potential confounding by manganese (Mn) exposure for both essential tremor and Parkinson's disease, the evidence is inadequate to determine that a causal relationship exists between Pb exposure and neurodegenerative diseases.

1.6.2 Cardiovascular Effects

The 2006 Pb AQCD (U.S. EPA, 2006b) concluded that there was a relationship between higher blood Pb and bone Pb and cardiovascular effects in adults, in particular increased BP and increased incidence of hypertension, and recent evidence strengthens this conclusion. For the evaluation of causal relationships with Pb exposure, evidence was grouped in categories using the U.S. Surgeon General's Report on Smoking as a guideline (CDC, 2004). In addition to hypertension (Section 4.4.7.1) these categories include subclinical atherosclerosis (Section 4.4.7.2), coronary heart disease (Section 4.4.7.3), and cerebrovascular disease (Section 4.4.7.4). Examination of measures of subclinical atherosclerosis provides the opportunity to assess the pathogenesis of vascular disease at an earlier stage. Studies that examine markers of subclinical atherosclerosis (such as PAD [i.e., ankle-brachial index]) and generalized atherosclerosis (i.e., IMT) are included in this category. Coronary heart disease (CHD) results from interruption of the blood supply to a part of the heart resulting from atherosclerosis of the coronary arteries, with acute injury and scarring leading to permanent damage to the heart muscles. A disrupted HRV has been associated with a higher mortality after MI and is used as a predictor of the physiological processes underlying CHD (Buccelletti et al., 2009). Studies that examine incidence of MI, IHD, HRV, and mortality from CHD, MI, or IHD are included in this category. Cerebrovascular disease describes a group of conditions involving the cerebral blood vessels that result in transient or permanent disruption of blood flow to the brain. These conditions include stroke, transient ischemic attack, and subarachnoid hemorrhage. Both hypertension and atherosclerosis are risk factors for cerebrovascular disease and the mechanisms for these outcomes also apply to cerebrovascular disease.

Hypertension

Prospective epidemiologic studies consistently find associations of blood and bone Pb levels with hypertension incidence and increased blood pressure (BP). These findings have been replicated across multiple high-quality studies comprising large and diverse populations. Further support is provided by multiple cross-sectional analyses. While the adjustment for specific factors varied by study, the collective body of epidemiologic evidence included adjustment for multiple potential key confounding factors, including age, diet, sex, body mass index (BMI), blood pressure lowering medication use, SES, race/ethnicity, alcohol consumption, cholesterol, smoking, pre-existing disease (i.e., diabetes), measures of renal function, and co-exposures (i.e., Cd) thus reducing the uncertainties related to confounding bias. Meta-analyses underscore the consistency and reproducibility of the Pb-associated increases in BP and hypertension (Navas-Acien et al., 2008; Nawrot et al., 2002). Nawrot et al. (2002) found that a doubling of concurrent blood Pb level (between 1 and >40 μg/dL) was associated with a 1 mmHg increase in systolic BP and a 0.6 mmHg increase in diastolic BP. Navas-Acien et al. (2008) found an association of higher bone Pb levels with increased BP in their pooled analysis. Although recent epidemiologic studies in adults report associations in populations with relatively low mean concurrent blood Pb levels, the majority of individuals in these adult populations were likely to have had higher levels of Pb exposure earlier in life. Thus, there is uncertainty concerning the specific Pb exposure level, timing, frequency, and duration contributing to the associations observed in the epidemiologic studies. A causal relationship of Pb exposure with hypertension is supported by evidence from experimental animal studies that demonstrate effects on BP after long-term Pb exposure resulting in mean blood Pb levels of greater than 10 μg/dL or greater (Figure 4-21). Further, there was no evidence of a threshold below which no significant association of blood Pb level with BP was observed among the NHANES II population, 20-74 years old between 1976 and 1980 with concurrent blood Pb levels ranging from 7-34 μg/dL (Schwartz, 1991). Relevant mode of action is demonstrated and coherence for the evidence of the effect of Pb exposure on BP and hypertension is further provided by epidemiologic evidence indicating associations with cardiovascular conditions related to increased BP including mortality, CHD, stroke, and cardiac failure. Thus, the overall evidence is sufficient to conclude that there is a causal relationship between Pb exposure and hypertension.

Subclinical Atherosclerosis

A limited number of studies have evaluated markers of subclinical atherosclerosis following Pb exposure in humans or animals. An NHANES analysis of adults (1999-2000) found an association between concurrent blood Pb and PAD that was robust to

adjustment for cadmium (Cd) and other potential confounding factors (Navas-Acien et al., 2004). A second more recent analysis with adjustment for numerous potential confounders reported an increasing trend in the odds of PAD across concurrent blood Pb level groups in adults within the NHANES population (Muntner et al., 2005). Evidence of plausible biological mechanisms (e.g., oxidative stress, inflammation, endothelial cell dysfunction) is clearly described in the animal toxicological literature but animal studies have provided only limited evidence to suggest Pb exposure may initiate atherosclerotic vessel disease. Further, the specific Pb exposure level, timing, frequency, and duration contributing to the observed association with PAD is not discernable from the epidemiologic evidence. Thus, the combined limited epidemiologic and toxicological evidence is suggestive of a causal relationship between Pb exposure and subclinical atherosclerosis.

Coronary Heart Disease

Prospective epidemiologic studies of cohorts of adults during the period 1976-1994 consistently report that blood Pb level is associated with risk of CHD-related mortality from cardiovascular disease, specifically MI, IHD, and HRV (Figure 4-29 and Table 4-23). Several recent studies also report associations between biomarkers of Pb and incidence of CHD-related outcomes including a prospective analysis reporting an increased incidence of IHD (physician confirmed MI, angina pectoris) with blood and bone Pb levels. In addition, Weisskopf et al. (2009) found that patella bone Pb levels were associated with increased mortality from IHD (similar magnitude non-statistically significant associations were observed with tibia Pb levels) among men enrolled in the NAS. The level, timing, frequency, and duration of Pb exposure contributing to CHD in adult populations with higher past than recent exposure is not discernable from the evidence. However, coherence for the associations in humans is supported by the observation of thrombus formation in animals after long term Pb exposure (Sections 4.4.7.3 and 4.4.3) and mode of action for Pb-induced CHD (i.e., hypertension, HRV, increased corrected QT (QTc) interval, and corrected QRS complex (QRSc) duration in electrocardiogram [ECG]) in humans and animals (Sections 4.4.2 and 4.4.3.4). The overall evidence is sufficient to conclude that there is a causal relationship between Pb exposure and coronary heart disease.

Cerebrovascular Disease

Both hypertension and atherosclerosis are risk factors for cerebrovascular disease and the mechanisms for these outcomes also apply to cerebrovascular disease. Despite strong evidence for hypertension and CHD and Pb exposure, very few epidemiologic or

toxicological studies have examined the effects of Pb exposure on cerebrovascular disease (Section 4.4.7). These epidemiologic studies provide limited evidence for increased risk of mortality from stroke and are insufficient evidence to inform the presence or absence of a causal relationship between cerebrovascular disease and Pb exposure. Thus, the current evidence is inadequate to determine that a causal relationship exists between Pb exposure and cerebrovascular disease.

1.6.3 Renal Effects

Recent epidemiologic and toxicological studies evaluated in the current review support and expand upon the strong body of evidence presented in the 2006 Pb AQCD (U.S. EPA, 2006b) indicating that Pb exposure is associated with reduced kidney function (Section 4.5.5). The causal determination for reduced kidney function is informed by evidence for reduced GFR, reduced creatinine clearance, and increased serum creatinine.

Reduced Kidney Function

There are multiple high quality epidemiologic studies and clear biological plausibility but uncertainty regarding the potential for reverse causality to explain findings in humans. Among epidemiologic studies, key evidence is provided by the few available longitudinal studies which better characterized the temporal sequence between Pb exposure and changes in renal function by showing associations between baseline bone or blood Pb levels and reduced kidney function over time in men in the Boston, MA area and greater progression of kidney disease in CKD patients. Evidence from longitudinal studies also addressed the potential for reverse causality by showing the persistence of blood Pb-associated decrements in kidney function in the range of normal kidney function and demonstrated stronger associations than cross-sectional analyses of the same data. Cross-sectional adult studies provide supportive evidence but are weighed less than the prospective studies in conclusions because by design they do not inform directionality (i.e., reverse causality). Inconsistencies were noted in occupational studies and studies of children, and important study design limitations were noted in clinical trials of chelation in CKD patients. These inconsistencies and limitations preclude strong inferences from the results of these three study groups. Longitudinal studies found Pb-associated decrements in renal function in populations with mean blood Pb levels of 7 and 9 µg/dL. However, the contributions of higher past Pb exposures cannot be excluded. Animal toxicological studies provide clear biological plausibility with evidence for Pb-induced kidney dysfunction at blood Pb levels greater than 30 µg/dL; however, evidence in animals with blood Pb levels < 20 µg/dL is generally not available. Studies with mean

blood Pb levels between 20 and 30 µg/dL provide some evidence for dysfunction in kidney function measures (e.g., decreased creatinine clearance, increased serum creatinine, increased BUN). Animal studies also provide biological plausibility for the associations observed between blood Pb levels and reduced kidney function with evidence for Pb-induced hypertension, renal oxidative stress and inflammation, morphological changes, and increased uric acid. Collectively, the evidence integrated across epidemiologic and toxicological studies with uncertainties related to the potential for reverse causation, is suggestive of a causal relationship between Pb exposures and reduced kidney function among adults.

1.6.4 Immune System Effects

The cumulative body of epidemiologic and toxicological evidence from the 2006 Pb AQCD (U.S. EPA, 2006b) and the current assessment describes several effects of Pb exposure on the immune system related to a shift from T-derived lymphocyte helper (Th)1 - to Th2 -type responses, including an increase in atopic and inflammatory conditions and a decrease in host resistance (Section 4.6.8). Outcomes related to an increase in atopic and inflammatory conditions (Section 4.6.8.1) include asthma, allergy, increased IgE, and mode of action endpoints such as selective differentiation of Th2 cells, increased production of Th2 cytokines, B cell activation, and inflammation. Outcomes related to decreased host resistance (Section 4.6.8.2) include enhanced susceptibility to bacterial and viral infection, suppressed delayed type hypersensitivity (DTH), and those describing mode of action, i.e., decreased production of Th1 cytokines, reduced phagocyte function, and increased inflammation. A small body of studies indicates the effects of Pb exposure on autoimmunity (Section 4.6.8.3).

Atopic and Inflammatory Conditions

Prospective studies in a few populations of children ages 1-5 years indicate associations of asthma and allergy with prenatal cord blood Pb levels or blood Pb levels measured sometime before the outcome, with a cross-sectional study providing supporting evidence with associations with concurrent blood Pb level. Prospective design, lack of selective participation of subjects, and objective assessment of outcomes reduce the likelihood of undue selection bias and reverse causation. These few studies varied in their consideration for potential confounding by SES and exposure to smoking or allergens. Thus, uncertainty remains regarding residual confounding in associations observed between blood Pb levels and asthma and allergy in children. The evidence for asthma and allergy is supported by cross-sectional associations found between higher concurrent

blood Pb levels in children and higher IgE, an important mediator of asthma and allergy. The biological plausibility for the effects of Pb on IgE is provided by consistent findings in animals with gestational or gestational-lactational Pb exposures, with some evidence at blood Pb levels relevant to humans. In epidemiologic studies, higher IgE and higher asthma prevalence were examined and found mostly in children with concurrent blood Pb levels >10 µg/dL. Coherence for the evidence of Pb-associated increases in asthma, allergy, and IgE is found with evidence for most of the examined endpoints related to mode of action, i.e., Pb-induced increases in Th2 cytokine production and inflammation in animals. Neither toxicological nor epidemiologic evidence clearly identifies an individual critical lifestage or duration of Pb exposure associated with atopic and inflammatory conditions but points to an influence of gestational and cumulative Pb exposures. The combined epidemiologic evidence in a few populations and toxicological evidence supporting a relationship between Pb exposure and asthma, allergy, and shift to a Th2 phenotype as an underlying mode action but some uncertainty regarding potential confounding is sufficient to conclude that a causal relationship is likely to exist between Pb exposures and an increase in atopic and inflammatory conditions.

Decreases in Host Resistance

Much of the evidence on decreased host resistance was available in the 2006 Pb AQCD (U.S. EPA, 2006b) and is summarized in Section 4.6.5.1 (and Section 4.6.8.2). Animal toxicological observations are the primary contributors to the evidence for Pb-induced decreased host resistance. Several studies in rodents show that dietary Pb exposure producing relevant blood Pb levels (7-25 µg/dL) results in increased susceptibility to bacterial infection and suppressed DTH. Further, coherence is found with evidence describing modes of action, including suppressed production of Th1 cytokines and decreased macrophage function in animals. These effects were found with gestational, lactational, adult-only, and lifetime Pb exposures of animals, without an individual critical lifestage of exposure identified. A few cross-sectional epidemiologic studies indicate Pb-associated increases in respiratory infections but limitations, including the lack of rigorous methodology and consideration for potential confounding produce uncertainty in the epidemiologic evidence for decreased host resistance in humans. The consistent toxicological evidence in animals for increased susceptibility to bacterial infection, suppressed DTH, and related modes of action but uncertainty in the epidemiologic evidence in humans is sufficient to conclude that a causal relationship is likely to exist between Pb exposure and decreased host resistance.

Autoimmunity

Toxicological evidence describes the potential of Pb to increase autoimmunity, with a few previous studies showing Pb-induced generation of auto-antibodies (Hudson et al., 2003; Bunn et al., 2000; El-Fawal et al., 1999; Waterman et al., 1994) and recent studies providing indirect evidence by showing formation of neoantigens that could result in the formation of auto-antibodies (Table 4-34). Several observations were made in animals injected with Pb, which is a route of exposure with less relevance to humans. Higher levels of auto-antibodies also were found in Pb-exposed battery workers; however, implications are limited because of the high blood Pb levels (range: 10-40 µg/dL) of some of the workers and lack of consideration for potential confounding by several factors, including other occupational exposures (El-Fawal et al., 1999). Because results from both available toxicological and epidemiologic studies do not sufficiently inform Pb-induced generation of auto-antibodies with relevant Pb exposures, the evidence is inadequate to determine if there is a causal relationship between Pb exposure and autoimmunity.

1.6.5 Hematological Effects

Recent toxicological and epidemiologic studies support evidence presented in in previous assessments including the 2006 Pb AQCD (U.S. EPA, 2006b) describes the effect of exposure to Pb on hematological outcomes such as RBC survival and function (Section 4.7.4.1) and altered heme synthesis (Section 4.7.4.2) . Endpoints considered within the category of RBC survival and function include alterations in multiple hematological parameters (e.g., Hb, Hct, MCV), oxidative stress (altered antioxidant enzyme activities, decreased cellular glutathione [GSH], and increased lipid peroxidation), increased cytotoxicity in RBC precursor cells, and mode of action endpoints such as decreased intracellular calcium concentrations $[Ca^{2+}]_i$, decreased adenosine-triphosphase (ATPase) activity, and increased phosphatidylserine expression. Endpoints related to altered heme synthesis include decreased activities of ALAD and ferrochelatase, and decreased levels of Hb.

Decreased Red Blood Cell Survival and Function

Experimental animal studies demonstrate that exposures via drinking water and gavage, resulting in blood Pb levels relevant to humans, alter several hematological parameters, increase measures of oxidative stress and increase cytotoxicity in red blood cell (RBC) precursor cells. Some of these effects have been observed in animal toxicological studies with exposures resulting in blood Pb levels 2-7 µg/dL. Support for these findings is

provided by biologically plausible modes of action including decreased intracellular calcium concentrations $[Ca^{2+}]_i$, decreased ATPase activity, and increased phosphatidylserine expression. Epidemiologic studies find associations in both adults and children of blood Pb levels with altered hematological endpoints, increased measures of oxidative stress, and altered hematopoiesis. Although the majority of these epidemiologic studies are limited by their lack of rigorous methodology, some studies in children did adjust for some potential confounding factors including age, sex, mouthing behavior, anemia, dairy product consumption, maternal age, education, employment, marital status, family structure, SES-related variables, strengthening their support for findings in experimental animals. Collectively, the strong evidence from toxicological studies that is supported by findings from mode of action and epidemiologic studies is sufficient to conclude that there is a causal relationship between Pb exposures and decreased RBC survival and function.

Heme Synthesis

Altered heme synthesis is demonstrated by a small, but consistent, body of studies in adult animals reporting that exposures via drinking water and gavage resulting in blood Pb levels relevant to humans (e.g., 6.5 µg/dL result in decreased ALAD and ferrochelatase activities. Supporting this evidence is a larger body of ecotoxicological studies that demonstrate decreased ALAD activity across a wide range of taxa exposed to Pb. Epidemiologic studies find associations in both adults and children between higher blood Pb levels and decreased ALAD and ferrochelatase activities. Although the majority of these studies are limited by their lack of rigorous methodology and consideration for potential confounding, some studies in children did adjust for or consider potential confounding factors (i.e. age, sex, urban/rural residence, height, weight, BMI), strengthening their support for the findings in the animal toxicological studies. Evidence for altered heme synthesis is also provided by a large body of toxicological and epidemiologic studies that report decreased Hb concentrations in association with Pb exposure or blood Pb levels. Collectively, the strong evidence from toxicological and ecotoxicological studies that is supported by findings from epidemiologic studies is sufficient to conclude that there is a causal relationship between Pb exposures and altered heme synthesis.

1.6.6 Reproductive and Developmental Effects

Many epidemiologic and toxicological studies of the effects of Pb on reproductive and developmental outcomes have been conducted since the 2006 Pb AQCD. The evaluation

of causal relationships with Pb exposure focuses on four areas: developmental effects (Section 4.8.5.1), birth outcomes (Section 4.8.5.2), male reproductive function (Section 4.8.5.3), and female reproductive function (Section 4.8.5.4).

Development

In cross-sectional epidemiologic studies of girls (ages 6-18 years) with mean and/or median concurrent blood Pb levels from 1.2-9.5 µg/dL consistent associations with delayed pubertal onset (measured by age at menarche, pubic hair development, and breast development) were observed. Although fewer studies were conducted in boys overall, associations between blood Pb levels and delayed puberty onset in boys (ages 8-15 years) were observed in cross-sectional and one longitudinal study (mean and/or median blood Pb levels 3-9.5 µg/dL). Potential confounders considered in the epidemiologic studies of both boys and girls that performed regression analyses varied across studies, with few studies considering confounding by nutritional factors. A limitation across most of the epidemiologic studies of blood Pb levels and delayed puberty is their cross-sectional design, which does not allow for an understanding of temporality. There is uncertainty with regard to the exposure frequency, timing, duration, and level that contributed to the associations observed in these studies. Experimental animal studies demonstrate that puberty onset in both males and females is delayed with Pb exposure. A recent animal study indicates that delayed pubertal onset may be one of the more sensitive developmental effects of Pb exposure with effects observed after gestational exposures leading to blood Pb levels in the female pup of 1.3-13 µg/dL. Experimental animal studies have also reported delayed male sexual maturity as measured with sex organ weight, among other outcomes, seeing significant decrements at blood Pb levels of 34 µg/dL. Findings from epidemiologic studies of the effect of Pb on postnatal growth are inconsistent and findings from the toxicological literature of the effect of Pb exposure are mixed with recent growth findings showing adult onset male obesity after gestational and lactational Pb exposure. Toxicological studies demonstrated effects of Pb exposure on other organ systems (effects on the eye, and alterations in the hematopoietic, hepatic systems and teeth.) The collective body of evidence integrated across epidemiologic and toxicological studies, based on the findings of delayed pubertal onset among males and females, is sufficient to conclude that there is a causal relationship between Pb exposure and developmental effects.

Birth Outcomes

Overall, epidemiologic studies of the association of various Pb exposure indicators with preterm birth report inconsistent findings. A recent epidemiologic study reported no

association between maternal blood Pb and neural tube defects. Some associations were observed between Pb and low birth weight when epidemiologic studies used measures of postpartum maternal bone Pb or air exposures. The associations were less consistent for maternal blood Pb measured during pregnancy or at delivery or umbilical cord and placenta Pb (maternal blood Pb or umbilical cord and placenta Pb were the biomarkers most commonly used in studies of low birth weight) but some associations between increased Pb biomarker levels and decreased low birth weight/fetal growth were observed. The effects of Pb exposure during gestation in animal toxicological studies included mixed findings with some studies showing reduction in litter size, implantation, and birth weight, and some showing no effect. Because some associations were observed in well-conducted epidemiologic studies of preterm birth and low birth weight/fetal growth, the evidence is suggestive of a causal relationship between Pb exposure and birth outcomes.

Male Reproductive Function

Key evidence is provided by toxicological studies in rodents, non-human primates, and rabbits showing detrimental effects on semen quality, sperm and fecundity/fertility with supporting evidence in epidemiologic studies of associations between blood Pb levels and detrimental effects on sperm. Pb exposures resulting in blood Pb levels from 5-43 µg/dL induced lower sperm quality and sperm production rate, sperm DNA damage, and histological or ultrastructural damage to the male reproductive organs. These effects were found in animals exposed to Pb during peripuberty or as adults for 1 week to 3 months. Pb exposure of male rats also was associated with subfecundity in female mates and lower fertilization of eggs in vitro. Detrimental effects of Pb on sperm were observed in epidemiologic studies with concurrent blood Pb levels of 25 µg/dL and greater among men occupationally exposed; however, these studies were limited because of their lack of consideration of potential confounding factors, including occupational exposures other than Pb. Additional epidemiologic studies among men with lower Pb biomarker levels were limited to infertility clinic studies that may lack generalizability; however, a well-conducted epidemiologic study that controlled for other metals as well as smoking reported a positive association with various detrimental effects in sperm (Telisman et al., 2007). The median concurrent blood Pb level in this study was 4.92 µg/dL. The specific timing, frequency, duration and level of Pb exposure associated with the blood Pb level and effects observed is not discernable from the epidemiologic evidence, however. Mode of action support is provided by several recent animal toxicological studies that showed that Pb induced oxidative stress within the male sex organs, increase apoptosis of spermatocytes and germ cells, and impaired germ cell structure and function. Based on the consistency and coherence of findings for the detrimental effects of Pb exposure on

sperm and semen in the toxicological literature, the support from epidemiologic studies, and biological plausibility provided by mode of action evidence, the evidence is sufficient to conclude that there is a causal relationship between Pb exposures and male reproductive function.

Female Reproductive Function

Epidemiologic and toxicological studies of reproductive function among females investigated whether Pb biomarker levels were associated with hormone levels, fertility, estrus cycle changes, and morphology or histology of female reproductive organs including the placenta (Section 4.8.5.4). Toxicological studies of experimental animals reported in the 2006 Pb AQCD (U.S. EPA, 2006b) demonstrated associations between Pb exposure and female reproductive function, although little evidence was provided by epidemiologic studies. Some studies have shown associations with concurrent blood Pb levels and altered hormone levels in adults, with inconsistency across studies may be due to the different hormones examined and the different timing in the menstrual and life cycles. There is some evidence of a potential relationship between Pb exposure and female fertility, but findings are also mixed. The majority of the epidemiologic studies are cross-sectional, and adjustment for potential confounders varies from study to study, with some potentially important confounders, such as BMI, not included in all studies. Also, most of the studies have small samples sizes and are generally of women attending infertility clinics. Animal toxicological studies that employ relevant prenatal or early postnatal Pb exposures observe that Pb contributes to placental pathology and inflammation, decreased ovarian antioxidant capacity, altered ovarian steroidogenesis and aberrant gestational hormone levels. Although epidemiologic and toxicological studies provide information on different exposure periods, both types of studies support the conclusion that Pb possibly affects at least some aspects of female reproductive function. Overall, the relationship observed with female reproductive outcomes, such as fertility, placental pathology, and hormone levels in some epidemiologic and toxicological studies, is sufficient to conclude that evidence is suggestive of a causal relationship between Pb exposure and female reproductive function.

1.6.7 Cancer

The toxicological literature provides the strong evidence for the effect of long-term exposure (i.e., 18 months or 2 years) to high concentrations of Pb (> 2,600 ppm) on cancer. The consistent evidence indicating Pb-induced carcinogenicity in animal models is substantiated by the mode of action findings from multiple high-quality toxicological

studies in animal and in vitro models from different laboratories. Based on such evidence, IARC has classified inorganic Pb compounds as a probable human carcinogen and the National Toxicology Program has listed Pb and Pb compounds as "reasonably anticipated to be human carcinogens." Strong evidence from animal toxicological studies demonstrates an association between Pb and cancer, genotoxicity or epigenetic modification. Carcinogenicity in animal toxicology studies with relevant routes of Pb exposure has been reported in the kidneys, testes, brain, adrenals, prostate, pituitary, and mammary gland, albeit at high doses of Pb. Epidemiologic studies of cancer incidence and mortality reported inconsistent results; one strong epidemiologic study demonstrated an association between blood Pb and increased cancer mortality, but the other studies reported weak or no associations. In the 2006 Pb AQCD, various indicators of Pb exposure were found to be associated with stomach cancer, and a recent study on stomach cancer and occupational Pb exposure reported mixed findings depending on the type of Pb exposure (organic Pb, inorganic Pb, or Pb from gasoline emissions). Similarly, some studies in the 2006 Pb AQCD reported associations between Pb exposure indicators and lung cancer. Recent epidemiologic studies of lung cancer focused on occupational exposures and reported inconsistent associations. The majority of epidemiologic studies of brain cancer had null results overall, but positive associations between Pb exposure indicators and brain cancer were observed among individuals with certain genotypes. Overall, the consistent and strong body of evidence from toxicological studies on carcinogenicity and potential modes of action but inconsistent epidemiologic evidence is sufficient to conclude that a causal relationship is likely to exist between Pb exposure and cancer.

1.7 Ecological Effects of Pb

Sections 1.7.1 and 1.7.2 are summaries of the evidence evaluated in Chapter 6 in which the effects of Pb on terrestrial and aquatic ecosystems are presented separately. The evidence supporting ecological causal determinations is synthesized across endpoints (reproduction, growth, survival, neurobehavioral effects, hematological effects, physiological stress) common to terrestrial, freshwater and saltwater biota in Section 1.7.3 (Table 1-3). An integration of the evidence across endpoints examined in both human health and ecological studies follows (Section 1.8). Consideration of atmospheric deposition of Pb as related to ecological effects is discussed under policy relevant considerations (Section 1.9.7).

1.7.1 Summary of Effects on Terrestrial Ecosystems

Historically, Pb poisoning is one of the earliest recognized toxicoses of terrestrial biota, occurring primarily through ingestion of spent shot by birds (Section 6.3.4.3). At the time of the 1977 Pb AQCD, few studies of Pb exposure and effects in wild animals other than birds were available. A limited number of rodent trapping studies and observations from grazing animals near smelters provided evidence for differences in Pb sensitivity among species and these findings were further supported in the 1986 and 2006 Pb AQCDs (U.S. EPA, 2006b, 1986b, 1977). Commonly observed effects of Pb on terrestrial organisms include decreased survival, reproduction, and growth, as well as effects on development, behavior, and ALAD activity (U.S. EPA, 2006b, 1986b, 1977).

In plants, Pb effects have been studied for several decades. At the time of the 1977 Pb AQCD, it was understood that Pb uptake in plants varied with species and with the size of the pool of Pb in the soil, and that most of the Pb taken up from the soil by plants other than trees remains in the roots, with translocation to other portions of the plant varying with species (U.S. EPA, 1977). Plant growth was recognized as an endpoint of Pb toxicity in plants in the 1977 Pb AQCD and additional effects of Pb on growth processes were reported in subsequent Pb AQCDs (U.S. EPA, 2006b, 1986b, 1977). In the 1977 Pb AQCD evidence for effects of Pb on forest-nutrient cycling and shifts in arthropod community composition was found in one study conducted in the vicinity of a smelting complex. In subsequent AQCDs, other ecosystem-level effects, including decreased species diversity, changes in floral and faunal community composition, and decreasing vigor of terrestrial vegetation have been reported near stationary sources of Pb (U.S. EPA, 2006b, 1986b, 1977; Watson et al., 1976).

Pb is either deposited directly onto plant surfaces, or onto soil where it can bind with organic matter or dissolve in pore water. The amount of Pb dissolved in soil pore water determines the impact of soil Pb on terrestrial ecosystems to a much greater extent than the total amount present. It has long been established that the amount of Pb dissolved in soil solution is controlled by at least six factors: (1) solubility equilibria; (2) adsorption-desorption relationship of total Pb with inorganic compounds; (3) adsorption-desorption reactions of dissolved Pb phases on soil organic matter; (4) pH; (5) cation exchange capacity (CEC); and (6) aging. Since 2006, further studies have contributed to the understanding of the role of pH, CEC, organic matter, and aging. Smolders et al. (2009) demonstrated that the two most important determinants of both Pb solubility and toxicity in soils are pH and CEC. However, they had previously shown that experimental aging, primarily in the form of initial leaching following addition of Pb, decreases soluble metal fraction by approximately one order of magnitude (Smolders et al., 2009). Since 2006, organic matter has been confirmed as an important influence on

Pb sequestration, leading to longer-term retention in soils with higher organic matter content, and also creating the potential for later release of deposited Pb. Aging, both under natural conditions and simulated through leaching, was shown to substantially decrease bioavailability to plants, microbes, and vertebrates.

Evidence over several decades of research, previously reviewed in Pb AQCDs and in more recent studies, shows that Pb accumulates in terrestrial plants, invertebrates and vertebrates. Studies with herbaceous plant species growing at various distances from smelters added to the existing strong evidence that atmospherically transported Pb is taken up by those plants. In most species tested, soil Pb taken up by the roots is not translocated into the stem and leaves. These studies did not establish the relative proportion that originated from atmospheric Pb deposited in the soil, as opposed to that taken up directly from the atmosphere through the leaves. In trees, studies have found that soil Pb generally is translocated to other parts, in contrast to herbaceous plants, and recent studies have shown that the proportion of Pb that is taken up through the leaves and trunk is likely substantial. One study attempted to quantify this proportion Pb that is taken up directly from the atmosphere suggested it amounts to 50% of the Pb contained in Scots pine (*Pinus sylvestris*) in Sweden (Klaminder et al., 2005).

Since the 2006 Pb AQCD, various species of terrestrial snails have been found to accumulate Pb from both diet and soil. Recent studies with earthworms have found that both internal concentration of Pb and mortality increase with decreasing soil pH and CEC, and the importance of the interaction of those factors with soil Pb has been strongly confirmed, but only very partially quantified. Tissue concentration differences have been found between species of earthworms that burrow in different soil layers, but it is unknown whether those tissue concentration differences are a direct result of species differences, a result of differences in soil variables such as in pH and CEC, or interactions among those factors. Because earthworms often sequester Pb in granules, some authors have suggested that earthworm Pb is not bioavailable to their predators. There is some evidence that earthworm activity increases Pb availability in soil, but it is inconsistent. In various arthropods collected at contaminated sites, recent studies found gradients in accumulated Pb that corresponded to gradients in soil with increasing distance from stationary sources.

There are a few recent studies of Pb bioavailability and uptake in birds since the 2006 Pb AQCD. Several found tissue levels in birds that indicated exposure to Pb, but none of the locations for these studies was in proximity to stationary anthropogenic sources, and the origin of the Pb could not be identified. A study at the Anaconda Smelter Superfund site found increasing Pb accumulation in gophers with increasing soil Pb around the location of capture. A study of swine fed various Pb-contaminated soils

showed that the form of Pb determined accumulation. Recent studies were able to measure Pb in the components of various food chains that included soil, plants, invertebrates, and vertebrates. They confirmed that trophic transfer of Pb is pervasive, but no consistent evidence of trophic magnification was found.

Evidence in this review further supports the findings of the previous Pb AQCDs that biological effects of Pb on terrestrial organisms vary with species and lifestage, duration of exposure, form of Pb, and soil characteristics. In photosynthetic organisms, experimental studies have added to the existing evidence of photosynthesis impairment in plants exposed to Pb, and have found damage to photosystem II due to alteration of chlorophyll structure, as well as decreases in chlorophyll content in diverse taxa, including lichens and mosses. Evidence of oxidative stress in response to Pb exposure has also been observed in plants. Reactive oxygen species were found to increase in broad bean and tomato plants exposed to increasing concentrations of soil Pb, and a concomitant increase in superoxide dismutase, glutathione, peroxidases, and lipid peroxidation, as well as decreases in catalase were observed in the same plants. Monocot, dicot, and bryophytic taxa grown in Pb-contaminated soil or in experimentally spiked soil all responded to increasing exposure with increased antioxidant activity. In addition, reduced growth was observed in some experiments, as well as genotoxicity, decreased germination, and pollen sterility.

In terrestrial invertebrates, evidence for Pb effects has included neurological and reproductive endpoints. Recently published studies have shown neuronal damage in nematodes exposed to concentrations of Pb [2.5 μM (0.5 mg Pb/L)] in laboratory settings, accompanied by behavioral abnormalities. Reproductive adverse effects were found at lower exposure in younger nematodes, and effects on longevity and fecundity were shown to persist for several generations. Increased mortality was found in earthworms, but was strongly dependent on soil characteristics including pH, CEC, and aging. Snails exposed to Pb through either topical application or through consumption of Pb-exposed plants had increased antioxidant activity, and decreased food consumption, growth, and shell thickness. Effects on arthropods exposed through soil or diet varied with species and exposure conditions, and included diminished growth and fecundity, endocrine and reproductive anomalies, and body malformations. Within each study, increasing concentration of Pb in the exposure medium generally resulted in increased effects, but the relationship between concentration and effects varied between studies, even when the same medium, e.g., soil, was used. Evidence suggested that aging and pH are important modifiers.

ALAD was identified in the 1977 Pb AQCD as a sensitive indicator of exposure to Pb in rats and waterfowl, and became regarded as a biomarker of exposure in many terrestrial

vertebrates. Other effects of Pb on vertebrates reviewed in Pb AQCDs and the current document include decreased white blood cell counts and behavioral anomalies observed in amphibians and reptiles. However, large differences in effects were observed at the same concentration of Pb in soil, depending on whether the soil was freshly amended or field-collected from contaminated areas. As in most studies where the comparison was made, effects were smaller when field-collected soils were used. In some birds, maternal elevated blood Pb level was associated in recent studies with decreased hatching success, smaller clutch size, high corticosteroid level, and abnormal behavior. Some species evidenced little or no effect of elevated blood Pb level. Effects of dietary exposure were studied in several mammalian species, and cognitive, endocrine, immunological, and growth effects were observed.

Recent evidence reviewed in Sections 6.3.6 and 6.3.12.7 demonstrates that exposure to Pb is generally associated with negative effects in terrestrial ecosystems. It also demonstrates that many factors, including species and various soil physiochemical properties, interact strongly with Pb concentration to modify those effects. In these ecosystems, where soil is generally the main component of the exposure route, Pb aging is a particularly important factor, and one that may be difficult to reproduce experimentally. Without quantitative characterization of those interactions, characterizations of exposure-response relationships would likely not be transferable outside of experimental settings. Since the 2006 Pb AQCD, few studies of exposure-response have been conducted, and results have been inconsistent. Table 6-4 summarizes studies of reproduction, growth, and survival in terrestrial organisms that have been published since 2006, and in which concentration-response data were reported.

Recent evidence of effects of Pb at the community and ecosystem levels of biological organization include several studies of the ameliorative effects of mycorrhizal fungi on plant growth in the presence of Pb, attributed to decreased uptake of Pb by plants, although both mycorrhizal fungus and plant were negatively affected at the exposures assessed. Most recently published research on community and ecosystem-level effects of Pb has focused on soil microbial communities, which have been shown to be impacted in both composition and activity. Many of the recent studies of effects on soil microbial communities have taken place in environments contaminated with multiple metals, and some have attempted to separate the effects of individual metals when possible. Soil microbial activity was generally diminished, but in some cases recovered over time. Species and genotype composition were consistently altered, and those changes were long-lasting or permanent. Recent studies have addressed differences in sensitivity between species explicitly, and have clearly demonstrated high variability between related species, as well as within larger taxonomic groupings. Mammalian no observed effect concentration (NOEC) values expressed as blood Pb levels were shown to vary by

a factor of 8, while avian blood NOECs varied by a factor of 50 (Buekers et al., 2009). Protective effects of dietary Ca^{2+} have been found in plants, birds, and invertebrates.

1.7.2 Summary of Effects on Aquatic Ecosystems

Effects of Pb on plants, invertebrates, and vertebrates are reported for both freshwater and saltwater ecosystems. Although effects of Pb exposure are likely mediated through common mode(s) of action across freshwater and marine/estuarine taxa, these ecosystems are considered separately because of different environmental and physiological factors that influence Pb toxicity such as bioavailability of the metal, form of Pb, water quality parameters and adaptations in freshwater and saltwater organisms. Toxicity of Pb also varies by organism, lifestage and duration of exposure. (U.S. EPA, 2006b, 1986a). Closely related organisms can vary greatly in bioaccumulation of Pb and other non-essential metals as well as in their susceptibility to Pb. Pb effects on aquatic biota were previously assessed in the 1977 Pb AQCD, the 1986 Pb AQCD and the 2006 Pb AQCD (U.S. EPA, 2006b, 1986a, 1977).

Exposure of freshwater and estuarine organisms to Pb, and associated effects, are tied to terrestrial systems via watershed processes (Section 6.2). Atmospherically-derived Pb can enter aquatic systems through runoff from terrestrial systems or via direct deposition over a water surface. In aquatic ecosystems affected by Pb, exposures are most likely characterized as low dose, chronic exposures. Once Pb enters surface waters, its solubility and subsequent bioavailability are influenced by Ca^{2+} concentration, pH, alkalinity, total suspended solids, and dissolved organic carbon (DOC), including humic acids. In saltwater, higher levels of ions additionally affect Pb bioavailability. In sediments, Pb bioavailability may be influenced by the presence of other metals, sulfides, iron (Fe-) and manganese (Mn-)oxides, and physical disturbance. Recent studies provide further evidence for the role of modifying factors such as pH, DOC, and hardness. Toxicity of the same concentration of Pb can vary greatly under different experimental conditions.

As recognized in the 2006 Pb AQCD and further supported in this review, uptake of Pb by aquatic invertebrates and vertebrates may preferentially occur via exposure routes other than direct absorption from the water column such as ingestion of contaminated food and water, uptake from sediment pore waters, or incidental ingestion of sediment (U.S. EPA, 2006b). Currently available models for predicting bioavailability focus on acute toxicity and do not consider all possible routes of uptake. They are therefore of limited applicability, especially when considering species-dependent differences in uptake and bioaccumulation of Pb. Recent evidence supports the 2006 Pb AQCD

conclusion that processes such as Pb adsorption, complexation, and chelation alter bioavailability to aquatic organisms.

Biological Effects of Pb on Freshwater Plants, Invertebrates and Vertebrates

Recent evidence further supports the findings of the previous Pb AQCDs that waterborne Pb is highly toxic to freshwater plants, invertebrates and vertebrates, with toxicity varying with species and lifestage, duration of exposure, form of Pb, and water quality characteristics. Concentration-response data from freshwater organisms indicate that there is a gradient of response to increasing Pb concentration and that some effects in sensitive species are observed at concentrations of Pb quantified in U.S. surface waters (Table 1-2).

The toxicity of Pb to aquatic algae and plants has been recognized in earlier EPA reviews of this metal. In the 1977 Pb AQCD, differences in sensitivity to Pb among different species of algae were reported and concentrations of Pb varied within and between genera. This observation was subsequently generalized across aquatic taxa (U.S. EPA, 1977). At the time of the 1977 Pb AQCD, the information available on effects of Pb on freshwater plants was limited. For plants in general, Pb was recognized to affect photosynthesis, mitosis, and growth, but at concentrations much higher than typically found in the environment. Effects of Pb on plants reported in subsequent Pb AQCDs included decreased growth, deformation of cells, and blocking of the pathways that lead to pigment synthesis, thus affecting photosynthesis.

Effects of Pb on aquatic plants supported by additional evidence in this review include oxidative damage, decreased photosynthesis, and reduced growth. Most recent studies report effects on growth at concentrations much higher than Pb typically encountered in the environment, however, some sublethal endpoints such as effects on chlorophyll were reported at concentrations in the 100 to 200 µg Pb/L range, albeit still much higher than those typically encountered in U.S. surface waters (Table 1-1). Elevated levels of antioxidant enzymes are commonly observed in aquatic plant, algae, and moss species exposed to Pb (U.S. EPA, 1977) and recent evidence continues to support this observation. Recent studies on uptake of Pb by aquatic plants support the findings of previous Pb AQCDs that all such plants with roots tend to sequester larger amounts of Pb in their roots than in their shoots, and provide additional evidence for species differences in compartmentalization of sequestered Pb and in responses to Pb in water and sediments. Exposure-response relationships in which increasing concentrations of Pb leads to increasing effects have consistently been reported in freshwater algae and macrophytes, suggesting that effects on growth and antioxidant activity are also occurring at lower

concentrations, however, most current observations of Pb effects in freshwater plants are at concentrations that exceed Pb concentration values available for U.S. surface waters (Table 1-1).

The largest body of evidence for effects of Pb at or near concentrations encountered in U.S. surface waters is from invertebrates. In the 1986 Pb AQCD (U.S. EPA, 1986a) and 2006 Pb AQCD (U.S. EPA, 2006b), reduced reproduction, growth, and survival were reported in various species of freshwater invertebrates. In the 2006 Pb AQCD, concentrations at which effects were observed in aquatic invertebrates ranged from 5 to 8,000 µg Pb/L. Recent evidence for effects of Pb on reproduction, growth, and survival supports findings in previous Pb AQCDs (Table 6-5). In a series of 48-hour acute toxicity tests using a variety of natural waters across North America, LC_{50} values ranged from 29 to 180 µg Pb/L tests with the cladoceran *Ceriodaphnia dubia* (Esbaugh et al., 2011). In this same species, increased DOC leads to an increased mean EC_{50} for reproduction as low as 25 µg Pb/L. Reproductive and growth effects have also been reported in rotifer, midge and mayfly species near the range of Pb concentrations encountered in freshwater habitats. Several studies in this review have provided evidence of growth effects at lower concentrations. Among the most sensitive species, growth of juvenile freshwater snails (*Lymnaea stagnalis*) was inhibited at an EC_{20} of <4 µg Pb/L (Grosell and Brix, 2009; Grosell et al., 2006b). A chronic value of 10 µg Pb/L, obtained in 28-day exposures of 2-month-old freshwater mussel (*Lampsilis siliquoidea*) juveniles, was the lowest genus-mean chronic value ever reported for Pb (Wang et al., 2010f).

Since the 2006 Pb AQCD, there is additional evidence for Pb effects on antioxidant enzymes, lipid peroxidation, stress response and osmoregulation in aquatic invertebrates, as well as additional information on Pb bioaccumulation. Recent studies using stable isotopes have enabled simultaneous measurement of uptake and elimination in several aquatic organisms to assess the relative importance of water versus dietary uptake. In uptake studies of various invertebrates, Pb was mainly found in the gills and digestive gland/hepatopancreas.

Pb effects on freshwater vertebrates were previously assessed in the 1977 Pb AQCD, the 1986 Pb AQCD and the 2006 Pb AQCD (U.S. EPA, 2006b, 1986a, 1977). Evidence of toxicity of Pb and other metals to freshwater organisms goes back to early observations of contamination of natural areas by Pb mining leading to extirpation of fish from streams (U.S. EPA, 1977). Recent evidence supports the findings of effects on survival, reproduction, and behavior reported in previous Pb AQCDs for freshwater vertebrates. In a series of 96-hour acute toxicity tests with fathead minnow conducted in a variety of natural waters across North America, LC_{50} values ranged from 41 to 3,598 µg Pb/L (Esbaugh et al., 2011). Reproductive effects associated with water quality parameters

were also noted with this species (Mager et al., 2010). In fish, several recent studies on behavioral effects of Pb indicate decreased prey capture rate, slower swim speed and decline in startle response and visual contrast with Pb exposure. These reported effects provide additional evidence for toxicity of Pb to fish. Chronic NOEC and EC_{10} values reported for trout, a sensitive species, are within the range of Pb occasionally encountered in U.S. surface waters (Table 6-2).

Observed responses of fish to Pb reported in the 1986 Pb AQCD and the 2006 Pb AQCD included inhibition of heme formation, alterations in brain receptors, effects on blood chemistry and hormonal systems, and decreases in some enzyme activities (U.S. EPA, 2006b, 1986a). Since the 2006 Pb AQCD, possible molecular targets for Pb neurotoxicity have been identified in fish and additional mechanisms of Pb toxicity have been elucidated in the fish gill and the fish renal system. In the 2006 Pb AQCD, amphibians were considered to be relatively tolerant to Pb. Observed responses to Pb exposure included decreased enzyme activity (e.g., ALAD reduction) and changes in behavior. Since the 2006 Pb AQCD, studies conducted at concentrations approaching environmental levels of Pb have indicated sublethal effects on tadpoles including deformities and decrements in growth and swimming ability.

In the 2006 Pb AQCD, adverse effects were found in freshwater fish at concentrations ranging from 10 to >5,400 μg Pb/L, generally depending on water quality variables (e.g., pH, hardness, salinity). Additional testing of Pb toxicity under conditions of varied alkalinity, DOC, and pH has been conducted since the last review. Effects in fish observed in recent studies fall within the range of concentrations observed in the previous Pb AQCD. Recent evidence also supports the 2006 conclusions that the gill is a major site of Pb uptake in fish, and that there are species differences in the rate of Pb accumulation and distribution of Pb within the organism. The anterior intestine has been newly identified as a site of uptake of Pb through dietary exposure studies. At the time of the publication of the 2006 Pb AQCD, trophic transfer of Pb through aquatic food chains was considered to be negligible. Measured concentrations of Pb in the tissues of aquatic organisms were generally higher in algae and benthic organisms than in consumers at higher trophic levels, indicating that Pb was bioconcentrated but not biomagnified. Some studies published since the 2006 Pb AQCD support the potential for transfer of Pb in aquatic food webs, while other studies indicate that Pb concentration decreases with increasing trophic level.

Ecosystem-level effects associated with Pb reported in previous Pb AQCDs include alteration of predator-prey dynamics, species richness, species composition, and biodiversity. Since the 2006 Pb AQCD, additional evidence for community and ecosystem level effects of Pb reviewed in Sections 6.4.7 and 6.4.12.7 have been observed

primarily in microcosm studies or field studies near contaminated areas (mining, effluent). Findings from field studies of aquatic communities in the vicinity of heavily contaminated sites include changes in species composition and species richness, predator/prey interactions, nutrient cycling and energy flow; however, Pb is often found coexisting with other metals and other stressors, which risk confounding the observed effects. Recent studies provide evidence in additional habitats for these community and ecological-level effects, specifically in aquatic macrophyte communities and sediment-associated communities. Different species may exhibit different responses to Pb-impacted ecosystems dependent not only upon other environmental factors (e.g., temperature, pH), but also on species sensitivity, lifestage, or seasonally-affected physiological state. Aquatic ecosystems with low pH and low dissolved organic matter are likely to be the most sensitive to the effects of atmospherically-deposited Pb.

Biological Effects of Pb on Saltwater Plants, Invertebrates and Vertebrates

In general, Pb toxicity to marine/estuarine plants, invertebrates and vertebrates is less well characterized than toxicity to Pb in freshwater systems due to an insufficient quantity of studies on saltwater organisms. In marine algae, effects on growth are observed in the most sensitive species at Pb concentrations that exceed amounts measured in the open sea or estuaries (Table 1-1). The majority of available studies of Pb effects on saltwater organisms are for invertebrate species. Evidence for Pb effects on reproduction, growth and survival as well as neurobehavioral, hematological and physiological stress endpoints are coherent with findings in freshwater invertebrates although most effects are observed at concentrations above 100 µg Pb/L which exceeds Pb typically encountered in seawater (Table 1-1). Fewer studies are available for Pb in marine sediments. In the amphipod, *Elasmopus laevis*, onset to reproduction was significantly delayed at 118 mg/Pb kg sediment; a concentration that the authors indicate is below the current marine sediment regulatory guideline for Pb (218 mg Pb/kg sediment) (Ringenary et al., 2007; NOAA, 1999). In the same study, no effects of Pb on adult survival in 28-day or 60-day sediment exposures were observed. Additional studies on reproduction, growth, and survival in marine invertebrates report effects above the range considered for causal determinations (Table II, Preamble). Several field monitoring studies with marine bivalves have used ALAD as a biomarker for Pb exposure and correlated ALAD inhibition to increased Pb tissue content. Field and laboratory studies provide evidence for antioxidant response to Pb exposure, however, most effects are observed at concentrations of Pb that are higher than concentrations detected in marine environments. No recent evidence for effects of Pb on marine vertebrates in controlled exposures was available for review.

1.7.3 Determinations of Causality for Effects on Ecosystems

Table 1-3 Summary of Pb causal determinations for plants, invertebrates, and vertebrates.

Level		Effect	Terrestrial[a]	Freshwater[a]	Saltwater[a]
Community- and Ecosystem-Level		Community and Ecosystem Effects (Sections 6.3.12.7, 6.4.12.7, and 6.4.21.7)	Likely Causal	Likely Causal	Inadequate
Population–Level Endpoints	**Organism–Level Responses**	Reproductive and Developmental Effects - Plants (Sections 6.3.12.1, 6.4.12.1, and 6.4.21.1)	Inadequate	Inadequate	Inadequate
		Reproductive and Developmental Effects - Invertebrates (Sections 6.3.12.1, 6.4.12.1, and 6.4.21.1)	Causal	Causal	Suggestive
		Reproductive and Developmental Effects - Vertebrates (Sections 6.3.12.1, 6.4.12.1, and 6.4.21.1)	Causal	Causal	Inadequate
		Growth - Plants (Sections 6.3.12.2, 6.4.12.2, and 6.4.21.2)	Causal	Likely Causal	Inadequate
		Growth - Invertebrates (Sections 6.3.12.2, 6.4.12.2, and 6.4.21.2)	Likely Causal	Causal	Inadequate
		Growth - Vertebrates (Sections 6.3.12.2, 6.4.12.2, and 6.4.21.2)	Inadequate	Inadequate	Inadequate
		Survival - Plants (Sections 6.3.12.3, 6.4.12.3, and 6.4.21.3)	Inadequate	Inadequate	Inadequate
		Survival - Invertebrates (Sections 6.3.12.3, 6.4.12.3, and 6.4.21.3)	Causal	Causal	Inadequate
		Survival - Vertebrates (Sections 6.3.12.3, 6.4.12.3, and 6.4.21.3)	Likely Causal	Causal	Inadequate
		Neurobehavioral Effects - Invertebrates (Sections 6.3.12.4, 6.4.12.4, and 6.4.21.4)	Likely Causal	Likely Causal	Inadequate
		Neurobehavioral Effects - Vertebrates (Sections 6.3.12.4, 6.4.12.4, and 6.4.21.4)	Likely Causal	Likely Causal	Inadequate
	Sub-organismal Responses	Hematological Effects - Invertebrates (Sections 6.3.12.5, 6.4.12.5, and 6.4.21.5)	Inadequate	Likely Causal	Suggestive
		Hematological Effects - Vertebrates (Sections 6.3.12.5, 6.4.12.5, and 6.4.21.5)	Causal	Causal	Inadequate
		Physiological Stress - Plants (Sections 6.3.12.6, 6.4.12.6, and 6.4.21.6)	Causal	Likely Causal	Inadequate
		Physiological Stress - Invertebrates (Sections 6.3.12.6, 6.4.12.6, and 6.4.21.6)	Likely Causal	Likely Causal	Suggestive
		Physiological Stress - Vertebrates (Sections 6.3.12.6, 6.4.12.6, and 6.4.21.6)	Likely Causal	Likely Causal	Inadequate

[a]Conclusions are based on the weight of evidence for causal determination in Table II of the ISA Preamble. Ecological effects observed at or near ambient Pb concentrations measured in soil, sediment and water in the most recent available studies (Table 1-1). were emphasized and studies generally within one to two orders of magnitude above the reported range of these values were considered in the body of evidence for terrestrial (Section 6.3.12), freshwater (Section 6.4.12) and saltwater (Section 6.4.21) ecosystems.

1.7.3.1 Effects on Development and Reproduction

Evidence from invertebrate and vertebrate studies from Pb AQCDs and in this review indicates that Pb is affecting reproductive performance in multiple species. Various endpoints have been measured in multiple taxa of terrestrial and aquatic organisms to assess the effect of Pb on development, fecundity, and hormone homeostasis, and they have demonstrated the presence of adverse effects. Reproductive effects are important when considering effects of Pb because impaired fecundity at the organism level of biological organization can result in a decline in abundance and/or extirpation of populations, decreased taxa richness, and decreased relative or absolute abundance at the community level (Suter et al., 2005; U.S. EPA, 2003a). The evidence is sufficient to conclude that there is a causal relationship between Pb exposures and developmental and reproductive effects in terrestrial (Section 6.3.12.1) and freshwater (Section 6.4.12.1) invertebrates and vertebrates. Although there is less evidence for reproductive and developmental effects of Pb in marine systems, available evidence is suggestive of a causal relationship between Pb exposure and reproductive and developmental effects in saltwater invertebrates (Section 6.4.21.1). The evidence is inadequate to conclude that there is a causal relationship between Pb exposures and developmental and reproductive effects in saltwater vertebrates and in either terrestrial or aquatic plants.

Recent evidence for developmental and reproductive endpoints in terrestrial invertebrates shown to be affected by Pb include hatching success in collembolans, increased development time in fruit flies and aphids, and disrupted hormone homeostasis in moths. These studies have generally used Pb concentrations that exceed Pb soil concentrations found at most U.S. locations (Table 1-1), but many of them included multiple concentrations, and responses increased with increasing concentration. In terrestrial vertebrates, recent evidence for decreased sperm count and quality in deer at a location contaminated by mining, and for decreased testis weight in lizards, support previous associations between Pb exposure and reproductive and developmental effects. Few studies are available that specifically address reproductive effects of Pb exposure in either terrestrial or aquatic plants.

In terrestrial invertebrates, Pb can alter developmental timing, hatching success, sperm morphology, and hormone homeostasis. In fruit flies, Pb exposure increased time to pupation and decreased pre-adult development. Sperm morphology was altered in earthworms exposed to Pb-contaminated soils. Pb may also disrupt hormonal homeostasis in invertebrates as studies with moths have suggested. Evidence of

multi-generational toxicity of Pb is also present in terrestrial invertebrates, specifically springtails, mosquitoes, carabid beetles, and nematodes where decreased fecundity in progeny of Pb-exposed individuals was observed. However, effects have only been studied in a small number of species.

For freshwater invertebrates, exposure to Pb under controlled conditions has provided evidence for reproductive effects on sensitive taxa (gastropods, amphipods, cladocerans) at or near the range of Pb concentration values available for U.S. surface waters (Table 1-1). Reproductive effects were reported to begin at 19 µg Pb/L for the snail *Lymnaea palustris* and 27 µg Pb/L for Daphnia sp. as reported in the 1986 Pb AQCD (U.S. EPA, 1986b). In a 42-day chronic study reviewed in the 2006 Pb AQCD, the LOEC for reproduction was 3.5 µg Pb/L in amphipods receiving both waterborne and dietary Pb (Besser et al., 2005). Several recent studies in snails, rotifers and other freshwater invertebrates support previous findings of adverse impacts to reproduction (Table 6-5) . Reproductive effects have also been observed in multi-generational studies with aquatic invertebrates. Larval settlement rate and rate of population increase was decreased in rotifers and marine amphipods. Rotifers have a reduced fertilization rate associated with Pb exposure that appears to be due to decreased viability of sperm and eggs.

In freshwater vertebrates there is evidence for reproductive and developmental effects of Pb. Recent evidence in frogs and freshwater fish continues to support developmental and reproductive effects of Pb in aquatic vertebrates reported in earlier Pb AQCDs. Pb-exposure in tadpoles has been demonstrated to delay metamorphosis, decrease larval size, produce subtle skeletal malformations, and to result in slower swimming speed. Previous Pb AQCDs have reported developmental effects in fish, specifically spinal deformities in larvae at a concentration of 120 µg Pb/L. In the 2006 Pb AQCD, decreased spermatocyte development in rainbow trout was observed at 10 µg Pb/L and in fathead minnow testicular damage occurred at 500 µg Pb/L. In more recent studies, reproduction in fathead minnows was affected in breeding exposures following 300-day chronic toxicity testing. However, reproductive performance was unaffected in zebrafish *Danio rerio* exposed to Pb-contaminated prey. In fish, there is recent evidence of Pb effects on steroid profiles from nominal exposure studies.

In terrestrial vertebrates, evidence from Pb AQCDs and more recent evidence support an association between Pb exposure and observed adverse reproductive effects. In mammals, few studies in the field have addressed Pb specifically: most available data in wild or grazing animals are from near smelters, where animals are co-exposed to other metals. Evidence obtained using mammals in the context of human health research demonstrates adverse effects of Pb on sperm, and on onset of puberty in males and females (Chapter 4), which is coherent with the partial evidence from mammals in the wild. Other

reproductive endpoints including spontaneous abortions, pre-term birth, embryo development, placental development, low birth weight, subfecundity, hormonal changes, and teratology were also affected, but less consistently. Recent toxicological data from animal studies support trans-generational effects, a finding that is also an area of emerging interest in ecology.

Many studies of effects on reproductive and developmental endpoints in terrestrial invertebrates and vertebrates have been conducted with soil Pb concentrations exceeding those found in most U.S. locations. Recent and past studies that include multiple, increasing concentrations of Pb, from background level to levels greater than those associated with heavily contaminated sites, showed exposure-dependent responses. For some sensitive aquatic species, recent evidence supports previous findings of reproductive and developmental effects of Pb and differential lifestage response at or near concentrations of Pb reported from natural environments.

1.7.3.2 Effects on Growth

Alterations in the growth of an organism can impact population, community and ecosystem level variables. Evidence is sufficient to conclude that there is a causal relationship between Pb exposures and effects on growth in terrestrial plants (Section 6.3.12.2) and freshwater invertebrates (Section 6.4.12.2). Evidence is sufficient to conclude that a causal relationship is likely to exist between Pb exposure and effects on growth in terrestrial invertebrates and freshwater plants. Evidence is inadequate to establish a causal relationship between Pb exposures and effects on growth in terrestrial and aquatic vertebrates and saltwater biota (Section 6.4.21.2).

Evidence for effects of Pb on growth is strongest in terrestrial plants. In invertebrates, evidence for effects of Pb on growth has been observed most extensively in freshwater taxa, with inhibition in sensitive species occurring in or near the range of Pb concentration values found in surveys of U.S. surface waters (Table 1-1). Vertebrates, particularly terrestrial, have been the object of a comparatively much smaller number of studies of the effects of Pb on growth. Growth effects observed in both invertebrates and vertebrates, however, underscore the importance of lifestage to overall Pb susceptibility. In general, juvenile organisms are more sensitive than adults. Evidence for growth effects of Pb in freshwater and terrestrial plant species is primarily supported by earlier Pb AQCDs. In aquatic invertebrates, the weight of the evidence continues to support growth effects of Pb with several recent studies reporting effects at ≤ 10 µg Pb/L, specifically in snails and mussels (Table 6-5). Also, growth effects in frogs are reported at lower concentrations in the current document than in earlier reviews.

There is evidence over several decades of research that Pb inhibits photosynthesis and respiration in plants, both of which reduce growth (U.S. EPA, 2006b, 1977). Many toxicity studies conducted in laboratory and greenhouse settings have reported effects on plants. These effects are typically observed in laboratory studies with high exposure concentrations or in field studies near stationary sources and heavily contaminated sites, but studies that include multiple concentrations of Pb show increased response with increasing concentration. Pb has been shown to affect photosystem II, altering the pigment structure, and decreasing the efficiency of visible light absorption by affected plants. Decreases in chlorophyll *a* and *b* content have been observed in various algal and plant species. Most primary producers experience EC_{50} values for growth in the range of 1,000 to 100,000 µg Pb/L with minimal inhibition of growth observed as low as 100 µg Pb/L (U.S. EPA, 2006b).

Growth effects of Pb on aquatic invertebrates are reviewed in the draft *Ambient Aquatic Life Water Quality Criteria for Lead* (U.S. EPA, 2008b) and the 2006 Pb AQCD (U.S. EPA, 2006b). In the 2006 Pb AQCD, the LOEC for growth of freshwater amphipods *Hyalella azteca* in 42-day chronic exposure to Pb was 16 µg Pb/L (Besser et al., 2005). Recent studies summarized in Table 6-5 provide additional evidence for effects on growth of aquatic invertebrates, with some effects observed at ≤ 10 µg Pb/L. Growth of juvenile freshwater snails *L. stagnalis* was inhibited below the lowest concentration tested resulting in an EC_{20} <4 µg Pb/L (Grosell and Brix, 2009; Grosell et al., 2006b). In the same study, the NOEC was 12 µg Pb/L and the LOEC was 16 µg Pb/L. The authors indicated that the observed effect level for Pb was very close to the current U.S. EPA water quality criteria for Pb (3.3 µg Pb/L normalized to test water hardness) (Grosell and Brix, 2009). In the freshwater mussel, fatmucket (*L. siliquoidea*) juveniles were the most sensitive lifestage (Wang et al., 2010f). A chronic value of 10 µg Pb/L in a 28-day exposure of 2-month-old fatmucket juveniles was the lowest genus mean chronic value ever reported for Pb. Growth effects are also reported in marine invertebrates at higher concentrations of Pb than sensitive freshwater invertebrates.

In Pb AQCDs, a few studies have reported growth effects of Pb on vertebrates including fish (growth inhibition), birds (changes in juvenile weight gain), and frogs (delayed metamorphosis, smaller larvae). A recent study reviewed in this ISA supports findings of growth effects in frogs and suggests that these effects may be occurring at lower concentrations than previously reported: the growth rate of tadpoles of the northern leopard frog exposed nominally to 100 µg Pb/L from embryo to metamorphosis was slower than the growth rate of the controls (Chen et al., 2006b). In this study, Pb concentrations in the tissues of tadpoles were quantified and the authors reported that they were within the range of reported tissue concentrations reported in wild-caught populations. Reports of Pb-associated growth effects in fish are inconsistent.

1.7.3.3 Effects on Survival

Survival is a biologically important response that may have a direct impact on population size and can lead to effects at the community and ecosystem level of biological organization. The evidence is sufficient to conclude that there is a causal relationship between Pb exposures and survival in terrestrial invertebrates (Section 6.3.12.3) and freshwater invertebrates and vertebrates (Section 6.4.12.3). Evidence is sufficient to conclude that a causal relationship is likely to exist between Pb exposure and survival in terrestrial vertebrates (Section 6.3.12.3). The evidence is inadequate to conclude that there is a causal relationship between Pb exposure and survival in terrestrial and freshwater plants (Section 6.3.12.3, and Section 6.4.12.3), as well as in all saltwater biota (Section 6.4.21.3). There is evidence for mortality in saltwater organisms at concentrations that greatly exceed Pb concentrations typically encountered in seawater. In general, marine organisms are less sensitive to Pb than freshwater species.

In terrestrial vertebrates, evidence for Pb effects on survival is primarily supported by Pb AQCDs with no recent studies reporting effects on survival at lower concentrations. For aquatic invertebrates recent studies support previous associations between Pb exposure and mortality at concentrations near the range of Pb concentration values available for U.S. surface waters (Table 1-1) in cladocerans, amphipods, and rotifers (Table 6-5). In aquatic vertebrates, there is recent evidence for effects in fish at <100 µg Pb/L. Pb is generally not phytotoxic to freshwater or terrestrial plants at concentrations found in the environment away from stationary sources and heavily contaminated sites, probably due to the fact that plants often sequester large amounts of Pb in roots, and that translocation to other parts of the plant is limited.

The relationship between Pb exposure and decreased survival rate has been well demonstrated in terrestrial and aquatic species, as presented in Sections 6.3.12.3, 6.4.12.3, 6.4.21.3, and in previous Pb AQCDs. Toxicological studies have established LC_{50} values for some species of plants, invertebrates, and vertebrates. From the LC_{50} data on Pb in this review and previous Pb AQCDs, a wide range of sensitivity to Pb is evident across taxa. LC_{50} values are usually much higher than Pb concentrations near contaminated sites, although physiological dysfunction that adversely impacts the fitness of an organism often occurs well below concentrations that result in mortality.

Freshwater aquatic invertebrates are generally more sensitive to Pb exposure than other taxa, with survival adversely impacted in a few species in laboratory studies at concentrations near typical ambient levels. Freshwater biota that exhibit sensitivity to Pb in the upper range of Pb concentrations measured in U.S. waters [median 0.50 µg Pb/L, range 0.04 to 30 µg Pb/L (U.S. EPA, 2006b)], include some species of gastropods, amphipods, cladocerans, and rotifers although the toxicity of Pb is highly dependent upon

water quality variables such as DOC, hardness, and pH. For example, amphipods tested under various water conditions exhibited sensitivity to Pb at <10 µg Pb/L (U.S. EPA, 2006c) and the present document). These impacted species may include endangered species or candidates for the endangered species list, such as the freshwater mussel *Lampsilis rafinesqueana* (Neosho mucket). The EC_{50} for foot movement (a measure of viability) for newly transformed juveniles of this species was 188 µg Pb/L. Other aquatic invertebrates such as odonates may be tolerant of Pb concentrations that greatly exceed Pb detected in aquatic ecosystems.

Terrestrial invertebrates typically tolerate high concentrations of Pb relative to concentrations found in most uncontaminated soils. In the 1986 Pb AQCD it was reported that Pb at environmental concentrations occasionally found near roadsides and smelters (10,000 to 40,000 µg Pb/g dry weight [mg Pb/kg]) can eliminate populations of bacteria and fungi on leaf surfaces and in soil. LC_{50} values for soil nematodes vary from 10-1,550 mg Pb/kg dry weight dependent upon soil organic matter content and soil pH (U.S. EPA, 2006b). In earthworms, 14 and 28 day LC_{50} values typically fall in the range of 2,400-5,800 mg Pb/kg depending upon the species tested.

Data on mortality of saltwater species associated with exposure to Pb is limited; however, in general, marine organisms are less sensitive to this metal than freshwater organisms and the highest toxicity is observed in juveniles. In one study, effects of Pb on survival at environmentally relevant concentrations of Pb in diet have been demonstrated through a simulated marine food chain in which the primary producer, the microalgae *Tetraselmis suecica*, was exposed nominally to 20 µg Pb/L and subsequently fed to brine shrimp *Artemia franciscana*, (mean Pb content 12 to 15 µg Pb/g) which were consumed by white-leg shrimp *Litopenaeus vannamei*, itself consumed by grunt fish *Haemulon scudderi* representing the top of the marine food chain (Soto-Jiménez et al., 2011b). Survival of brine shrimp was 25 to 35% lower than the control and both white shrimp and grunt fish had significantly higher mortalities than controls.

In vertebrates, toxicity is observed in terrestrial avian and mammalian species in laboratory studies over a wide range of doses (<1 to >1,000 mg Pb/kg body weight per day) as reviewed for the development of ecological soil screening levels (Eco-SSLs) (U.S. EPA, 2005b). The NOAELs for survival ranged from 3.5 to 3,200 mg Pb/kg per day. In freshwater vertebrates there is considerable historic information on Pb toxicity to fish. Recent studies support earlier AQCD findings of Pb effects on fish survival and indicate effects at lower concentrations when testing with juvenile lifestages. In a series of 96-hour acute toxicity tests with fathead minnow conducted in a variety of natural waters across North America, LC_{50} values ranged from 41 to 3,598 µg Pb/L and no Pb toxicity occurred in three highly alkaline waters (Esbaugh et al., 2011). Thirty day

LC_{50} values for larval fathead minnows ranged from 39 to 1,903 µg Pb/L in varying concentrations of DOC and Ca^{2+} (as $CaSO_4$) (Grosell et al., 2006a). In a recent study of rainbow trout fry at 2-4 weeks post-swim up, the 96-hour LC_{50} was 120 µg Pb/L at a hardness of 29 mg/L as calcium carbonate ($CaCO_3$), a value much lower than in testing with older fish (Mebane et al., 2008). In the same study, two chronic (>60 day) tests were conducted with rainbow trout and the LC_{20} values for survival were 34 µg Pb/L in the 69 day test and 113 µg Pb/L in the 62 day test.

1.7.3.4 Neurobehavioral Effects

Overall, the evidence from terrestrial and freshwater systems is sufficient to conclude that a causal relationship is likely to exist between Pb exposures and neurobehavioral effects in invertebrates and vertebrates (Sections 6.3.12.4 and 6.4.12.4). Evidence is inadequate to conclude that there is a causal relationship between Pb exposure and neurobehavioral endpoints in saltwater species (Section 6.4.21.4).

Observations from laboratory studies reported in Chapter 6 and previous Pb AQCDs have shown adverse effects of Pb on neurological endpoints in both terrestrial and freshwater animal taxa. Studies that consider mode-of-action and molecular targets of Pb toxicity in biota are now available for a few species. Recent studies have continued adding to the evidence from both invertebrate and vertebrate studies that Pb adversely affects behaviors such as food consumption, avoidance, and escape from predators, behavioral thermoregulation, and prey capture. These changes are likely to decrease the overall fitness of the organism. Recent evidence includes reports of behavioral responses across a larger variety of organisms including fish larvae born from Pb-exposed adults and reptiles, while some impairments in feeding and escaping behaviors were reported for the first time.

Central nervous system effects in fish recognized in previous Pb AQCDs include effects on spinal neurons and brain receptors. Recent evidence from this review identifies possible molecular targets for Pb neurotoxicity in fish. Additionally, there is recent evidence for neurotoxic action of Pb in invertebrates with exposure to Pb observed to cause changes in the morphology of gamma aminobutyric acid (GABA)-motor neurons in nematodes (*Caenorhabditis elegans*) (Du and Wang, 2009).

Decreased food consumption of Pb-contaminated diet has been demonstrated in some invertebrates (snails) and vertebrates (lizards, pigs, fish). Behavioral effects in grunt fish *H. scudderi*, occupying the top level of a simulated marine food chain included lethargy and decreased food intake in a 42-day feeding study (Soto-Jiménez et al., 2011b). These fish were fed white shrimp exposed to Pb via brine shrimp that were initially fed

microalgae cultured nominally at 20 µg Pb/L. In the same study, surfacing, reduction of motility, and erratic swimming were observed in the white shrimp after 30 days of exposure to Pb via diet. Pb may also decrease the ability of an organism to capture prey or escape predation. For example, Pb exposure has been demonstrated to adversely affect prey capture ability of certain fungal and fish species, and the motility of nematodes was adversely affected in Pb-contaminated soils (Wang and Xing, 2008). Prey capture ability was decreased in 10-day-old fathead minnows born from adult fish exposed to 120 µg Pb/L for 300 days, then subsequently tested in a 21-day breeding assay (Mager et al., 2010). Altered pattern of escape swimming in larval zebrafish exposed to Pb as embryos was reported at low nominal concentrations of Pb (2 and 6 µg Pb/L). Other behavioral effects of Pb observed in fish include increased hyperactivity and decreased ability to detect visual contrast. In a laboratory study, Pb-exposed gull chicks exhibited abnormal behaviors such as decreased walking, erratic behavioral thermoregulation and food begging that could make them more vulnerable in the wild (Burger and Gochfeld, 2005). The chicks were exposed to Pb via injection to produce feather Pb concentration approximately equivalent to those observed in wild gulls. Lizards exposed to Pb through diet in the laboratory exhibited abnormal coloration and posturing behaviors. These findings show strong coherence with findings from studies in laboratory animals that show that Pb induces changes in learning and memory (Section 4.3.2.3), as well as attention (Section 4.3.3) and motor function (Section 4.3.7).

1.7.3.5 Hematological Effects

Based on observations in both terrestrial and freshwater organisms and additionally supported by toxicological and epidemiological findings in laboratory animals and humans, evidence is sufficient to conclude that there is a causal relationship between Pb exposures and hematological effects in terrestrial and aquatic vertebrates (Sections 6.3.12.5 and 6.4.12.5). The evidence is sufficient to conclude that a causal relationship is likely to exist between Pb exposures and hematological effects in freshwater invertebrates and inadequate to conclude that there is a causal relationship between Pb exposures and hematological effects in terrestrial invertebrates. Limited evidence from marine invertebrates is suggestive of a causal relationship between Pb exposures and hematological effects (Section 6.4.21.5). The mode of action of Pb on ALAD activity is likely mediated through a common pathway in terrestrial, freshwater and saltwater organisms.

Recent studies add support to the strong body of evidence presented in Pb AQCDs that Pb exposure is associated with hematological responses in terrestrial and aquatic vertebrates. Lower ALAD activity has been significantly correlated with elevated blood

Pb levels in fish and mammals. In the 1986 Pb AQCD, decreases in RBC ALAD activity following Pb exposure were well documented in birds and mammals (U.S. EPA, 1986a). The draft *Ambient Aquatic Life Water Quality Criteria for Lead* summarized several studies of ALAD activity in fish (U.S. EPA, 2008b). Further evidence from the 2006 Pb AQCD and this review suggests that this enzyme is an indicator for Pb exposure across a wide range of taxa. Since the 2006 Pb AQCD, evidence of Pb effects on ALAD activity has been found in additional species of invertebrates and fish, and has been identified in bacteria. ALAD activity has been shown to vary greatly between species. In addition to consideration of ALAD activity, there is recent evidence for deceased white blood cell counts in amphibians affected by Pb exposure. The consistency and coherence of these findings of effects on ALAD activity in vertebrates are also supported by some evidence of Pb-induced alterations of blood chemistry in fish reported in the 2006 Pb AQCD (U.S. EPA, 2006b). This evidence is strongly coherent with observations from human epidemiologic and animal toxicology studies where a causal relationship was identified between Pb exposure and decreased RBC survival and function, and altered heme synthesis in humans and laboratory animals (Sections 1.6.5 and 4.7).

In environmental assessments of metal-impacted habitats, ALAD is a recognized biomarker of Pb exposure in invertebrates as well as vertebrates (U.S. EPA, 2006b). Recent field studies of ALAD activity include observations in songbirds and owls near historical mining areas and in bivalves collected from freshwater and estuarine environments. Evidence for hematological effects of Pb in saltwater invertebrates is limited primarily to field monitoring studies with bivalves.

1.7.3.6 Effects on Physiological Stress

Evidence is sufficient to conclude that there is a causal relationship between Pb exposures and physiological stress in terrestrial plants (Section 6.3.12.6). Evidence is sufficient to conclude that a causal relationship is likely to exist between Pb exposures and physiological stress in terrestrial invertebrates and vertebrates (Section 6.3.12.6) as well as freshwater plants, invertebrates and vertebrates (Section 6.4.12.6). Further evidence in saltwater invertebrates is suggestive of a causal relationship between Pb exposures and physiological stress (Section 6.4.21.6). Evidence is inadequate to conclude that there is a causal relationship between Pb exposure and physiological stress responses in saltwater plants and vertebrates.

Endpoints associated with physiological stress received no consideration prior to the 2006 Pb AQCD. Studies reviewed in the 2006 Pb AQCD reported stress-related effects including upregulation of antioxidant enzymes and increased lipid peroxidation (U.S.

EPA, 2006b). Recent evidence in additional species of terrestrial and freshwater plants, invertebrates and vertebrates support, and expand upon findings in the previous Pb AQCD. Some of these studies report findings within one to two orders of magnitude of the range of Pb concentrations measured in terrestrial and freshwater environments (Table 1-1). Recent studies include evidence for production of reactive oxygen species in terrestrial plant species and in freshwater algae and fish in response to Pb exposure.

In the current document and the 2006 Pb AQCD (U.S. EPA, 2006b), there is strong evidence of upregulation of antioxidant enzymes and increased lipid peroxidation associated with Pb exposure in many species of plants, invertebrates and vertebrates. In plants, increases of antioxidant enzymes with Pb exposure occur in algae, aquatic mosses, floating and rooted aquatic macrophytes, and terrestrial species. Most observations of antioxidant responses in plants typically occur at concentrations of Pb higher than found in the environment. However, in a few terrestrial plant species, increases of antioxidant enzymes occur at concentrations approaching the average Pb concentrations in U.S. soils (Table 1-1) and limited transplantation studies with aquatic plants indicate elevated antioxidant enzyme activity associated with Pb levels measured in sediments at polluted sites. There is evidence for antioxidant activity in invertebrates, including gastropods, mussels, and crustaceans, in response to Pb exposure. Some recent evidence for invertebrate antioxidant responses in freshwater bivalves, and marine bivalve and crustacean species indicates effects at Pb concentrations associated with polluted sites. Markers of oxidative damage are also observed in fish, amphibians, and mammals, both in the laboratory and in exposed natural environments. Across all biota, there are differences in the induction of antioxidant enzymes that appear to be species-dependent.

Additional stress responses observed in terrestrial and freshwater invertebrates include elevated heat shock proteins, osmotic stress and decreased glycogen levels. Heat shock protein induction by Pb exposure has been observed in zebra mussels and mites. Tissue volume regulation is adversely affected in freshwater crabs and glycogen levels decreased in freshwater snails following Pb exposure. Although correlated with Pb exposure, these responses are non-specific and may be altered with exposure to any number of environmental stressors.

Upregulation of antioxidant enzymes and increased lipid peroxidation are considered to be reliable biomarkers of stress, and suggest that Pb exposure induces a stress response in those organisms, which may increase susceptibility to other stressors and reduce individual fitness. The oxidative stress responses associated with Pb exposure are consistent in terrestrial biota and in freshwater organisms. Furthermore, these responses are also observed in experimental animal studies.

1.7.3.7 Community and Ecosystem Effects

More evidence for Pb toxicity to terrestrial and aquatic biota has been reported from single-species assays in laboratory studies than from whole ecosystem studies. The evidence is strong for effects of Pb on growth, reproduction, and survival in very diverse species, but considerable uncertainties exist in generalizing effects observed under particular, small-scale conditions, up to the ecosystem level of biological organization. At the ecosystem level, the presence of multiple stressors, variability in field conditions, and differences in bioavailability of Pb make it difficult to measure the magnitude of effects, and to quantify relationships between ambient concentrations of Pb and ecosystem response. However, the cumulative evidence that has been reported for Pb effects at higher levels of biological organization and for endpoints in single species with direct relevance to population and ecosystem level effects (i.e., development and reproduction, growth, survival) is sufficient to conclude that a causal relationship is likely to exist between Pb exposures and the alteration of species richness, species composition and biodiversity in terrestrial and freshwater ecosystems (Sections 6.3.12.7 and 6.4.12.7). Evidence is inadequate to conclude that there is a causal relationship between Pb exposure and effects at higher levels of biological organization in saltwater ecosystems (Section 6.4.21.7).

Ecosystem-level studies *in situ* are complicated by the frequent confounding of Pb exposure in Pb-polluted sites with other factors such as other trace metals and acidic deposition. In those natural systems, Pb is often found co-existing with other stressors, and observed effects may be due to cumulative toxicity. In laboratory studies and simulated ecosystems, where it is possible to isolate the effect of Pb, this metal has been shown to alter competitive behavior of species, predator-prey interactions, and contaminant avoidance. At higher levels of biological organization, these effects may change species abundance and community structure. Uptake of Pb into aquatic and terrestrial organisms and its effects on survival, growth, and reproductive endpoints at the organism level are expected to have ecosystem-level consequences. Where evidence of effects is observed at the ecosystem level of organization, evidence from lower levels brings consistency and plausibility for causality.

Most direct evidence of community and ecosystem level effects is from near stationary sources and contaminated sites where Pb concentrations are higher than typically observed in the environment. For terrestrial systems, evidence of impacts on natural ecosystems near smelters, mines, and other industrial sources of Pb has been assembled in previous decades. Those impacts include decreases in species diversity and changes in floral and faunal community composition. For freshwater systems, the literature focuses on evaluating ecological stress from Pb originating from urban and mining effluents

rather than atmospheric deposition. Some organisms exhibit contaminant avoidance behaviors when exposed to Pb-contaminated areas. For example, snails and fish avoid higher concentrations of Pb while frogs and toads lack avoidance response. Recent evidence, published since the 2006 Pb AQCD indicates that some species of worms will avoid Pb-contaminated soils (Langdon et al., 2005).These dynamics are likely to change species abundance and community structure at higher levels of biological organization.

Recent studies continue to demonstrate associations between Pb exposures and effects at higher levels of biological organization that were shown in field and microcosm studies in previous Pb AQCDs. Recent studies on plant and soil microbial communities and sediment-associated and aquatic plant communities increase the total number of types of ecological associations impacted by Pb. In terrestrial ecosystems, most studies show decreases in microorganism abundance, diversity, and function with increasing soil Pb concentration. Specifically, shifts in nematode communities, bacterial species, and fungal diversity have been observed. Furthermore, presence of arbuscular mycorrhizal fungi may protect plants growing in Pb-contaminated soils. Increased plant diversity ameliorated effects of Pb contamination on a microbial community.

In aquatic ecosystems, Pb effects reviewed in the 2006 Pb AQCD (U.S. EPA, 2006b) included reduced species abundance, richness and diversity, decreased primary productivity, and altered predator-prey interactions. Since the 2006 Pb AQCD, there is further evidence for effects of Pb in sediment-associated communities in both saltwater and freshwater systems. Community structure and nematode diversity were altered in a microcosm study with marine sediments (Mahmoudi et al., 2007). Sediment-bound Pb contamination appears to differentially affect members of the benthic invertebrate community, potentially altering ecosystem dynamics in small urban streams (Kominkova and Nabelkova, 2005). Although surface water Pb concentrations in monitored streams were determined to be very low, concentrations of the metal in sediment were high enough to pose a risk to the benthic community (e.g., 34-101 mg Pb/kg). These risks were observed to be linked to benthic invertebrate functional feeding group, with collector-gatherer species exhibiting larger body burdens of heavy metals than benthic predators and collector-filterers.

Changes to aquatic plant community composition have been observed in the presence of elevated surface water Pb concentrations. A shift toward more Pb-tolerant species is also observed in terrestrial plant communities near smelter sites (U.S. EPA, 2006b). Certain types of plants such as rooted and submerged aquatic plants may be more susceptible to aerially-deposited Pb resulting in shifts in Pb community composition. High Pb sediment concentrations are linked to shifts in amphipod communities inhabiting plant structures.

1.8 Integration of Health and Ecological Effects

The health and ecological effects considered for causal determination are summarized in Table 1-4. The health outcomes were those related to the nervous, cardiovascular, renal, and immune system, effects on heme synthesis and RBC function, reproductive and developmental effects, and cancer. The ecological endpoints considered for causal determination were: community and ecosystem level effects, reproductive and developmental effects, growth, survival, neurobehavioral effects, hematological effects, and physiological stress. The evidence relating to specific ecological endpoints is also integrated across aquatic and terrestrial habitats. Further, the substantial overlap between the ecological and health endpoints considered in the causal determinations allowed the integration of the evidence across these disciplines.

Table 1-4 Summary of causal determinations for health and ecological effects.

Outcome/Effect	Human Health Causal Determination[a]	Ecological Receptors Causal Determination[a]
Nervous System Effects[b]	Causal Relationship: Cognition, Attention, Impulsivity and Hyperactivity in Children	Likely Causal Relationship: Neurobehavioral Effects in Terrestrial and Freshwater Invertebrates and Vertebrates
Cardiovascular Effects	Causal Relationship: Hypertension and Coronary Heart Disease	N/A[e]
Renal Effects	Likely Causal Relationship: Reduced Kidney Function	N/A[e]
Immune Effects	Likely Causal Relationship: Atopic and Inflammatory Conditions, Decreased Host Resistance	N/A[e]
Hematological Effects[c]	Causal Relationship: RBC Function and Survival, Altered Heme Synthesis	Causal Relationship: ALAD Activity in Terrestrial and Freshwater Vertebrates Likely Causal Relationship: ALAD activity in Freshwater Invertebrates
Reproductive and Developmental Effects[d]	Causal Relationship: Development and Male Reproductive Function	Causal Relationship: Invertebrates and Vertebrates
Cancer	Likely to be a causal relationship	N/A[e]

Table 1-4 (Continued): Summary of causal determinations for health and ecological effects.

Outcome/Effect	Human Health Causal Determination[a]	Ecological Receptors Causal Determination[a]
Mortality	N/A[e] (The strongest evidence of Pb-induced mortality in humans was observed for cardiovascular disease related mortality and this evidence was considered in determining the causal relationship between Pb exposure and coronary heart disease.)	Causal Relationship: Survival Terrestrial Invertebrates and Freshwater Invertebrates and Vertebrates Likely Causal Relationship: Terrestrial Vertebrates
Growth	N/A[e] (There is mixed evidence from toxicological and epidemiologic studies of Pb effects on postnatal growth, which was considered in determining the causal association between Pb exposure and developmental effects.)	Causal Relationship: Terrestrial Plants and Freshwater Invertebrates Likely Causal Relationship: Freshwater Plants and Terrestrial Invertebrates
Physiological Stress	N/A[e] (In Human Health, oxidative stress was considered as an upstream event in the modes of action of Pb, leading downstream to various effects. Ecological literature commonly uses oxidative stress as a proxy indicator of overall fitness, and thus treats it as an effect.)	Causal Relationship: Terrestrial Plants Likely Causal Relationship: Terrestrial and Freshwater Invertebrates and Vertebrates and Freshwater Plants
Community and Ecosystem Level Effects	N/A[e]	Likely Causal Relationship: Terrestrial and Freshwater Ecosystems

[a] In drawing conclusions regarding the causal relationship between Pb exposure and human health effects, evidence in the range of relevant pollutant exposures or biomarker levels was considered. Evidence from toxicological studies of effects observed in experimental animals at biomarker levels (e.g. blood Pb) comparable to those currently experienced by the U.S. general population were emphasized. Generally, studies with dietary exposures resulting in blood Pb levels within one order of magnitude above the upper end of the distribution of U.S. blood Pb levels were considered in forming concusions, with the majority of studies reporting blood Pb levels below 30 µg/dLIn forming conclusions, Ecological effects observed at or near ambient Pb concentrations measured in soil, sediment and water in the most recent available studies (Table 1-1) were emphasized and studies generally within one to two orders of magnitude above the reported range of these values were considered in the body of evidence for terrestrial, freshwater and saltwater ecosystems.

[b] In ecological receptors, the causal determination was developed considering neurobehavioral effects that can be observed in toxicological studies of animal models and studies of ecological effects in vertebrates and invertebrates.

[c] The ecological evidence considered for the causal determination included ALAD activity, blood cell count, and altered serum profiles.

[d] For health effects the strongest evidence was for delayed onset of puberty and detrimental effects on sperm. In the ecological literature, a wide range of endpoints, including embryonic development, multigenerational studies, delayed metamorphosis, and altered steroid profiles, was considered.

[e] N/A, not applicable, i.e., Endpoints were not directly comparable for the health and ecological evidence.

1.8.1 Modes of Action Relevant to Downstream Health and Ecological Effects

The diverse health and ecological effects of Pb are mediated through multiple, interconnected modes of action. This section summarizes the principal cellular/subcellular effects contributing to modes of action for human health endpoints associated with Pb exposure and the concentrations at which those effects are observed. Then, effects of Pb observed in aquatic and terrestrial species (Section 1.7) are evaluated along with evidence from epidemiological and laboratory animal studies to determine the extent to which common modes of action can be inferred from the observed effects. The rationale for this approach is that the mechanism of Pb toxicity is likely conserved from invertebrates to vertebrates to humans in some organ systems.

Each of the modes of action discussed in Section 4.2 has the potential to contribute to the development of a number of Pb-induced health effects (Table 1-4). Evidence for the majority of these modes of action is observed at low blood Pb levels in humans and laboratory animals, between 2 and 5 µg/dL, and at doses as low as the picomolar range in animals and cells. The concentrations eliciting the modes of action (reported in Table 1-5) are drawn from the available data and do not imply that these modes of action are not acting at lower exposure levels or that these doses represent the threshold of the effect. Also, the data in presented this table does not inform regarding the exposure frequency and duration required to elicit a particular MOA.

Ecosystem studies have presented evidence for the occurrence of many of these modes of action in animals, and to some degree in plants, however the connection to ecological outcomes must usually be inferred because ecological studies are typically not designed to address mode of action directly. The level at which Pb elicits a specific effect is more difficult to establish in terrestrial and aquatic systems due to the influence of environmental variables on Pb bioavailability and toxicity and substantial species differences in Pb susceptibility.

Table 1-5 Modes of action, their related health effects, and information on concentrations eliciting the MOAs.

Mode of Action [Related Health Effects (ISA Section)]	Concentrations or Doses (Conditions)[a]	
	Blood Pb	**Dose**
Altered Ion Status [All Health Effects of Pb; Chapter 4]	3.5 µg/dL (Mean in cord blood; association with cord blood Ca^{2+}ATPase pump activity) Huel et al. (2008)	0.00005 µM free Pb^{2+} (In vitro; 30 minutes; calmodulin activation assay) Kern et al. (2000)
Protein Binding [Renal (4.5), Heme Synthesis and RBC Function (4.7)]	17.0 µg/dL (Concurrent mean in adult workers with wildtype metallothionein expression; increased BP susceptibility) Chen et al. (2010a)	50 µM Pb glutamate (In vitro; 24 hours; increased nuclear protein in neurological cell) Klann and Shelton (1989)
Oxidative Stress [All Heath Effects of Pb (Chapter 4)]	5.4 µg/dL (Concurrent mean in adult male workers; decreased CAT activity in blood) Conterato et al. (2013)	0.1 µM Pb acetate (In vitro; 48 hours; decreased cellular GSH in neuroblastoma cells) Chetty et al. (2005)
Inflammation [Nervous System (4.3), Cardiovascular (4.4), Renal (4.5), Immune (4.6), Respiratory (4.6.5 and 4.9.6), Hepatic (4.9.1)]	Among males with concurrent blood Pb ≥ 2.5 µg/dL (Increased serum TNF-α and blood WBC count) Kim et al. (2007)	0.01 µM Pb acetate (In vitro; 48 hours; increased cellular PGE_2 in neuroblastoma cells) Chetty et al. (2005)
Endocrine Disruption [Reproductive and Developmental Effects (4.8), Endocrine System (4.9.3) , Bone and Teeth (4.9.4)]	1.7 µg/dL (Lowest blood Pb level at which a relationship could be detected in adult women with both ovaries removed; increased serum follicle stimulating hormone [FSH]) Krieg (2007)	10 µM Pb nitrate (In vitro; 30 minutes; displaced GHRH binding to rat pituitary receptors) Lau et al. (1991)
Cell Death/Genotoxicity [Cancer (4.10), Reproductive and Developmental Effects (4.8), Bone and Teeth (4.9.4)]	3.3 µg/dL (Concurrent median in adult women; increased rate of hypoxanthine guanine phospho ribosyltransferase reporter gene [HPRT] mutation frequency) Van et al. (2004)	0.03 µM Pb acetate (In vitro; 18 hours; increased formation of micronuclei) Bonacker et al. (2005)

[a]This table provides examples of studies that report effects with low doses or concentration; they are not the full body of evidence used to characterize the weight of the evidence. In addition, the levels cited are reflective of the data and methods available and do not imply that these modes of action are not acting at lower Pb exposure or blood Pb levels or that these doses represent the threshold of the effect. Additionally, the blood concentrations and doses (indicating Pb exposure concentrations from in vitro systems) refer to the concentrations and doses at which these modes of action were observed. While the individual modes of action are related back to specific health effects sections (e.g., Nervous System, Cardiovascular), the concentrations and doses given should not be interpreted as levels at which those specific health effects occur.

The alteration of cellular ion status (including disruption of Ca^{2+} homeostasis, altered ion transport mechanisms, and perturbed protein function through displacement of metal cofactors) appears to be the major unifying mode of action underlying all subsequent modes of action in plants, animals, and humans (Figure 4-1). Pb can interfere with endogenous cation homeostasis, necessary as a cell signal carrier mediating normal cellular functions. Pb is able to displace metal ions, such as Zn, Mg, and Ca^{2+}, from proteins due to the flexible coordination numbers and multiple ligand binding ability of Pb, leading to abnormal conformational changes to proteins and altered protein function. Disruption of ion transport leading to increased intracellular Ca^{2+} levels is due in part to the alteration of the activity of transport channels and proteins, such as Na^{+}/K^{+}ATPase and voltage-sensitive Ca^{2+} channels. Pb can interfere with these proteins through direct competition between Pb and the native metals present in the protein metal binding domain or through disruption of proteins important in Ca^{2+}-dependent cell signaling, such as protein kinase C (PKC) or calmodulin.

This competition between metals has been reported not only in human systems, but also in fish, snails, and plants. Altered Ca^{2+} channel activity and binding of Pb with Na^{+}/K^{+}ATPase in the gills of fish disrupts the Na^{+} and Cl^{-} homeostasis, which may lead to ionoregulatory failure and death. Ca^{2+} influx and ionoregulation has also been shown to be inhibited by Pb exposure in a sensitive species of snail, leading to a reduction in snail growth. In plants, substitution of the central atom of chlorophyll, Mg, by Pb prevents light-harvesting, resulting in a breakdown of photosynthesis. Pb-exposed animals also have decreased cellular energy production due to perturbation of mitochondrial function.

Disruption of ion transport not only leads to altered Ca^{2+} homeostasis, but can also result in perturbed neurotransmitter function. Evidence for these effects in Pb-exposed experimental animals and cell cultures has been linked to altered neurobehavioral endpoints and other neurotoxicity. Neurobehavioral changes that may decrease the overall fitness of the organism have also been observed in aquatic and terrestrial invertebrate and vertebrate studies. There is evidence in tadpoles and fish to suggest Pb may alter neurotransmitter concentrations, possibly resulting in some of these neurobehavioral changes.

Altered cellular ion status following Pb exposure can result in the inhibition of heme synthesis. Pb exposure is commonly associated with altered hematological responses in aquatic and terrestrial invertebrates, experimental animals, and human subjects. The proteins involved in heme synthesis that are affected by Pb are highly conserved across species, which may account for the common response seen in human health and ecological studies. This evolutionarily conserved response to Pb is likely the result of the

competition of Pb with the necessary metal cofactors in the proteins involved in heme synthesis.

Although Pb will bind to proteins within cells through interactions with side group moieties, thus potentially disrupting cellular function, protein binding of Pb may represent a mechanism by which cells protect themselves against the toxic effects of Pb. Intranuclear and intracytosolic inclusion body formation has been observed in the kidney, liver, lung, and brain following Pb exposure in experimental animals. A number of unique Pb binding proteins have been detected, constituting the observed inclusion bodies. The major Pb binding protein in blood is ALAD with carriers of the ALAD-2 allele potentially exhibiting higher Pb binding affinity. Inhibition of ALAD activity is a widely recognized response to Pb in environments where Pb is present and is considered to be biomarker of Pb exposure in both terrestrial and aquatic biota. Additionally, metallothionein is an important protein in the formation of inclusion bodies and mitigation of the toxic effects of Pb. Protein binding of Pb is a recognized mechanism of Pb detoxification in some terrestrial and aquatic biota. For example, plants can sequester Pb through binding with phytochelatin and some fish have the ability to store accumulated Pb in heat-stable proteins.

A second major mode of action of Pb is the development of oxidative stress, due in many instances to the antagonism of normal metal ion functions. Disturbances of the normal redox state of tissues can cause toxic effects and is involved in the majority of health and ecological outcomes observed after Pb exposure. The origin of oxidative stress produced after Pb exposure is likely a multi-pathway process. Studies in humans and experimental animals provide evidence to conclude that oxidative stress results from oxidation of δ-ALA, NAD(P)H oxidase activation, membrane and lipid peroxidation, and antioxidant enzyme depletion. Evidence of increased lipid peroxidation associated with Pb exposure exists for many species of plants, invertebrates, and vertebrates. Enhanced lipid peroxidation can also result from Pb potentiation of Fe^{2+} initiated lipid peroxidation and alteration of membrane composition after Pb exposure. Increased Pb-induced ROS will also sequester and inactivate biologically active nitric oxide or nitric oxide radical (NO), leading to the increased production of the toxic product nitrotyrosine, increased compensatory NOS, and decreased sGC protein. Pb-induced oxidative stress not only results from increased ROS production but also through the alteration and reduction in activity of the antioxidant defense enzymes. The biological actions of a number of these enzymes are antagonized due to the displacement of the protein functional metal ions by Pb. Increased ROS are often followed by a compensatory and protective upregulation in antioxidant enzymes, such that this observation is indicative of oxidative stress conditions. A number of studies in plants, invertebrates, and vertebrates present evidence of increased antioxidant enzymes with Pb exposure. Additionally, continuous ROS

production may overwhelm this defensive process leading to decreased antioxidant activity and further oxidative stress and injury.

In a number of organ systems Pb-induced oxidative stress is accompanied by misregulated inflammation. Pb exposure will modulate inflammatory cell function, production of proinflammatory cytokines and metabolites, inflammatory chemical messengers, and proinflammatory signaling cascades. Cytokine production is skewed toward the production of proinflammatory cytokines like TNF-α and IL-6 as well as leading to the promotion of Th2 response and suppression of Th1cytokines and Th1-related responses.

Pb is a potent endocrine disrupting chemical. Steroid receptors and some endocrine signaling pathways are known to be highly conserved over a broad expanse of animal phylogeny. Pb can disrupt the HPG axis evidenced in humans, other mammals, and fish, by a decrease in serum hormone levels, such as FSH, LH, testosterone, and estradiol. Pb interacts with the hypothalamic-pituitary level hormone control causing a decrease in pituitary hormones, altered growth dynamics, inhibition of LH secretion, and reduction in StAR protein. Pb has also been shown to alter hormone receptor binding likely due to interference of metal cations in secondary messenger systems and receptor ligand binding and through generation of ROS. Pb disrupts hormonal homeostasis in invertebrates necessary for reproduction and development. Pb also may disrupt the HPT axis by alteration of a number of thyroid hormones, possibly due to oxidative stress. These studies have been conducted in humans and other animals, including cattle; however the results of these studies are mixed.

Genotoxicity and cell death has been investigated after Pb exposure in humans, animals, plants, and cell models. High level Pb exposure to humans leads to increased DNA damage, however lower blood Pb levels have been associated with these effects in experimental animals and cells. Reports vary on the effect of Pb on DNA repair activity; however, a number of studies report decreased repair processes following Pb exposure. There is some evidence in plants, earthworms, freshwater mussels and fish for DNA damage associated with Pb exposure. There is evidence of mutagenesis and clastogenicity in highly exposed humans, however weak evidence has been shown in animals and cells based systems. Human occupational studies provide limited evidence for micronucleus formation (blood Pb levels >10 µg/dL), supported by Pb-induced effects in both animal and cell studies. Micronucleus formation has also been reported in amphibians. Animal and plant studies have also provided evidence for Pb-induced chromosomal aberrations. The observed increases in clastogenicity may be the result of increased oxidative damage to DNA due to Pb exposure, as co-exposures with antioxidants ameliorate the observed toxicities. Limited evidence of epigenetic effects is available, including DNA

methylation, mitogenesis, and gene expression. Altered gene expression may come about through Pb displacing Zn from multiple transcriptional factors, and thus perturbing their normal cellular activities. Consistently positive results have provided evidence of increased apoptosis of various cell types following Pb exposure.

Overall, Pb-induced health and ecological effects can occur through a number of interconnected and evolutionarily well conserved modes of action that generally originate with the alteration of ion status.

1.9 Policy Relevant Considerations

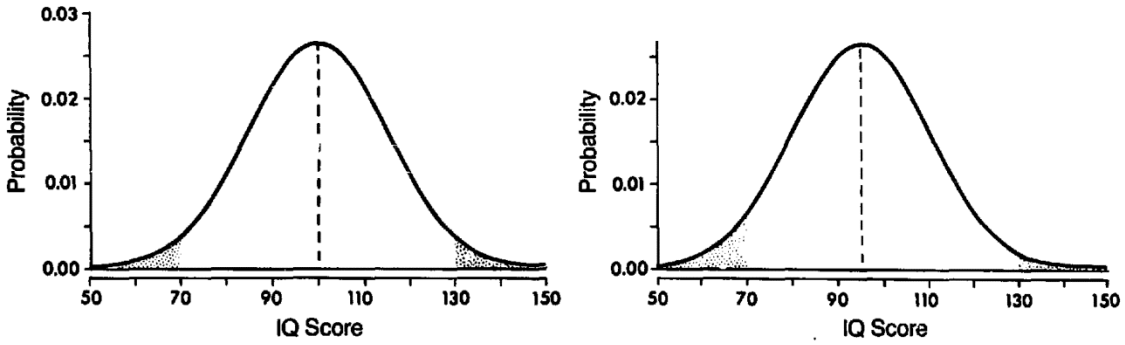
1.9.1 Public Health Significance

The rationale for establishing the public health significance of the various health endpoints associated with Pb exposure is multifaceted. The 2006 Pb AQCD (U.S. EPA, 2006b) concluded that neurodevelopmental effects in children and cardiovascular effects in adults were among the effects best substantiated as occurring at the lowest blood Pb levels, and that these categories of effects were clearly of the greatest public health concern. The evidence reviewed in the current assessment supports and builds upon this conclusion. Evidence in a few cohorts of children that indicated the supralinear concentration-response blood Pb-FSIQ relationships, did not identify a threshold for Pb-associated neurodevelopmental effects in the range of blood Pb levels examined (Sections 1.9.3 and 4.3.13).

The World Health Organization (WHO) definition of "health" is "the state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO, 1948). By this definition, decrements in health status that are not severe enough to result in the assignment of a clinical diagnosis might reflect a decrement in the well-being of an individual. Further, deficits in subtle indices of health or well-being may not be observable except in aggregate, at the population level, so the critical distinction between population and individual risk is essential for interpreting the public health significance of study findings. This concept of population risk is relevant to the interpretation of findings regarding both IQ and blood pressure in the assessment of their public health significance.

Weiss et al. (1988) discusses the hypothetical impact of a small shift in a population distribution of IQ Score. As shown in Figure 1-1, these authors anticipate that even a small shift in the population mean IQ may be significant from a public health perspective because such a shift could yield a larger proportion of individuals functioning in the low

range of the IQ distribution, which is associated with increased risk of educational, vocational, and social failure (Section 4.3.13), as well as reduce the proportion of individuals with high IQ scores.



Note: Two distributions of intelligence test scores. (Left): Based on a mean of 100 (the standardized average, with a standard deviation of 15. (Right):Demonstrating a 5% reduction model, based on a mean score of 95. This is a conceptual model that assumes that the incremental concentration-response between Pb exposure and IQ is similar across the full range of IQ, and is not based on actual data. The figure shows that the effect of a small shift in population mean IQ score may result in a larger proportion of individuals with IQ scores below 70 and a smaller proportion with IQ scores above 130.

Source: Reprinted with permission of Elsevier; from Weiss et al. (1988)

Figure 1-1 Distributions of IQ scores.

It is also important to note that the change in a population mean observed in an epidemiologic study may be small compared to the standard error of measurement for the outcome. Measurement error in the outcome can affect the likelihood of detecting an association but if a study is large enough it will have adequate statistical power to detect small changes at the population level. Bias may be introduced if the measurement error of the outcome is highly correlated with the exposure. There is no evidence to suggest that individuals with higher blood Pb levels test systematically lower than their true IQ.

Pb-associated changes in blood pressure also increase an individual's risk for health effects that are of greater clinical consequence than is suggested by a small individual change in blood pressure. Nawrot et al. (2002) found that a doubling of blood Pb was associated with an approximate 1 mmHg increase in systolic blood pressure. Results from the Framingham Heart Study show that higher levels of blood pressure, even within the nonhypertensive range, increase the risk of cardiovascular disease (Kannel, 2000a, b). A continuous graded increase in cardiovascular risk is observed as blood pressure increases, with no evidence of a threshold value. Most events arise not in the most severe

cases, but mainly in those with high normal blood pressure (i.e., mild hypertension). Kannel (2000a) emphasized that systolic blood pressure exerts a strong influence on more serious cardiovascular events, as it is the primary cause of hypertension and its adverse cardiovascular sequelae. Pb-associated effects on cardiovascular morbidity outcomes such as ischemic heart disease (Section 4.4.3.6) and mortality (Section 4.4.5) have also been observed. In addition, some groups within the population can be at greater risks for cardiovascular effects; as summarized in Chapter 5, there is evidence for increased cardiovascular effects based on race/ethnicity and several genetic markers. Overall, while some of the specific health endpoints that have been associated with Pb exposure are small physiological changes in an individual, these changes can represent substantial risk at the population level.

1.9.2 Air-Pb–to–Blood-Pb Relationships

The 1986 Pb AQCD described epidemiologic studies of relationships between air Pb and blood Pb. Much of the pertinent earlier literature for children described in the 1986 Pb AQCD was included in a meta-analysis by Brunekreef (1984). Based on the studies available at that time, the 1986 Pb AQCD concluded that "the blood Pb versus air Pb slope β is much smaller at high blood and air levels." This is to say that the slope β was much smaller for occupational exposures where high blood Pb levels (>40 μg/dL) and high air Pb levels (much greater than 10 $\mu g/m^3$) prevailed relative to lower environmental exposures which showed lower blood Pb and air Pb concentrations (<30 μg/dL and <3 $\mu g/m^3$). For those environmental exposures, it was concluded that the relationship between blood Pb and air Pb "…for direct inhalation appears to be approximately linear in the range of normal ambient exposures (0.1-2.0 $\mu g/m^3$)" (pp 1–98 of the 1986 Pb AQCD). In addition to the meta-analysis of Brunekreef (1984), more recent studies have provided data from which estimates of the blood Pb-air Pb slope can be derived for children (Table 1-6, Table 3-12). The range of estimates from these studies is 4-9 μg/dL per $\mu g/m^3$, which encompasses the estimate from the Brunekreef (1984) meta-analysis. Most studies have described the blood Pb-air Pb relationship as either log-log (Schnaas et al., 2004; Hayes et al., 1994; Brunekreef, 1984), which predicts an increase in the blood Pb-air Pb slope with decreasing air Pb concentration or linear (Hilts, 2003; Tripathi et al., 2001; Schwartz and Pitcher, 1989), which predicts a constant blood Pb-air Pb slope regardless of air Pb concentrations. These differences may simply reflect model selection by the investigators; alternative models are not reported in these studies.

The blood Pb-air Pb slope may also be affected in some studies by the inclusion of parameters (e.g., soil Pb) that may account for some of the variance in blood Pb attributable to air Pb. Other factors that likely contribute to the derived blood Pb-air Pb

slope include differences in the populations examined and Pb sources, which varied among individual studies. See Section 3.5 for a detailed discussion of studies that inform air Pb-to blood-Pb relationships.

Table 1-6 Summary of estimated slopes for blood Pb to air Pb relationships in children.

Reference	Study Methods	Model Description	Blood Pb–Air Pb Slope[a]
Brunekreef (1984)	**Location:** Various countries **Years:** 1974-1983 **Subjects:** Children (varying age ranges, N>190,000) **Analysis:** Meta analysis of 96 child populations from 18 study locations	**Model:** Log-Log **Blood Pb:** 5-76 µg/dL (mean range for studies) **Air Pb:** 0.1-24 µg/m^3 (mean range for studies)	All children: 4.6 (1.5)[b] Children <20 µg/dL: 4.8 (0.54)[c]
Hayes et al. (1994)	**Location:** Chicago, IL **Years:** 1974-1988 **Subjects:** 0.5-5 yr (N = 9,604) **Analysis:** Regression of quarterly median blood Pb and quarterly mean air Pb	**Model:** Log-Log **Blood Pb:** 10-28 µg/dL (quarterly median range) **Air Pb:** 0.05-1.2 µg/m^3 (quarterly mean range)	8.2 (0.62)[d]
Hilts (2003)	**Location:** Trail, BC **Years:** 1996-2001 **Subjects:** 0.5-5 yr, 1996-2000; 0.5-3 yr, 2001 (Estimated N = 220-460, based on 292-536 blood Pb measurements/yr with 75-85% participation). **Analysis:** Regression of blood Pb screening and community air Pb following upgrading of a local smelter	**Model:** Linear **Blood Pb:** 4.7-11.5 µg/dL (annual geometric mean range) **Air Pb:** 0.03-1.1 µg/m^3 (annual geometric mean range)	7.0 (0.48)[e]
Schwartz and Pitcher (1989), U.S. EPA (1986a)	**Location:** Chicago, IL **Years:** 1976-1980 **Subjects**: Black children, 0-5 yr (N = 5,476) **Analysis:** Multivariate regression of blood Pb with mass of Pb in gasoline (derived from gasoline consumption data and Pb concentrations in gasoline for the U.S.)	Model: Linear **Blood Pb:** 18-27 µg/dL (mean range)[f] **Air Pb:** 0.36-1.22 µg/m^3 (annual maximum quarterly mean)[h]	8.6 (0.75)[g]

Table 1-6 (Continued): Summary of estimated slopes for blood Pb to air Pb relationships in children.

Reference	Study Methods	Model Description	Blood Pb–Air Pb Slope[a]
Tripathi et al. (2001)	**Location:** Mumbai, India (multiple residential locations) **Years:** 1984-1996 **Subjects:** 6-10 yr (N = 544) **Analysis:** Regression of residential location-specific average blood Pb and air Pb data	**Model:** Linear **Blood Pb:** 8.6-14.4 µg/dL (GM range for residential locations) **Air Pb:** 0.11-1.18 µg/m^3 (GM range for residential locations)	3.6 (0.45)[i]

[a]Slope is predicted change in blood Pb (µg/dL per µg/m^3) evaluated at ± 0.01 µg/m^3 from central estimate of air Pb for the study (shown in parentheses). The central estimate for the Brunekreef (1984) study, is the median of air Pb concentrations, since it was a meta-analysis; for all other studies the mean is presented. For multiple regression models, this is derived based only on air Pb coefficient and intercept. Depending on the extent to which other variables modeled also represent air Pb, this method may underestimate the slope attributable to air pathways. In single regression models, the extent to which non-modeled factors, unrelated to air Pb exposures, exert an impact on blood Pb that co-varies with air Pb may lead to the slope presented here to over represent the role of air Pb.

[b]ln(PbB) = ln(PbA) × 0.3485 + 2.853

[c]ln(PbB) = ln(PbA) × 0.2159 + 2.620

[d]ln(PbB) = ln(PbA) × 0.24 + 3.17

[e]PbB = PbA × 7.0

[f]Observed blood Pb values not provided; data are for regressed adjusted blood Pb.

[g]PbB = PbA × 8.6

[h]Based on data for the U.S. [1986 Pb AQCD, (U.S. EPA, 1986a)].

[i]PbB =Pb A × 3.6

GM, geometric mean; GSD, geometric standard deviation; PbB, blood Pb concentration (µg/dL); PbA, air-Pb concentration (µg/m^3)

1.9.3 Concentration-Response Relationships for Human Health Effects

Concentration response (C-R) relationships have been examined most extensively in studies of neurodevelopmental effects in children. Although relatively few studies examined the shape of the concentration-response relationship between Pb in blood or bone and effects in adults, several recent studies of adult endpoints (i.e., cognitive function, cardiovascular and mortality effects) add to the evidence. Some of the populations examined (e.g., NHANES, NAS) are likely to have had higher past than recent Pb exposure. Other populations (e.g., worker populations) studied have ongoing exposure to Pb. As described elsewhere in the document (Sections 3.3, 4.3, 4.4, and 4.5), the interpretation of the study findings depends on the exposure history and the choice of the biomarker in the context of what is known about that exposure history. There is uncertainty regarding the frequency, duration, timing and level of exposure contributing to the blood Pb or bone Pb levels in the adult populations studied.

Cognitive and Behavioral Effects in Children

With each successive Pb AQCD and supplement, the epidemiologic and toxicological study findings show that progressively lower blood Pb levels or Pb exposures are associated with cognitive deficits in children (Section 4.3.13). For example, effects were observed in association with blood Pb levels in the range of 10-15 µg/dL in the 1986 Addendum (U.S. EPA, 1986c) and 1990 Supplement (U.S. EPA, 1990a), and 10 µg/dL and lower in the 2006 Pb AQCD (U.S. EPA, 2006b). No evidence of a threshold for the effects of Pb on neurodevelopmental effects has been reported across the range of blood Pb levels examined in epidemiologic studies.

Compelling evidence for a larger decrement in cognitive function per unit increase in blood Pb among children with lower mean blood Pb concentrations compared to children with higher mean blood Pb concentrations was presented in the 2006 Pb AQCD. Key evidence was provided by studies that examined prenatal or early childhood blood Pb levels or considered peak blood Pb levels in schoolaged children or concurrent blood Pb levels in young children age 2 years (Section 4.3.12, Figure 4-16, and Table 4-16) (Téllez-Rojo et al., 2006) as well as the international pooled analysis of seven prospective cohort studies by Lanphear et al. (2005), a subsequent reanalysis of these data focusing on the shape of the concentration response function (Rothenberg and Rothenberg, 2005).

Attenuation of C-R relationships at higher exposure or dose levels has been reported in the occupational literature for a range of exposures. Reasons proposed to explain the attenuation include greater exposure measurement error and saturation of biological mechanisms at higher levels as well depletion of the pool of susceptible individuals at higher exposure levels (Stayner et al., 2003). Possible explanations specific to nonlinear relationships observed in studies of Pb exposure in children include a lower incremental effect of Pb due to covarying risk factors such as low SES, poor caregiving environment, and higher exposure to other environmental factors (Schwartz, 1994), differential activity of mechanisms at different exposure levels, and confounding by omitted or misspecified variables. Review of the evidence did not reveal a consistent set of covarying risk factors to explain the differences in blood Pb IQ C-R relationship across high and low Pb exposure groups observed in epidemiologic studies. Nonlinear concentration-response relationships including U- or inverted U-shaped curves for various endpoints, including those related to cognitive impairment were demonstrated in the toxicological literature. However, these toxicological findings are distinct from epidemiologic findings of supralinear relationships in that some U- or inverted U-shaped relationships do not indicate Pb-induced impairments at higher exposure concentrations.

The supralinear relationship reported in multiple prospective studies does not provide evidence of a threshold for Pb-associated cognitive function decrements. For example, as

detailed in Section 4.3.12, higher blood Pb levels at age 2 years were associated with FSIQ decrements in children aged 10 years whose blood Pb levels were in the range of 1.0-9.3 µg/dL, e.g.(Bellinger, 2008). Supporting evidence was provided by Pb-associated decrements in academic performance observed in fourth grade children with earlier childhood blood Pb levels categorized as 2 µg/dL versus 1 µg/dL (Miranda et al., 2009; 2007a). The lack of a reference population with blood Pb levels reflecting still lower Pb exposures limits the ability to identify a threshold in the current population. Toxicological studies showed that lower Pb exposures (e.g., 50 ppm in drinking water) induced learning and memory impairments in animals compared to control exposures or higher Pb exposures (e.g., 150 ppm). Additional toxicological evidence suggests that mechanisms may be differentially activated at lower and higher Pb exposures, and reduced long-term potentiation (LTP) and hippocampal glutamate release with lower Pb exposures may provide explanation for the impaired learning and memory observed with lower Pb exposures in some animal studies.

Studies of Pb Effects in Adults

The shape of the C-R function (e.g., linear versus non-linear) was not examined in most studies of the association of Pb biomarkers with cognitive function in adults (Sections 4.3.2.7 and 4.3.13). Log-linear models were used to fit the data in NHANES analyses. Nonlinearity in the relationship between bone Pb and cognitive function among participants in the BMS and NAS cohorts was examined with the use of quadratic terms, penalized splines, or visual inspection of bivariate plots. There was some evidence for nonlinearity in prospective analyses of the NAS cohort (Figure 4-7 and Figure 4-8), but not all results indicated a larger decrement in cognitive function per unit increase in bone Pb level in the lower end of the bone Pb distribution. In the BMS cohort, observation of a statistically nonsignificant quadratic bone Pb term indicated that a linear model fit the relationship between tibia Pb level and various tests of cognitive function.

A meta-analysis of human studies found that each doubling of blood Pb level (between 1 and >40 µg/dL measured concurrently in most studies of adults for which past exposures were likely higher than current exposures) was associated with a 1 mmHg increase in systolic BP and a 0.6 mmHg increase in diastolic BP (Nawrot et al., 2002). In this analysis, effect sizes were adjusted for the purpose of pooling them depending on whether a linear or log (common or natural) linear model was used. The functional form of the C-R relationship was examined in few individual studies of cardiovascular effects (Section 4.4.2.1). Weaver (2010), reported that a logarithmic function of blood Pb level better described data from a cohort of Korean workers than the linear form. Only a small number of studies that focused on Pb-induced hypertension in experimental animals have

included more than two exposure concentrations, and these studies appear to show a nonlinear concentration-response (Figure 4-21).

Studies investigating both all-cause and cardiovascular mortality report both linear and non-linear relationships (Section 4.4.5). Although associations are consistently reported, findings regarding the shape of the C-R relationship between blood Pb level and mortality in NHANES analyses were mixed. For example, in the NAS cohort, C-R relationships between bone Pb and mortality were approximately linear for patella Pb on the log(heart rate [HR]) scale for all cardiovascular disease (CVD), but appear nonlinear for IHD (Weisskopf et al., 2009). It is important to note the wide confidence limits, which increase uncertainty at the lower and upper bounds of patella Pb levels. The strongest associations were observed between mortality and baseline patella Pb concentration while tibia Pb levels were more weakly associated with CVD mortality.

1.9.4 Pb Exposure and Neurodevelopmental Deficits in Children

As discussed in Section 3.3.5, blood Pb may reflect both recent exposures as well as past exposures because Pb is both taken up by and released from the bone. The relative proportion of blood Pb from recent versus past exposure is uncertain in the absence of specific information about the pattern of exposure contributing to observed blood Pb levels. This uncertainty is greater in adults and older children, than in young children who do not have lengthy exposure histories. Several lines of evidence, which are summarized below, inform the interpretation of epidemiologic studies of young children with regard to the patterns of exposure that contribute to observed health effects.

Pb can cross the placenta to affect the developing fetal nervous system and fetal Pb exposure can occur from recent maternal exposure or from mobilization of bone Pb stores from past exposures (Section 3.2.2.4). In very young children, ages <2 years, decrements in mental development, as assessed with MDI, was associated with higher prenatal (maternal and cord) and concurrent blood Pb levels (Section 4.3.2.2). Thus, both postnatal child and maternal Pb exposures may contribute to neurodevelopmental effects in children from infancy to age 2 years. There is some evidence that the relative influence of maternal Pb levels on postnatal blood Pb level is substantially reduced soon after birth (Section 3.4). There was also a good correlation between child blood Pb level and child hand Pb loading ($R^2 = 0.70$) in a study following children living in a contaminated area, indicating the influence of concurrent Pb exposures on blood Pb during the early childhood years (Simon et al., 2007). In another study (Carbone et al., 1998) blood Pb levels of infants aged 6-12 months were significantly lower than their neonatal cord blood Pb levels (2.24 µg/dL versus 4.87 µg/dL). Among infants born with blood Pb levels

of greater than 7 μg/dL, who were followed for a week, there was a dramatic drop in the blood Pb (Carbone et al., 1998).

Epidemiologic studies consistently show that blood Pb levels measured during various lifestages or time periods throughout childhood, as well as averaged over multiple years during childhood, are associated with cognitive function decrements (Section 4.3.11). An international pooled analysis of seven prospective studies found that increments in concurrent and peak blood Pb levels were associated with a decrease in FSIQ measured between ages 5 and 10 years (Lanphear et al., 2005). In individual studies, postnatal (early childhood and concurrent) blood Pb levels are also consistently associated with cognitive function decrements in children and adolescents (Figure 4-2, Table 4-3, Table 4-14).

Exposure metrics based on blood Pb measurements at different ages in childhood are typically highly correlated. For example, analyses of serial blood Pb concentrations measured in longitudinal epidemiologic studies find relatively strong correlations (e.g., r = 0.5-0.8) among each child's individual blood Pb concentrations measured after 6-12 months of age (Section 3.3.2). Consequently, the relative importance of various exposure metrics, which are measured during different lifestages and time periods, is difficult to discern in epidemiologic studies. Evidence in rodents and monkeys, however, indicates that Pb exposures during multiple lifestages and time periods, including prenatal only, prenatal plus lactational, postnatal only, lifetime are observed to induce impairments in learning (Rice, 1992b, 1990; Rice and Gilbert, 1990b). These findings are consistent with the understanding that the nervous system continues to develop (i.e., synaptogenesis and synaptic pruning remains active) throughout childhood and into adolescence.

1.9.5 Reversibility and Persistence of Neurotoxic Effects of Pb

The 2006 Pb AQCD concluded that the human and animal evidence suggest that the neurotoxic effects of Pb are not generally reversible (U.S. EPA, 2006b). Chelation studies in humans and animals show that chelation decreases total body Pb burden, but does not necessarily exert evident effects on Pb-induced cognitive deficits. For example, analysis of multi-center study data indicates that medical interventions involving chelation therapy (e.g., Succimer use) do not fully reverse cognitive deficits associated with early Pb exposure (Liu et al., 2002).

The persistence of neurodevelopmental effects from comparatively low-level Pb exposure was considered in the 2006 Pb AQCD (U.S. EPA, 2006b), with some evidence suggesting that the effects of Pb on neurodevelopmental outcomes persisted into adolescence and young adulthood. The toxicological evidence continues to support a

range of effects with prenatal and early postnatal Pb exposures that persist to adulthood (Sections 4.3.2.3 and 4.3.3.1). In rats, persistent neurobehavioral deficits were observed with prenatal, preweaning, and postweaning Pb exposure. In monkeys, impairments were found in learning and short-term memory at ages 7 to 8 years (Rice and Karpinski, 1988) and in attention at ages 9 to 10 years (Gilbert and Rice, 1987) with lifetime Pb exposure that did not begin until postnatal day 400 and that produced peak blood-Pb levels <15 or 25 μg/dL and steady-state levels 11 and 13 μg/dL, indicating that postnatal juvenile Pb exposures were sufficient to produce neurodevelopmental deficits.

A number of mechanisms, including changes in neurogenesis, synaptogenesis and synaptic pruning, long term potentiation, and neurotransmitter function have been identified that provide biological plausibility for epidemiologic and toxicological findings of persistent cognitive and behavioral effects that result from Pb exposures during prenatal and early childhood periods. Furthermore, the normal dynamic and rapid rate of development that occurs early in life in the CNS makes insults early in life especially problematic in that they can permanently change the trajectory of brain development such that there are little or no compensatory pathways to replace the lost potential for proper brain development (Bayer, 1989).

The persistence of effects appears to depend on the duration and window of exposure as well as other factors that may affect an individual's ability to recover from an insult. Several studies have observed improved cognition in children with declining blood Pb levels (Hornung et al., 2009; Chen et al., 2005a; Liu et al., 2002; Ruff et al., 1993). There is evidence that some cognitive effects of prenatal Pb exposure may be transient and that recovery is greater among children reared in households with more optimal caregiving characteristics and in children whose concurrent blood Pb levels were low (Bellinger et al., 1990); the animal toxicology literature supports these findings using studies of Pb-exposed animals that live in enriched environments. However, the extent to which such improvement represents biological reversibility of Pb-related effects, the influence of enrichment related intervention, or the development of compensatory mechanisms remains uncertain.

Toxicological studies in the 2006 Pb AQCD highlighted the importance of Pb exposure during early life in promoting Alzheimer's-like pathologies in the adult rodent brain, with Pb-induced neurodegeneration and formation of neurofibrillary tangles in aged animals in which blood Pb levels had returned to control levels after an earlier life Pb exposure (U.S. EPA, 2006b). Sensitive windows of early life Pb exposure or a Pb biomarker and have been associated with changes in adulthood as demonstrated with animal models of neurodegeneration, i.e., neurofibrillary tangle formation. Behavioral or cognitive testing in these animal models has not been performed to assess these changes. These effects are

not reflective of concurrent blood Pb levels at the age of manifestation of the pathology but instead are associated with an earlier life Pb exposure.

1.9.6 Populations Potentially At-Risk for Health Effects

The NAAQS are intended to protect public health with an adequate margin of safety. In so doing, protection is provided for both the population as a whole and those groups potentially at increased risk for health effects from exposure to the air pollutant for which each NAAQS is set (Preface to this ISA). To facilitate the identification of populations at increased risk for Pb-related health effects, studies have evaluated various factors that may contribute to susceptibility and/or vulnerability to Pb. These factors include genetic background, race and ethnicity, sex, age, diet, pre-existing disease, SES, and characteristics that may modify exposure or the response to Pb. Table 1-7 and Table 5-5 provide an overview of the factors examined as potentially increasing the risk of Pb-related health effects based on the recent evidence integrated across disciplines. They are classified according to the criteria discussed in the introduction to Chapter 5.

In consideration of the evidence base as a whole (e.g., stratified and longitudinal analyses) and integrating across disciplines of toxicokinetics, exposure, and health, there is adequate evidence to conclude that children are an at-risk population. It is recognized that Pb can cross the placenta and affect the developing nervous system of the fetus (Section 3.2.2.4). Children may have increased exposure to Pb compared with adults because children's behaviors and activities (including increased hand-to-mouth contact, crawling, and poor hand-washing), differences in diets, and biokinetic factors. There is evidence of increased risk to the cognitive effects of Pb exposure during several lifestages and time periods throughout gestation, childhood, and into adolescence (Section 4.3.12). Findings from magnetic resonance imaging (MRI) studies indicate that normal brain development remains dynamic throughout adolescence, and epidemiologic studies have linked concurrent blood Pb level (as well as other blood Pb metrics) in adolescents to cognitive function decrements and delinquent or criminal behavior (Section 4.3.4). Delays in puberty onset (Section 4.8.1), and renal effects (Section 4.5.2.2), are also observed in association with concurrent blood Pb level in cross-sectional studies of adolescents. Since the populations of older children in these studies generally had higher past exposures, the current evidence does not clearly establish the link between a time and duration of Pb exposure and the observed health effects in the adolescent populations studied. Elevated biomarkers levels, which may be related to remobilization of stored Pb during bone loss and/or higher historical Pb exposures, are observed in older adults. Studies of older adults report inconsistent findings for effect measure modification of Pb-related mortality by age and no

modification of other health effects was studied. However, toxicological studies support the possibility of age-related differences in Pb-related health effects. The overall evidence, based on limited epidemiologic evidence but support from toxicological studies and differential exposure studies, is suggestive that older adults are potentially at risk of Pb effects. However, there are uncertainties related to the exposure profile associated with the effects in older populations.

Table 1-7 Summary of evidence for factors that potentially increase the risk of Pb-related health effects.

Factor Evaluated	Classification
Childhood (Sections 5.2.1, 5.3.1)	Adequate
Older Adulthood (Sections 5.2.1 and 5.3.1)	Suggestive
Sex (Sections 5.2.2, 5.3.2)	Suggestive
Genetics (Sections 5.3.3)	Suggestive
Pre-existing Disease[a] (Section 5.3.4)	Suggestive
Smoking Status (Section 5.3.5)	Inadequate
Socioeconomic Status (SES) (Sections 5.2.4, 5.3.6)	Suggestive
Race/Ethnicity (Sections 5.2.3, 5.3.7)	Adequate
Proximity to Pb Sources (Section 5.2.5)	Adequate
Residential Factors (Section 5.2.6)	Adequate
Body Mass Index (BMI) (Section 5.3.8)	Inadequate
Alcohol Consumption (Section 5.3.9)	Inadequate
Nutrition (Section 5.3.10)	Adequate
Stress (Section 5.3.11)	Suggestive
Maternal Self-Esteem (Section 5.3.12)	Inadequate
Cognitive Reserve[a] (Section 5.3.13)	Inadequate
Other Metals (Section 5.3.14)	Suggestive

[a]Possible mediator

The evidence regarding the other at-risk factors listed in the table above is summarized in detail in Section 5.4. Some studies suggest that males at some ages have higher blood Pb levels than comparably aged females; this was supported by stratifying the total sample of NHANES subjects. Sex-based differences appeared to be prominent among the adolescent and adult age groups but were not observed among the youngest age groups (1-5 years and 6-11 years). Studies of effect measure modification of Pb and various health endpoints by sex were inconsistent; although it appears that there are some

differences in associations for males and females. This is also observed in toxicological studies. Overall, there is suggestive evidence to conclude that sex is a potential at-risk factor, with adolescent and adult males typically demonstrating higher blood Pb levels, although evidence regarding health outcomes is limited due to inconsistencies in whether males or females are at greater risk of certain outcomes in relation to Pb exposure.

Regarding race and ethnicity, recent data suggest that the difference in blood Pb levels between black and white subjects is decreasing over time, but black subjects still tend to have higher Pb body burden and Pb exposures than white subjects. Compared to whites, non-white populations were observed to be more at risk of Pb-related health effects. Studies of race/ethnicity provide adequate evidence that race/ethnicity is an at-risk factor based on the higher exposure observed among non-white populations and some modification observed in studies of associations between Pb levels and health effects. For example two investigators report (Table 5-5), reported modification by race/ethnicity in an analysis of hypertension among NHANES III participants. Muntner et al. (2005) sons of the highest quartile of blood Pb to the lowest, the odds ratio for hypertension was 1.54 (95% CI: 0.99, 2.39) among Mexican Americans, 1.44 (95% CI: 0.89, 2.32) among Non-Hispanic Blacks and 1.10 (95% 0.87, 1.41) among Non-Hispanic Whites (Scinicariello et al., 2010).

The gap between SES groups with respect to Pb body burden appears to be diminishing. However, biomarkers of Pb exposure have been shown to be higher among lower SES groups even in recent studies in which differences among SES groups have lessened. Studies of SES and its relationship with Pb-related health effects are few and report inconsistent finding regarding low SES as a potential at-risk factor. Overall, the evidence is suggestive that low SES is a potential at-risk factor for Pb-related health effects.

There is adequate evidence that proximity to areas with Pb sources, including areas with large industrial sources, is associated with increased Pb exposure. Relatively high concentrations of ambient air Pb have been measured near sources, compared with large urban areas without sources and high Pb exposures have been documented near Superfund sites. NHANES analyses report increased Pb biomarker levels related to increase house dust Pb levels, homes built after 1950, and renovation of pre-1978 homes. Thus, there is adequate evidence that residing in a residence with sources of Pb exposures will increase the risk of Pb exposure and associated health effects.

There is suggestive evidence to conclude that various genetic variants potentially modify the associations between Pb and health effects. Epidemiologic and toxicological studies reported that ALAD variants may increase the risk of Pb-related health effects. Other genes examined whose variants may also affect risk of Pb-related health effects were VDR, DRD4, GSTM1, TNF-α, eNOS, and HFE. Overall the interaction between genetic

variants and Pb exposure were examined in a small number of studies and these types of analysis are potentially vulnerable to type II error if multiple statistical tests are conducted. However, there may be a large potential impact of Pb exposure in specific at-risk populations carrying specific gene variants. For example, Scinicariello et al. (2010) found that Non-Hispanic white carriers of the ALAD2 genetic variant in the highest blood Pb quartile had a 2-fold higher risk of hypertension compared with ALAD1 homozygous individuals (OR:2.00 [95%CI: 1.12, 3.55]). No evidence of effect modification of the association of Pb with blood pressure by ALAD genotype was observed in an occupational study of Korean Pb workers, however (Weaver et al., 2008). NAS subjects with the H63D polymorphism of the HFE gene had a larger Pb-associated increase in pulse pressure compared to those with the C282Y variant [i.e., 3.3 mmHg increase (95%CI: 0.16, 6.46) versus an 0.89 mmHg increase (95%CI 0-5.24) per 13 μg/g increase in tibia Pb (Zhang et al., 2010a)].

Diets sufficient in minerals such as calcium (Ca^{2+}), iron (Fe), and zinc (Zn) offer some protection from Pb exposure by preventing or competing with Pb for absorption in the GI tract. Additionally, those with Fe deficiencies were observed to be an at-risk population for Pb-related health effects in both epidemiologic and toxicological studies. Thus, there is adequate evidence across disciplines that some nutritional factors contribute to a population being at increased risk. Other nutritional factors, such as Ca^{2+}, Zn, and protein intake, demonstrated the potential to modify associations between Pb and health effects in toxicological studies.

There was suggestive evidence for several other factors as potentially increasing the risk of Pb-related health effects: pre-existing diseases/conditions, stress, and co-exposure with other metals. Pre-existing diseases/conditions have the potential to affect the risk of Pb-related health effects. Recent epidemiologic studies did not support modification of associations between Pb and health endpoints (i.e., mortality, HRV) by the prevalence of diabetes; however, past studies have found individuals with diabetes to be an at-risk population with regard to renal function. Studies of Pb biomarker levels and both renal effects and HRV demonstrated greater odds of the associations among hypertensive individuals compared to those who are normotensive. Stress was evaluated as a factor that potentially increases the risk of Pb-related effects on cognitive function in adults and hypertension and although limited by the small number of epidemiologic studies, increased stress was observed to exacerbate the effects of Pb. Toxicological studies supported this finding. High levels of other metals, such as Cd and Mn, were observed to result in greater effects for the associations between Pb and various health endpoints (e.g., renal function, cognitive function in children) but overall the evidence was limited. Finally, there was inadequate evidence to conclude that smoking, BMI, alcohol

consumption, maternal self-esteem, and cognitive reserve are potential at-risk factors due to limited quantities of studies regarding their effect on Pb-related health outcomes.

1.9.7 Ecological Effects and Corresponding Pb Concentrations

Information on the effects of atmospherically-deposited Pb on some ecosystem receptors in the vicinity of Pb sources is available from studies of terrestrial systems near mining and smelting operations where Pb, as well as other metals, is present in high concentrations. In these studies a decreasing gradient of exposure is observed, and effects in a species or population of interest typically decrease with increasing distance from the source. Thus, concentrations of Pb in moss, lichens and peat have been used to understand spatial and temporal distribution patterns of air Pb concentrations. In other environmental compartments such as sediment and aquatic biota, or in locations not close to Pb sources, evidence that would permit clear attribution of Pb effects to atmospheric deposition is insufficient. Pb that is released into air, soil, or water is then cycled through any or all of these media before reaching an ecological receptor. When a plant, invertebrate, or vertebrate is exposed to Pb, the proportion of observed effects attributable to Pb from atmospheric sources is difficult to assess due to a lack of information not only on deposition, but also on bioavailability, as affected by specific characteristics of the receiving ecosystem and on kinetics of Pb distribution in long-term exposure scenarios. Therefore, the connection between air concentration and ecosystem exposure continues to be poorly characterized for Pb, and the contribution of atmospheric Pb to specific sites is not clear.

Furthermore, the level at which Pb elicits a specific effect is difficult to establish in terrestrial and aquatic systems, due to the influence of other environmental variables on both Pb bioavailability and toxicity, and also to substantial species differences in Pb susceptibility. Current evidence indicates that Pb is bioaccumulated in biota; however, the sources of Pb in biota have only been identified in a few studies, and the relative contribution of Pb from all sources is usually not known. There are large differences in species sensitivity to Pb, and many environmental variables (e.g., pH, organic matter) determine the bioavailability and toxicity of Pb.

1.10 Summary

Table 1-8 characterizes the evidence in the 2006 Pb AQCD (U.S. EPA, 2006b) and previous assessments and compares it to the evidence evaluated in the current assessment. Evidence regarding both the health and ecological effects of Pb are

summarized. The purpose of the table is to highlight the extent to which recent evidence may contribute to current conclusions. The critical assessment of body of evidence as a whole, however, is discussed in Chapter 4 and Chapter 6 of this document, and summarized in Sections 1.6 and 1.7. With regard to ecological effects, evidence pointing to responses in species at ambient or near ambient concentrations is highlighted in the table.

Table 1-8 Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Health Outcomes:		
Nervous System Effects		
Children		
Cognitive Function in Children	The "overall weight of the available evidence provides clear substantiation of neurocognitive decrements being associated in young children with blood-Pb concentrations in the range of 5-10 µg/dL, and possibly lower." Prenatal, early childhood, lifetime average, and concurrent blood Pb levels were associated with decrements in IQ, learning and executive function. In some cases, concurrent blood Pb level was the strongest predictor.	Recent epidemiologic studies in children continue to demonstrate associations of concurrent blood Pb level with IQ decrements; most recent evidence describes associations of concurrent blood Pb levels with decrements in cognitive abilities related to executive function, and academic performance.
Externalizing Behaviors: Attention, Impulsivity and Hyperactivity in Children	Several epidemiologic studies reported associations between blood and tooth Pb levels and attention decrements in children ages 7-17 years and young adults 19-20 years. Most studies examined prenatal or lifetime average blood Pb levels (means 7, 14 µg/dL) or tooth Pb. The few studies of concurrent blood Pb levels did not find associations with attention in children ages 4-5 years. There were no studies specifically examining ADHD diagnosis. Uncertainty remained regarding whether Pb exposure was an independent predictor of neurobehavioral effects. Prenatal and postnatal Pb exposure was found to reduce ability to inhibit inappropriate responding and increase distractibility in animals.	Recent studies in children continue to support associations of blood Pb levels with attention decrements, impulsivity, and hyperactivity in children ages 7-17 years. A few case-control studies found higher concurrent blood Pb levels in children with diagnosed ADHD; however, because ADHD studies had various limitations,they were not a major consideration in drawing conclusions.
Externalizing Behaviors: Conduct Disorders in Children and Young Adults	Several epidemiologic studies reported associations between Pb exposure and behaviors related to conduct disorders as rated by parents and teachers and criminal offenses in children, adolescents, and young adults. Most studies examined blood Pb levels measured earlier in childhood (means 10-14 µg/dL), tooth Pb, or bone Pb. There was little examination of concurrent blood Pb levels.	Recent studies in children continue to support associations of parent and teacher ratings of behaviors related to conduct disorders with early childhood blood Pb levels and provide new evidence for concurrent blood Pb levels. Additional follow-up of previous cohorts to older ages, support associations of early childhood blood Pb levels or tooth Pb levels with criminal offenses in adults ages 19-24 years.
Internalizing Behaviors in Children	Several prospective studies reported associations of concurrent or childhood average blood, tooth, and bone Pb levels with parent or teacher ratings of withdrawn behavior and symptoms of depression, fearfulness, and anxiety in children ages 3-13 years.	The few recent available studies found associations between concurrent blood Pb level and higher ratings of internalizing behaviors in children ages 8-13 years but these studies had limited consideration for potential confounding.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Visual Function Decrements in Children	The selective action of Pb on retinal rod cells and bipolar cells (e.g., ERG effects) of animals is well documented in earlier AQCDs in animals and found in one study in children.	Additional evidence for retinal effects was found in female rats. High-level developmental Pb exposure did not affect visual acuity in infant monkeys.
Auditory Function Decrements in Childiren	The few available studies reported associations between concurrent blood Pb levels (population means 7-12 µg/dL) and increased hearing thresholds in children. There was coherence with findings in animals but with high Pb exposures (e.g., blood Pb levels 89-150 µg/dL).	The few available recent epidemiologic studies on auditory function in children examined children with high blood Pb levels (means >30 µg/dL) and did not consider potential confounding. Early postnatal Pb exposure of monkeys increased hearing thresholds.
Motor Function Decrements in Children	A small number of studies indicated associations of neonatal, earlier childhood average, lifetime average, and concurrent blood Pb levels (means: 5-12 µg/dL) with poorer fine and motor function in children ages 4.5-17 years. The few toxicological studies did not consistently find Pb-induced impairments in balance and coordination in animals with blood Pb levels >60 µg/dL.	The few recent epidemiologic studies did not consistently find associations between concurrent blood Pb level and decrements in fine motor function. A toxicological study found poorer balance in male mice with gestational plus early postnatal Pb exposure (peak blood Pb level: ≤10 µg/dL).
Adults		
Cognitive Function Decrements in Adults	Among environmentally-exposed adults, bone Pb levels but not blood Pb levels were associated with poorer cognitive performance. These findings point to an effect of long-term cumulative Pb exposure. Impaired learning, memory, and executive function found in adult animals after lifetime Pb exposures beginning in gestation or infancy.	Recent studies support previous findings and recent prospective studies provide new evidence of associations of bone Pb levels with subsequent declines in cognitive function in environmentally-exposed adults over 2-4 year periods.
Psychopathological Effects in Adults	Environmentally-exposed adults were not widely examined; however a study found associations of concurrent blood and tibia Pb level with self-reported symptoms of depression and anxiety in men. Several studies found higher prevalence of symptoms related to mood disorders and anxiety in Pb-exposed workers with mean blood Pb levels 15-38 µg/dL.	Concurrent blood Pb levels were associated with self-reported symptoms of major depressive disorder and general anxiety disorder among men and women participating in NHANES.
Auditory Function Decrements in Adults	A few studies found blood Pb level or cumulative Pb exposure duration to be associated with increased hearing thresholds and hearing loss in Pb-exposed workers.	A prospective study found higher tibia Pb level to be associated with a faster rate of increase in hearing threshold in environmentally-exposed men over a median of 23 years.
Visual Function Decrements in Adults	Decreased visual acuity found in adult monkeys with high blood Pb levels (50-115 µg/dL) after lifetime Pb exposure.	Additional evidence for retinal effects was found in female rats. A case-control study found higher retinal Pb levels in adults with macular degeneration but potential confounding was not considered. Pb-induced effects on ERGs in adult animals vary depending on timing and dose of exposure.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Neurodegenerative Diseases in Adults	In the limited body of epidemiologic studies, occupational Pb exposure and brain Pb levels were not associated with Alzheimer's disease. Blood Pb levels were not consistently associated with Amyotrophic Lateral Sclerosis among environmentally-exposed adults. A few studies found associations between occupational Pb exposure and Parkinson's disease and blood Pb levels and essential tremor. Each study had sufficient limitations. Toxicological studies found Pb-induced neuronal cell death loss and amyloid plaques in aged animals with lactational Pb exposures.	The few case-control studies reported associations of bone Pb levels with Parkinson's disease in environmentally-exposed adults and blood Pb levels with Amyotrophic Lateral Sclerosis and essential tremor. Limitations of previous studies apply to the recent evidence. Recent toxicological evidence suggests that early-life, not adult-only Pb exposure may be associated with neurodegeneration in adult animals.
Cardiovascular Effects		
Hypertension	A meta-analysis of numerous epidemiologic studies estimated that a doubling of blood Pb level (e.g., from 5 to 10 µg/dL) was associated with a 1 mmHg increase in systolic BP and a 0.6 mmHg increase in diastolic BP." Epidemiologic studies consistently demonstrated associations between Pb and incidence of hypertension with suggestive evidence that bone Pb may be associated with hypertension. Animal studies demonstrated that long-term exposure to Pb resulted in hypertension that persisted after cessation of exposure.	Recent epidemiologic and toxicological studies continue to support associations between long-term Pb exposure and increased BP. Recent studies, including those using bone Pb as a metric of cumulative exposure, continue to demonstrate associations of hypertension with Pb levels in adults. Recent studies have emphasized the interaction of cumulative exposure to Pb with other factors including stress.
Subclinical Atherosclerosis	One NHANES analysis reported an association of blood Pb with PAD	Limited evidence for Pb-induced subclinical atherosclerosis, including one high-quality epidemiologic study that reports an increasing trend in the odds of PAD and concurrent blood Pb level in adults. Recent toxicological studies describe a plausible biological mechanism.
Coronary Heart Disease	The evidence for an association of Pb with cardiovascular mortality was limited but supportive. A few cross-sectional studies indicated associations between Pb biomarker levels and increased risk of CHD outcomes (i.e., MI and left ventricular hypertrophy).	Recent studies address limitations of previous studies and provide additional evidence for an association of Pb with cardiovascular mortality in adults. Specific causes of mortality that were associated with Pb could be related to increased BP and hypertension.
Cerebrovascular Disease	Evidence available on the risk of cerebrovascular disease from Pb exposure was limited to one study of stroke.	Evidence for increased risk of mortality from stroke is inconsistent.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Renal Effects		
Reduced Kidney Function	Circulating and cumulative Pb was associated with longitudinal decline in renal function in adults. Toxicological studies demonstrated that initial accumulation of absorbed Pb occurred primarily in the kidneys and noted a hyperfiltration phenomenon during the first 3 months of exposure, followed by decrements in kidney function.	Recent epidemiologic and toxicological studies add to the body of evidence on Pb exposure and kidney dysfunction (e.g., lower creatinine clearance, higher serum creatinine, and lower GFR) in nonoccupationally-exposed adults.
Immune System Effects		
Increases in Atopic and Inflammatory Conditions	Children:	
	Several epidemiologic studies suggested that Pb exposure may be associated with effects on cellular and humoral immunity in children. The principal effect demonstrated increases in serum immunoglobulin E (IgE) levels with concurrent blood Pb levels >10 µg/dL. Toxicological evidence supported these findings with extensive evidence for prenatal and early postnatal Pb exposures skewing toward Th2 cytokine production and affecting downstream events such as increases in IgE and inflammation Several toxicological studies found a Pb-induced shift to Th2 cytokine production and a hyperinflammatory phenotype of macrophages in animals with long-term (>4 weeks) prenatal or postnatal Pb exposure.	Recent studies in children added to the evidence for associations of blood Pb levels with asthma, allergy, and IgE. The consistency and coherence of findings among related immune effects that support a shift from a Th1 to a Th2 phenotype supports the biological plausibility for epidemiologic observations of associations with asthma, allergy and inflammation-related effects in other organ systems.
	Adults:	
	Pb exposure-associated immune effects were not widely examined in environmentally-exposed adults.	A small body of recently available studies provide new evidence for increases in cytokines and other indicators of inflammation in association with higher concurrent blood Pb level. A few available toxicological studies find Pb-associated increases in cytokines and effects on dendritic cells in adult mice.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Decreases in Host Resistance	Toxicological evidence demonstrated Pb-induced increases in bacterial and viral infection and suppressed DTH in animals. These effects were supported by extensive evidence for prenatal and early postnatal Pb exposures decreasing Th1 cytokine production, for short-term prenatal Pb exposure decreasing nitric oxide production by macrophages), and for long-term (>4 weeks) exposure Pb exposure inducing a hyperinflammatory phenotype of macrophages in adult animals. A few epidemiologic studies found higher prevalence of respiratory infections in association with higher blood Pb levels in children and occupational Pb exposure in adults; however, studies did not consider potential confounding. In the large body of studies in occupationally-exposed adults, the most consistent findings were reduced neutrophil functionality in workers with blood Pb levels >14.8-91 µg/dL. Environmentally-exposed adults were not widely examined.	A small body of recent studies supports previous findings of decreased bacterial resistance and decreased IFN-γTh1 cytokine production in animals. Epidemiologic evidence is limited to an ecological study of soil and lichen Pb that lacked consideration for potential confounding.
Autoimmunity	A small number of toxicological studies found that prenatal and postnatal Pb treatment, several by i.p. injection, increased generation of auto-antibodies. A study found higher auto-antibodies to neural proteins in Pb-exposed workers with blood Pb levels 10-40 µg/dL	A recent toxicological study provided indirect evidence by showing Pb-induced increases in the activation of neo-antigen specific T cells, which have the potential to induce formation of auto-antibodies.
Hematologic System		
Red Blood Cell Function and Heme Synthesis	Children:	
	Pb exposure was associated with disruption in heme synthesis with increases in blood Pb levels of approximately 20 µg/dL sufficient to halve ALAD activity and inhibit ferrochelatase. Risk of clinical anemia in children becomes apparent at high blood Pb levels: 10% probability of anemia was estimated to be associated with ~20 µg/dL Pb at 1 year of age, 50 µg/dL at 3 years of age, and 75 µg/dL at 5 years of age.	Recent epidemiologic studies provide evidence that exposure to Pb is associated with numerous deleterious effects on the hematological system in children, including altered hematological parameters (Hb, MCV, MCH, RBC count), perturbed heme synthesis mediated through decreased ALAD and ferrochelatase activities, and oxidative stress.
	Adults:	
	Pb exposure was associated with disruption in heme synthesis with increases in blood Pb levels of approximately 20 µg/dL sufficient to halve ALAD activity and inhibit ferrochelatase. Exposures to Pb resulting in blood concentrations <40 µg/dL appear to be tolerated without decreases in blood hemoglobin or hematocrit, however changes in erythropoiesis do occur at these blood levels.	Recent epidemiologic studies provide evidence exposure to Pb is associated with numerous deleterious effects on the hematological system in adults, including altered hematological parameters (Hb, MCV, MCH, RBC count), perturbed heme synthesis mediated through decreased ALAD and ferrochelatase activities, decreased erythropoiesis, and oxidative stress.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Developmental and Reproductive Effects		
Development	Epidemiologic studies reported effects including delayed puberty in girls. Animal toxicological studies reported Pb-associated developmental effects on teeth, sensory organs, the GI system, the liver, and postnatal growth. Delayed puberty was also observed in both male and female populations in animal toxicology studies showing associations with dam blood Pb levels of ~40 µg/dL and pup blood Pb levels of 26 µg/dL.	Recent toxicological and epidemiologic studies provide evidence for delayed onset of puberty in males and females. Most studies found delayed onset of puberty was among children ages 6-18 years. These findings were supported by studies in the animal toxicological literature showing effects on puberty onset at blood Pb levels of 3.5-13 µg/dL.
Birth Outcomes	Toxicological studies reviewed concluded that Pb exposure can increase fetal mortality and produce sublethal effects, smaller litters, reduced birth weight, and fewer implantation sites. Epidemiologic studies on preterm birth and low birth weight/fetal growth reported inconsistent findings. Epidemiologic studies reported the possibility of small associations between increased Pb exposure and birth defects, and toxicological studies demonstrated associations between exposure to high doses of Pb and increased incidences of teratogenic effects.	Recent toxicological and epidemiologic studies have reported inconsistent findings for studies for birth defects, preterm birth, and low birth weight/fetal growth. A few well-conducted epidemiologic studies of preterm birth and low birth weight/fetal growth reported associations between increased Pb levels and decreased gestational age and birth weight/fetal growth.
Male Reproductive Function	Epidemiologic evidence suggested small associations between Pb exposure and male reproductive outcomes including perturbed semen quality and increased time to pregnancy. Associations between Pb exposure and male reproductive endocrine status were not observed in the occupational populations studied. Toxicological studies provided evidence that Pb produced effects on male and female reproductive junction and development and disrupts endocrine function.	Recent toxicological studies provide strong evidence for effects on sperm (blood Pb levels 5-43 µg/dL). Epidemiologic studies support the association observed in toxicological studies of Pb exposure and detrimental effects on sperm.
Female Reproductive Function	Toxicological studies reported that Pb exposure was associated with effects on female reproductive function that can be classified as alterations in female sexual maturation, effects on fertility and menstrual cycle, endocrine disruption, and changes in morphology or histology of female reproductive organs including the placenta. Epidemiologic studies on Pb and female reproductive function provided little evidence for an association between Pb biomarkers and effects on female reproduction and fertility.	Epidemiologic studies of Pb levels and hormones demonstrate associations but are inconsistent overall and there is a lack of large, well-conducted epidemiologic studies examining associations between Pb levels and fertility. Toxicological studies of Pb and effects on female reproduction demonstrate effects in some studies.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Cancer		
Cancer	Epidemiologic studies of highly exposed occupational populations suggest a relationship between Pb and cancers of the lung and the stomach; however the evidence is limited by the presence of various potential confounders, including metal co-exposures (e.g., to As, Cd), smoking, and dietary habits. The 2003 NTP and 2004 IARC reviews concluded that Pb and Pb compounds were probable carcinogens, based on limited evidence in humans and sufficient evidence in animals. Based on animal data and inadequate human data Pb and Pb compounds would be classified as likely carcinogens according to the EPA Cancer Assessment Guidelines for Carcinogen Risk Assessment.	The toxicological literature continues to provide the strongest evidence for Pb exposure and cancer with supporting evidence provided by the epidemiologic literature. Epidemiologic studies of cancer incidence and mortality reported inconsistent results.

Ecological/Welfare Effects:		
Endpoint	**Evidence in the 2006 Pb AQCD**	**Evidence in the 2013 Pb ISA**
Developmental and Reproductive Effects	Terrestrial Organisms:	
	No information on reproduction in plants.	There is an insufficient number of studies that consider Pb effects on plant reproduction.
	Limited evidence in invertebrates and vertebrates.	Recent studies in a few taxa expand the evidence for Pb effects on developmental and reproductive endpoints for invertebrates and vertebrates at concentrations that generally exceed Pb levels in U.S. soils. In some organisms, exposure-dependent responses in development and reproductive outcomes are observed in experiments where exposure increases from background concentrations to concentrations found in heavily exposed sites near stationary sources. Data on terrestrial species is coherent with toxicological data from mammals in the context of human health research.
	Aquatic Organisms:	
	No reviewed studies on reproductive effects in aquatic plants. Reproductive and developmental effects reported in a few species of invertebrates at <50 µg Pb/L and in fish at <150 µg Pb/L	Recent evidence supports previous findings of reproductive and developmental effects of Pb in freshwater invertebrates and vertebrates and differential lifestage response at near ambient concentrations of Pb in some organisms. For saltwater invertebrates there is limited evidence for effects on early development at Pb concentrations higher than typically detected in marine environments.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Growth	Terrestrial Organisms:	
	Pb inhibits photosynthesis and respiration in plants. Limited evidence for growth effects in soil invertebrates, avian and mammalian consumers.	Recent studies support previous findings of Pb effects on plant growth, with some evidence for exposure-dependent decreases in the biomass of some plant species grown in Pb-amended or Pb-contaminated soil. Recent data for soil invertebrates supports previous evidence of increasing effects on growth with increasing exposure. Limited studies considered effects on growth on vertebrates.
	Aquatic Organisms:	
	Evidence for growth effects in algae, aquatic plants and aquatic invertebrates Most primary producers experience EC_{50} values for growth in the range of 1,000 to 100,000 µg Pb/L	The weight of the evidence continues to support growth effects of Pb in freshwater plants and invertebrates. Recent studies on growth in freshwater invertebrates find effects of Pb at lower concentrations than previously reported. Growth inhibition in one species of freshwater snail was observed at <4 µg Pb/L in juveniles. Lowest genus mean chronic value for Pb reported at 10 µg Pb/L in a freshwater mussel.
Survival	Terrestrial Organisms:	
	No information on mortality in plants. Effects of Pb on invertebrates and vertebrates include decreased survival. In terrestrial and avian species toxicity was observed in laboratory studies over a wide range of doses (<1 to >1,000 mg Pb/kg body weight per day) (U.S. EPA, 2005b).	Recent studies in invertebrates and vertebrates support previous associations between Pb exposure and mortality.
	Aquatic Organisms:	
	No studies reviewed on mortality in plants at current concentrations of Pb in the environment. Pb impacted survival of some aquatic invertebrates at <20 µg Pb/L dependent upon water quality variables (i.e., DOC, hardness, pH). Range of 96-hour LC_{50} values in fathead minnow: 810->5,400 µg Pb/L	The weight of evidence continues to support Pb effects on survival of freshwater invertebrates and vertebrates and indicates that there are effects in a few species at lower concentrations than previously reported. Recent evidence for effects in a few freshwater invertebrates at <20 µg Pb/L Recent evidence in freshwater fish for impacts to survival at <100 µg Pb/L dependent upon water quality parameters and lifestage. 96- hour LC_{50} values as low as 41 µg Pb/L in fathead minnows tested in natural waters from across the U.S.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Neurobehavioral Effects	Terrestrial Organisms:	
	Exposure to Pb in laboratory studies and simulated ecosystems may alter species competitive behaviors, predator-prey interactions, and contaminant avoidance behaviors.	Recent studies continue to support previous evidence that Pb exposure is associated with behavioral alterations. Recent studies identify possible molecular targets for Pb neurotoxicity in invertebrates and there is new evidence in a few invertebrate and vertebrate species for behavioral effects associated with Pb exposure (i.e., feeding and escape behaviors).
	Aquatic Organisms:	
	Exposure to Pb has been shown to affect brain receptors in fish and may alter avoidance behaviors and predator-prey interactions.	Recent studies continue to support previous evidence that Pb exposure is associated with behavioral alterations. Recent studies identify possible molecular targets for Pb neurotoxicity in fish and provide additional evidence for Pb effects on behaviors in freshwater organisms that may impact predator avoidance (swimming).
Hematological Effects	Terrestrial Organisms:	
	Pb effects on heme synthesis were documented in the 1986 Pb AQCD and continue to be studied in terrestrial biota. Changes in ALAD are not always related to adverse effects but may simply indicate exposure. The linkage between effects of Pb on blood parameters is well documented; however, the linkage between hematological indicators and ecologically relevant effects is less well understood.	Consistent with previous studies, the weight of the evidence in recent studies continues to support findings of Pb effects on heme synthesis and ALAD enzyme activity. Recent studies in birds near historical mining areas and altered serum profiles and blood cell counts in vertebrates provide evidence for additional species in which hematological endpoints are potentially affected by Pb.
	Aquatic Organisms:	
	In metal impacted habitats, ALAD is a recognized biomarker of Pb exposure. Changes in ALAD are not always related to adverse effects but may simply indicate exposure. In fish, Pb effects on blood chemistry have been documented with Pb concentrations ranging from 100 to 10,000 µg Pb/L.	Consistent with previous studies, the weight of the evidence in recent studies continues to support findings of Pb effects on ALAD and expands this evidence to additional species of bacteria, invertebrates, and vertebrates as well as in recent studies on altered blood cell counts in vertebrates. Additional field studies in both fresh and saltwater bivalves report a correlation between Pb and ALAD activity.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Physiological Stress	Terrestrial Organisms:	
	Pb exposure may cause lipid peroxidation and changes in glutathione concentrations. There are species differences in resistance to oxidative stress.	Recent studies continue to support previous associations of Pb exposure with physiological stress. New evidence includes upregulation of antioxidant enzymes, production of reactive oxygen species and increased lipid peroxidation associated with Pb exposure in additional species of terrestrial plants, invertebrates and vertebrates. Increasing effects follow increasing experimental exposures from background concentrations to concentrations found in heavily exposed sites near stationary sources.
	Aquatic Organisms:	
	Pb exposure associated with alterations in enzymes involved in physiological stress responses.	Recent studies continue to support previous associations of Pb exposure with physiological stress. New evidence in freshwater organisms includes upregulation of antioxidant enzymes, production of reactive oxygen species and increased lipid peroxidation associated with Pb exposure. Changes in antioxidant activity are reported in some saltwater invertebrates. Observed effects generally occurred at concentrations that typically exceed Pb levels in U.S. waters with limited evidence for effects associated with Pb at polluted sites.

Table 1-8 (Continued): Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb.

Endpoint	Evidence in the 2006 Pb AQCD	Evidence in the 2013 Pb ISA
Community and Ecosystem Level Effects	Terrestrial Ecosystems:	
	Effects of Pb difficult to interpret because of the presence of other stressors including metals. The 1986 Pb AQCD reported shifts toward Pb-tolerant communities at 500 to 1,000 mg Pb/kg soil. In the 2006 Pb AQCD, decreased species diversity and changes in community composition were observed in ecosystems surrounding former smelters.	Recent evidence for effects of Pb in soil microbial communities adds to the body of evidence for effects at higher levels of biological organization. In addition, effects of Pb uptake on reproduction, growth, and survival at the species level are likely to lead to effects at the population, community, and ecosystem level. However, most evidence for Pb toxicity to terrestrial biota is from single-species assays, and there are important uncertainties in generalizing from effects observed under small-scale, controlled conditions, up to effects at the ecosystem level of biological organization.
	Aquatic Ecosystems:	
	Most evidence of community and ecosystem level effects is from near Pb sources, usually mining effluents. Effects of Pb difficult to interpret because of the presence of other stressors including metals. Generally, there is insufficient information available for single materials in controlled studies to permit evaluation of specific impacts on higher levels of organization (beyond the individual organism).	Recent evidence for Pb effects on sediment-associated and freshwater aquatic plant communities add to the body of evidence of effects at higher levels of biological organization. However, most evidence for Pb toxicity to aquatic biota is from single-species assays. Uncertainties exist in generalizing effects observed under small-scale, predicted conditions up to effects at the ecosystem-level however, uptake of Pb into aquatic organisms and subsequent effects on reproduction, growth, and survival at the species level are likely to lead to effects at the population, community, and ecosystem level.

References for Chapter 1

Ankley, GT; Bennett, RS; Erickson, RJ; Hoff, DJ; Hornung, MW; Johnson, RD; Mount, DR; Nichols, JW; Russom, CL; Schmieder, PK; Serrrano, JA; Tietge, JE; Villeneuve, DL. (2010). Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment [Review]. Environ Toxicol Chem 29: 730-741. http://dx.doi.org/10.1002/etc.34

Aufderheide, AC; Wittmers, LE, Jr. (1992). Selected aspects of the spatial distribution of lead in bone [Review]. Neurotoxicology 13: 809-819.

Bayer, SA. (1989). Cellular aspects of brain development [Review]. Neurotoxicology 10: 307-320.

Bellinger, D; Leviton, A; Sloman, J. (1990). Antecedents and correlates of improved cognitive performance in children exposed in utero to low levels of lead. Environ Health Perspect 89: 5-11.

Bellinger, DC. (2008). Email from David Bellinger, Harvard Medical School, to Jee-Young Kim, EPA. SUBJECT: Request for additional information on Bellinger and Needleman (2003). (EPA-HQ-OAR-2006-0735-5156). U.S. Environmental Protection Agency. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OAR-2006-0735-5156

Besser, JM; Brumbaugh, WG; Brunson, EL; Ingersoll, CG. (2005). Acute and chronic toxicity of lead in water and diet to the amphipod Hyalella azteca. Environ Toxicol Chem 24: 1807-1815. http://dx.doi.org/10.1897/04-480R.1

Bonacker, D; Stoiber, T; Bohm, KJ; Prots, I; Wang, M; Unger, E; Thier, R; Bolt, HM; Degen, GH. (2005). Genotoxicity of inorganic lead salts and disturbance of microtubule function. Environ Mol Mutagen 45: 346-353. http://dx.doi.org/10.1002/em.20100

Brunekreef, B. (1984). The relationship between air lead and blood lead in children: A critical review [Review]. Sci Total Environ 38: 79-123. http://dx.doi.org/10.1016/0048-9697(84)90210-9

Buccelletti, E; Gilardi, E; Scaini, E; Galiuto, L; Persiani, R; Biondi, A; Basile, F; Silveri, NG. (2009). Heart rate variability and myocardial infarction: systematic literature review and metanalysis [Review]. Eur Rev Med Pharmacol Sci 13: 299-307.

Buekers, J; Redeker, ES; Smolders, E. (2009). Lead toxicity to wildlife: Derivation of a critical blood concentration for wildlife monitoring based on literature data [Review]. Sci Total Environ 407: 3431-3438. http://dx.doi.org/10.1016/j.scitotenv.2009.01.044

Bunn, TL; Marsh, JA; Dietert, RR. (2000). Gender differences in developmental immunotoxicity to lead in a chicken: Analysis following a single early low-level exposure in ovo. J Toxicol Environ Health A 61: 677-693. http://dx.doi.org/10.1080/00984100050195152

Burger, J; Gochfeld, M. (2005). Effects of lead on learning in herring gulls: An avian wildlife model for neurobehavioral deficits. Neurotoxicology 26: 615-624. http://dx.doi.org/10.1016/j.neuro.2005.01.005

Carbone, R; Laforgia, N; Crollo, E; Mautone, A; Iolascon, A. (1998). Maternal and neonatal lead exposure in southern Italy. Neonatology 73: 362-366.

CDC (Centers for Disease Control and Prevention). (2004). The health consequences of smoking: A report of the Surgeon General. Washington, DC: U.S. Department of Health and Human Services. http://www.surgeongeneral.gov/library/smokingconsequences/

CDC (Centers for Disease Control and Prevention). (2013). Fourth national report on human exposure to environmental chemicals, updated tables, March 2013. U.S. Department of Health and Human Services. http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Mar2013.pdf

Chen, A; Dietrich, KN; Ware, JH; Radcliffe, J; Rogan, WJ. (2005a). IQ and blood lead from 2 to 7 years of age: Are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environ Health Perspect 113: 597-601. http://dx.doi.org/10.1289/ehp.7625

Chen, HI; Chiu, YW; Hsu, YK; Li, WF; Chen, YC; Chuang, HY. (2010a). The association of metallothionein-4 gene polymorphism and renal function in long-term lead-exposed workers. Biol Trace Elem Res 137: 55-62. http://dx.doi.org/10.1007/s12011-009-8564-x

Chen, TH; Gross, JA; Karasov, WH. (2006b). Sublethal effects of lead on northern leopard frog (Rana pipiens) tadpoles. Environ Toxicol Chem 25: 1383-1389. http://dx.doi.org/10.1897/05-356R.1

Chetty, CS; Vemuri, MC; Campbell, K; Suresh, C. (2005). Lead-induced cell death of human neuroblastoma cells involves GSH deprivation. Cell Mol Biol Lett 10: 413-423.

Cho, SH; Richmond-Bryant, J; Thornburg, J; Portzer, J; Vanderpool, R; Cavender, K; Rice, J. (2011). A literature review of concentrations and size distributions of ambient airborne Pb-containing particulate matter. Atmos Environ 45: 5005-5015. http://dx.doi.org/10.1016/j.atmosenv.2011.05.009

Conterato, GMM; Bulcão, RP; Sobieski, R; Moro, AM; Charão, MF; de Freitas, FA; de Almeida, FL; Moreira, APL; Roehrs, M; Tonello, R; Batista, BL; Grotto, D; Barbosa, F, Jr; Garcia, SC; Emanuelli, T. (2013). Blood thioredoxin reductase activity, oxidative stress and hematological parameters in painters and battery workers: Relationship with lead and cadmium levels in blood. J Appl Toxicol 33: 142-150. http://dx.doi.org/10.1002/jat.1731

Du, M; Wang, D. (2009). The neurotoxic effects of heavy metal exposure on GABAergic nervous system in nematode Caenorhabditis elegans. Environ Toxicol Pharmacol 27: 314-320. http://dx.doi.org/10.1016/j.etap.2008.11.011

El-Fawal, HAN; Waterman, SJ; De Feo, A; Shamy, MY. (1999). Neuroimmunotoxicology: Humoral assessment of neurotoxicity and autoimmune mechanisms [Review]. Environ Health Perspect 107: 767-775.

Esbaugh, AJ; Brix, KV; Mager, EM; Grosell, M. (2011). Multi-linear regression models predict the effects of water chemistry on acute lead toxicity to Ceriodaphnia dubia and Pimephales promelas. Comp Biochem Physiol C Toxicol Pharmacol 154: 137-145. http://dx.doi.org/10.1016/j.cbpc.2011.04.006

Field, MP; Sherrell, RM. (2003). Direct determination of ultra-trace levels of metals in fresh water using desolvating micronebulization and HR-ICP-MS: Application to Lake Superior waters. J Anal At Spectrom 18: 254-259. http://dx.doi.org/10.1039/b210628k

Gilbert, SG; Rice, DC. (1987). Low-level lifetime lead exposure produces behavioral toxicity (spatial discrimination reversal) in adult monkeys. Toxicol Appl Pharmacol 91: 484-490.

Grosell, M; Brix, KV. (2009). High net calcium uptake explains the hypersensitivity of the freshwater pulmonate snail, Lymnaea stagnalis, to chronic lead exposure. Aquat Toxicol 91: 302-311. http://dx.doi.org/10.1016/j.aquatox.2008.10.012

Grosell, M; Gerdes, R; Brix, KV. (2006a). Influence of Ca, humic acid and pH on lead accumulation and toxicity in the fathead minnow during prolonged water-borne lead exposure. Comp Biochem Physiol C Toxicol Pharmacol 143: 473-483. http://dx.doi.org/10.1016/j.cbpc.2006.04.014

Grosell, M; Gerdes, RM; Brix, KV. (2006b). Chronic toxicity of lead to three freshwater invertebrates - Brachionus calyciflorus, Chironomus tentans, and Lymnaea stagnalis. Environ Toxicol Chem 25: 97-104. http://dx.doi.org/10.1897/04-654R.1

Hayes, EB, Orbach, H. G.; Fernandez, AM; Lyne, S; Matte, TD; McElvaine, MD. (1994). Long-term trends in blood lead levels among children in Chicago: Relationship to air lead levels. Pediatrics 93: 195-200.

Hilts, SR. (2003). Effect of smelter emission reductions on children's blood lead levels. Sci Total Environ 303: 51-58. http://dx.doi.org/10.1016/S0048-9697(02)00357-1

Hornung, RW; Lanphear, BP; Dietrich, KN. (2009). Age of greatest susceptibility to childhood lead exposure: A new statistical approach. Environ Health Perspect 117: 1309-1312.; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721877/

Hudson, CA; Cao, L; Kasten-Jolly, J; Kirkwood, JN; Lawrence, DA. (2003). Susceptibility of lupus-prone NZM mouse strains to lead exacerbation of systemic lupus erythematosus symptoms. J Toxicol Environ Health A 66: 895-918. http://dx.doi.org/10.1080/15287390306456

Huel, G; Sahuquillo, J; Debotte, G; Oury, JF; Takser, L. (2008). Hair mercury negatively correlates with calcium pump activity in human term newborns and their mothers at delivery. Environ Health Perspect 116: 263-267. http://dx.doi.org/10.1289/ehp.10381

Kannel, WB. (2000a). Elevated systolic blood pressure as a cardiovascular risk factor [Review]. Am J Cardiol 85: 251-255. http://dx.doi.org/10.1016/S0002-9149(99)00635-9

Kannel, WB. (2000b). Risk stratification in hypertension: New insights from the Framingham Study. Am J Hypertens 13: 3S-10S. http://dx.doi.org/10.1016/S0895-7061(99)00252-6

Kern, M; Wisniewski, M; Cabell, L; Audesirk, G. (2000). Inorganic lead and calcium interact positively in activation of calmodulin. Neurotoxicology 21: 353-363.

Kim, JH; Lee, KH; Yoo, DH; Kang, D; Cho, SH; Hong, YC. (2007). GSTM1 and TNF-alpha gene polymorphisms and relations between blood lead and inflammatory markers in a non-occupational population. Mutat Res Genet Toxicol Environ Mutagen 629: 32-39. http://dx.doi.org/10.1016/j.mrgentox.2007.01.004

Klaminder, J; Bindler, R; Emteryd, O; Renberg, I. (2005). Uptake and recycling of lead by boreal forest plants: Quantitative estimates from a site in northern Sweden. Geochim Cosmo Act 69: 2485-2496. http://dx.doi.org/10.1016/j.gca.2004.11.013

Klann, E; Shelton, KR. (1989). The effect of lead on the metabolism of a nuclear matrix protein which becomes prominent in lead-induced intranuclear inclusion bodies. J Biol Chem 264: 16969-16972.

Kominkova, D; Nabelkova, J. (2005). The risk assessment of heavy metals in the ecosystem of urban creeks. Water Sci Technol 53: 65-73. http://dx.doi.org/10.2166/wst.2006.298

Krieg, EF, Jr. (2007). The relationships between blood lead levels and serum follicle stimulating hormone and luteinizing hormone in the third national health and nutrition examination survey. Environ Res 104: 374-382. http://dx.doi.org/10.1016/j.envres.2006.09.009

Langdon, CJ; Hodson, ME; Arnold, RE; Black, S. (2005). Survival, Pb-uptake and behaviour of three species of earthworm in Pb treated soils determined using an OECD-style toxicity test and a soil avoidance test. Environ Pollut 138: 368-375. http://dx.doi.org/10.1016/j.envpol.2005.03.002

Lanphear, BP; Hornung, R; Khoury, J; Yolton, K; Baghurst, P; Bellinger, DC; Canfield, RL; Dietrich, KN; Bornschein, R; Greene, T; Rothenberg, SJ; Needleman, HL; Schnaas, L; Wasserman, G; Graziano, J; Roberts, R. (2005). Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. Environ Health Perspect 113: 894-899.

Lau, YS; Camoratto, AM; White, LM; Moriarty, CM. (1991). Effect of lead on TRH and GRF binding in rat anterior pituitary membranes. Toxicology 68: 169-179. http://dx.doi.org/10.1016/0300-483X(91)90019-W

Leggett, RW. (1993). An age-specific kinetic model of lead metabolism in humans. Environ Health Perspect 101: 598-616.

Liu, X; Dietrich, KN; Radcliffe, J; Ragan, NB; Rhoads, GG; Rogan, WJ. (2002). Do children with falling blood lead levels have improved cognition? Pediatrics 110: 787-791.

Mager, EM; Brix, KV; Grosell, M. (2010). Influence of bicarbonate and humic acid on effects of chronic waterborne lead exposure to the fathead minnow (Pimephales promelas). Aquat Toxicol 96: 135-144. http://dx.doi.org/10.1016/j.aquatox.2009.10.012

Mahler, BJ; Van Metre, PC; Callender, E. (2006). Trends in metals in urban and reference lake sediments across the United States, 1970 to 2001. Environ Toxicol Chem 25: 1698-1709.

Mahmoudi, E; Essid, N; Beyrem, H; Hedfi, A; Boufahja, F; Vitiello, P; Aissa, P. (2007). Individual and combined effects of lead and zinc on a free-living marine nematode community: Results from microcosm experiments. Exp Mar Bio Ecol 343: 217-226. http://dx.doi.org/10.1016/j.jembe.2006.12.017

Mebane, CA; Hennessy, DP; Dillon, FS. (2008). Developing acute-to-chronic toxicity ratios for lead, cadmium, and zinc using rainbow trout, a mayfly, and a midge. Water Air Soil Pollut 188: 41-66. http://dx.doi.org/10.1007/s11270-007-9524-8

Miranda, ML; Kim, D; Galeano, M; Paul, CJ; Hull, AP; Morgan, SP. (2007a). The relationship between early childhood blood lead levels and performance on end of grade tests. Environ Health Perspect 115: 1242-1247. http://dx.doi.org/10.1289/ehp.9994

Miranda, ML; Kim, D; Reiter, J; Overstreet Galeano, MA; Maxson, P. (2009). Environmental contributors to the achievement gap. Neurotoxicology 30: 1019-1024. http://dx.doi.org/10.1016/j.neuro.2009.07.012

Muntner, P; Menke, A; DeSalvo, KB; Rabito, FA; Batuman, V. (2005). Continued decline in blood lead levels among adults in the United States - The National Health and Nutrition Examination Surveys. Arch Intern Med 165: 2155-2161. http://dx.doi.org/10.1001/archinte.165.18.2155

Navas-Acien, A; Schwartz, BS; Rothenberg, SJ; Hu, H; Silbergeld, EK; Guallar, E. (2008). Bone lead levels and blood pressure endpoints: A meta-analysis. Epidemiology 19: 496-504. http://dx.doi.org/10.1097/EDE.0b013e31816a2400

Navas-Acien, A; Selvin, E; Sharrett, AR; Calderon-Aranda, E; Silbergeld, E; Guallar, E. (2004). Lead, cadmium, smoking, and increased risk of peripheral arterial disease. Circulation 109: 3196-3201. http://dx.doi.org/10.1161/01.CIR.0000130848.18636.B2

Nawrot, TS; Thijs, L; Den Hond, EM; Roels, HA; Staessen, JA. (2002). An epidemiological re-appraisal of the association between blood pressure and blood lead: A meta-analysis. J Hum Hypertens 16: 123-131.

NOAA (National Oceanic and Atmospheric Administration). (1999). Sediment quality guidelines developed for the national status and trends program. Silver Spring, MD: National Ocean Service.

NPS (U.S. National Park Service). (2011). WACAP database. http://www.nature.nps.gov/air/studies/air_toxics/WACAPreport.cfm

O'Flaherty, EJ. (1995). Physiologically based models for bone-seeking elements: V. Lead absorption and disposition in childhood [Review]. Toxicol Appl Pharmacol 131: 297-308. http://dx.doi.org/10.1006/taap.1995.1072

Rice, DC. (1990). Lead-induced behavioral impairment on a spatial discrimination reversal task in monkeys exposed during different periods of development. Toxicol Appl Pharmacol 106: 327-333. http://dx.doi.org/10.1016/0041-008X(90)90251-O

Rice, DC. (1992b). Lead exposure during different developmental periods produces different effects on FI performance in monkeys tested as juveniles and adults. Neurotoxicology 13: 757-770.

Rice, DC; Gilbert, SG. (1990b). Sensitive periods for lead-induced behavioral impairment (nonspatial discrimination reversal) in monkeys. Toxicol Appl Pharmacol 102: 101-109. http://dx.doi.org/10.1016/0041-008X(90)90087-B

Rice, DC; Karpinski, KF. (1988). Lifetime low-level lead exposure produces deficits in delayed alternation in adult monkeys. Neurotoxicol Teratol 10: 207-214. http://dx.doi.org/10.1016/0892-0362(88)90019-0

Ringenary, MJ; Molof, AH; Tanacredi, JT; Schreibman, MP; Kostarelos, K. (2007). Long-term sediment bioassay of lead toxicity in two generations of the marine amphipod Elasmopus laevis, SI Smith, 1873. Environ Toxicol Chem 26: 1700-1710. http://dx.doi.org/10.1897/06-303R1.1

Rothenberg, SJ; Rothenberg, JC. (2005). Testing the dose-response specification in epidemiology: Public health and policy consequences for lead. Environ Health Perspect 113: 1190-1195. http://dx.doi.org/10.1289/ehp.7691

Ruff, HA; Bijur, PE; Markowitz, M; Ma, YC; Rosen, JF. (1993). Declining blood lead levels and cognitive changes in moderately lead-poisoned children. JAMA 269: 1641-1646. http://dx.doi.org/10.1001/jama.1993.03500130055032

Sadiq, M. (1992). Lead in marine environments. In Toxic metal chemistry in marine environments. New York, NY: Marcel Dekker, Inc.

Schnaas, L; Rothenberg, SJ; Flores, MF; Martinez, S; Hernandez, C; Osorio, E; Perroni, E. (2004). Blood lead secular trend in a cohort of children in Mexico City (1987-2002). Environ Health Perspect 112: 1110-1115. http://dx.doi.org/10.1289/ehp.6636

Schwartz, J. (1991). Lead, blood pressure, and cardiovascular disease in men and women. Environ Health Perspect 91: 71-75.

Schwartz, J. (1994). Low-level lead exposure and children's IQ: A meta-analysis and search for a threshold. Environ Res 65: 42-55. http://dx.doi.org/10.1006/enrs.1994.1020

Schwartz, J; Pitcher, H. (1989). The relationship between gasoline lead and blood lead in the United States. J Offic Stat 5: 421-431.

Scinicariello, F; Yesupriya, A; Chang, MH; Fowler, BA. (2010). Modification by ALAD of the association between blood lead and blood pressure in the U.S. population: Results from the Third National Health and Nutrition Examination Survey. Environ Health Perspect 118: 259-264. http://dx.doi.org/10.1289/ehp.0900866

Shacklette, HT; Boerngen, JG. (1984). Element concentrations in soils and other surficial materials of the conterminous United States. (1270). Washington D.C.: Government Printing Office. http://pubs.usgs.gov/pp/1270/

Simon, DL; Maynard, EJ; Thomas, KD. (2007). Living in a sea of lead changes in blood- and hand-lead of infants living near a smelter. J Expo Sci Environ Epidemiol 17: 248-259. http://dx.doi.org/10.1038/sj.jes.7500512

Smolders, E; Oorts, K; van Sprang, P; Schoeters, I; Janssen, CR; McGrath, SP; McLaughlin, MJ. (2009). Toxicity of trace metals in soil as affected by soil type and aging after contamination: Using calibrated bioavailability models to set ecological soil standards. Environ Toxicol Chem 28: 1633-1642. http://dx.doi.org/10.1897/08-592.1

Soto-Jiménez, MF; Arellano-Fiore, C; Rocha-Velarde, R; Jara-Marini, ME; Ruelas-Inzunza, J; Voltolina, D; Frías-Espericueta, MG; Quintero-Alvarez, JM; Páez-Osuna, F. (2011b). Biological responses of a simulated marine food chain to lead addition. Environ Toxicol Chem 30: 1611-1617. http://dx.doi.org/10.1002/etc.537

Stayner, L; Steenland, K; Dosemeci, M; Hertz-Picciotto, I. (2003). Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. Scand J Work Environ Health 29: 317-324.

Suter, GW; Norton, SB; Fairbrother, A. (2005). Individuals versus organisms versus populations in the definition of ecological assessment endpoints. Integr Environ Assess Manag 1: 397-400. http://dx.doi.org/10.1002/ieam.5630010409

Telisman, S; Colak, B; Pizent, A; Jurasovic, J; Cvitkovic, P. (2007). Reproductive toxicity of low-level lead exposure in men. Environ Res 105: 256-266. http://dx.doi.org/10.1016/j.envres.2007.05.011

Téllez-Rojo, MM; Bellinger, DC; Arroyo-Quiroz, C; Lamadrid-Figueroa, H; Mercado-Garcia, A; Schnaas-Arrieta, L; Wright, RO; Hernandez-Avila, M; Hu, H. (2006). Longitudinal associations between blood lead concentrations lower than 10 microg/dL and neurobehavioral development in environmentally exposed children in Mexico City. Pediatrics 118: e323-e330. http://dx.doi.org/10.1542/peds.2005-3123

Tripathi, RM; Raghunath, R; Kumar, AV; Sastry, VN; Sadasivan, S. (2001). Atmospheric and children's blood lead as indicators of vehicular traffic and other emission sources in Mumbai, India. Sci Total Environ 267: 101-108. http://dx.doi.org/10.1016/S0048-9697(00)00770-1

U.S. EPA (U.S. Environmental Protection Agency). (1977). Air quality criteria for lead [EPA Report]. (EPA-600/8-77-017). Washington, DC. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=20013GWR.txt

U.S. EPA (U.S. Environmental Protection Agency). (1986a). Air quality criteria for lead [EPA Report]. (EPA/600/8-83/028aF-dF). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=32647

U.S. EPA (U.S. Environmental Protection Agency). (1986b). Air quality criteria for lead: Volume I of IV [EPA Report]. (EPA-600/8-83/028aF). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=32647

U.S. EPA (U.S. Environmental Protection Agency). (1986c). Lead effects on cardiovascular function, early development, and stature: An addendum to U.S. EPA Air Quality Criteria for Lead (1986) [EPA Report]. (EPA-600/8-83/028aF). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (1990a). Air quality criteria for lead: Supplement to the 1986 addendum [EPA Report]. (EPA/600/8-89/049F). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (1992). Framework for ecological risk assessment [EPA Report]. (EPA/630/R-92/001). Washington, DC. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30004UKJ.txt

U.S. EPA (U.S. Environmental Protection Agency). (2003a). Generic ecological assessment endpoints (GEAEs) for ecological risk assessment [EPA Report]. (EPA-630/P-02/004F). Washington, DC. http://www.epa.gov/raf/publications/pdfs/GENERIC_ENDPOINTS_2004.PDF

U.S. EPA (U.S. Environmental Protection Agency). (2003b). Guidance for developing ecological soil screening levels (Eco-SSLs): Review of background concentration for metals - Attachment 1-4 [EPA Report]. (OSWER Directive 92857-55). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (2005b). Ecological soil screening levels for lead: Interim final [EPA Report]. (OSWER Directive 9285.7-70). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (2006b). Air quality criteria for lead: Volume I of II [EPA Report]. (EPA/600/R-05/144aF). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/CFM/recordisplay.cfm?deid=158823

U.S. EPA (U.S. Environmental Protection Agency). (2006c). Air quality criteria for lead: Volume II of II [EPA Report]. (EPA/600/R-05/144bF). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/CFM/recordisplay.cfm?deid=158823

U.S. EPA (U.S. Environmental Protection Agency). (2007d). Guidance for developing ecological soil screening levels [EPA Report]. (OSWER Directive 92857-55). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (2008a). 2005 National Emissions Inventory data and documentation. Available online at http://www.epa.gov/ttn/chief/net/2005inventory.html (accessed November 1, 2010).

U.S. EPA (U.S. Environmental Protection Agency). (2008b). Ambient aquatic life water quality: Lead (draft) [EPA Report]. (EPA Contract No. 68-C-04-006). Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (2011a). 2008 National Emissions Inventory data and documentation. Available online at http://www.epa.gov/ttn/chief/net/2008inventory.html (accessed February 17, 2011).

U.S. EPA (U.S. Environmental Protection Agency). (2011c). Integrated review plan for the national ambient air quality standards for lead [EPA Report]. (EPA-452/R-11-008). Research Triangle Park, NC.

USGS (U.S. Geological Survey). (2012). 2010 minerals yearbook: Lead [advance release]. Washington, DC: U.S. Department of the Interior.

Van Larebeke, N; Koppen, G; Nelen, V; Schoeters, G; Van Loon, H; Albering, H; Riga, L; Vlietinck, R; Kleinjans, J. (2004). Differences in HPRT mutant frequency among middle-aged Flemish women in association with area of residence and blood lead levels. Biomarkers 9: 71-84. http://dx.doi.org/10.1080/13547500310001652160

Vandenhove, H; Olyslaegers, G; Sanzharova, N; Shubina, O; Reed, E; Shang, Z; Velasco, H. (2009). Proposal for new best estimates of the soil-to-plant transfer factor of U, Th, Ra, Pb and Po. J Environ Radioact 100: 721-732. http://dx.doi.org/10.1016/j.jenvrad.2008.10.014

Wang, DY; Xing, XJ. (2008). Assessment of locomotion behavioral defects induced by acute toxicity from heavy metal exposure in nematode Caenorhabditis elegans. J Environ Sci 20: 1132-1137. http://dx.doi.org/10.1016/S1001-0742(08)62160-9

Wang, N; Ingersoll, CG; Ivey, CD; Hardesty, DK; May, TW; Augspurger, T; Roberts, AD; van Genderen, E; Barnhart, MC. (2010f). Sensitivity of early life stages of freshwater mussels (Unionidae) to acute and chronic toxicity of lead, cadmium, and zinc in water. Environ Toxicol Chem 29: 2053-2063. http://dx.doi.org/10.1002/etc.250

Waterman, SJ; El-Fawal, HAN; Snyder, CA. (1994). Lead alters the immunogenicity of two neural proteins: A potential mechanism for the progression of lead-induced neurotoxicity. Environ Health Perspect 102: 1052-1056.

Watson, AP; Van Hook, RI; Jackson, DR; Reichle, DE. (1976). Impact of a lead mining smelting complex on the forest- floor litter arthropod fauna in the new lead belt region of southeast Missouri. (ORNL/NSF/EATC-30). Oak Ridge, Tennessee: Oak Ridge National Laboratory.

Weaver, VM. (2010). Further analysis of Korean lead worker data set with a focus on determining the functional form of the exposure-response relationship. Available online at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2011-0051-0028

Weaver, VM; Ellis, LR; Lee, BK; Todd, AC; Shi, W; Ahn, KD; Schwartz, BS. (2008). Associations between patella lead and blood pressure in lead workers. Am J Ind Med 51: 336-343. http://dx.doi.org/10.1002/ajim.20573

Wedding, JB; McFarland, AR; Cermak, JE. (1977). Large particle collection characteristics of ambient aerosol samplers. Environ Sci Technol 11: 387-390. http://dx.doi.org/10.1021/es60127a005

Weiss, B. (1988). Neurobehavioral toxicity as a basis for risk assessment [Review]. Trends Pharmacol Sci 9: 59-62.

Weisskopf, MG; Jain, N; Nie, HL; Sparrow, D; Vokonas, P; Schwartz, J; Hu, H. (2009). A prospective study of bone lead concentration and death from all causes, cardiovascular diseases, and cancer in the department of veterans affairs normative aging study. Circulation 120: 1056-1064. http://dx.doi.org/10.1161/circulationaha.108.827121

WHO (World Health Organization). (1948). Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946. In Constitution of the World Health Organization (pp. 2). Geneva, Switzerland. http://whqlibdoc.who.int/hist/official_records/constitution.pdf

Zhang, A; Park, SK; Wright, RO; Weisskopf, MG; Mukherjee, B; Nie, H; Sparrow, D; Hu, H. (2010a). HFE H63D polymorphism as a modifier of the effect of cumulative lead exposure on pulse pressure: The Normative Aging Study. Environ Health Perspect 118: 1261-1266. http://dx.doi.org/10.1289/ehp.1002251

Program Update

Airport Lead Monitoring

This Program Update provides a summary of the data currently available on concentrations of lead measured at 17 airport facilities in the U.S.

Concentrations of Lead at Airports

Outdoor concentrations of lead have greatly declined over the past few decades, in large part due to regulations that removed lead from fuels used in cars and trucks. However, lead continues to be emitted into the air from certain sources, such as ore and metal processing and aircraft that use leaded aviation gasoline (avgas). These aircraft are typically used for activities including business and personal travel, instructional flying, aerial surveys, agriculture, firefighting, law enforcement, medical emergencies, and express freight. Lead is not contained in jet fuel, which is used by commercial aircraft.

To protect the public from harmful levels of lead in outside air, EPA has established a National Ambient Air Quality Standard (NAAQS) for lead. In late 2008, EPA substantially strengthened this standard, revising the level from 1.5 micrograms per cubic meter ($\mu g/m^3$), to 0.15 $\mu g/m^3$, for a 3-month average concentration of lead in total suspended particles. This revised standard improves health protection for at-risk groups, especially children.

In conjunction with strengthening the lead NAAQS, EPA improved the existing lead monitoring network by requiring monitors to be placed in areas with sources such as industrial facilities and airports. State and local air quality agencies are now required to monitor near industrial facilities with estimated lead emissions of 0.50 tons or more per year and at airports with estimated emissions of 1.0 ton or more per year, as well as, on a case-by-case basis in locations where information indicates a significant likelihood of exceeding the standard. EPA required a 1-year monitoring study of 15 airports with estimated lead emissions between 0.50 and 1.0 ton per year in an effort to better understand how these emissions affect the air at and near airports. Airports for this 1-year monitoring study were selected based on factors such as the level of piston-engine aircraft activity and the predominant use of one runway due to wind patterns, in order to help evaluate airport characteristics that could lead to ambient lead concentrations that approach or exceed the lead NAAQS.

EPA United States Environmental Protection Agency

Office of Transportation and Air Quality
EPA-420-F-13-032
June 2013

As a result of these requirements, lead monitoring has been conducted at 17 airports. As of May 2013, states and local air authorities have collected and certified lead concentration data for at least 3 months from the 17 airports. The certified data are available in the table below. EPA anticipates having a full year of certified data from all 17 airports by May 2014, at which time the airport study will be complete.

Concentrations of Lead at Airports

Airport, State	Lead Design Value,* µg/m³
Auburn Municipal Airport, WA	0.06
Brookhaven Airport, NY	0.03
Centennial Airport, CO	0.02
Deer Valley Airport, AZ	0.04
Gillespie Field, CA	0.07
Harvey Field, WA	0.02
McClellan-Palomar Airport, CA	0.17
Merrill Field, AK	0.07
Nantucket Memorial Airport, MA	0.01
Oakland County International Airport, MI	0.02
Palo Alto Airport, CA	0.12
Pryor Field Regional Airport, AL	0.01
Reid-Hillview Airport, CA	0.09
Republic Airport, NY	0.01
San Carlos Airport, CA	0.33
Stinson Municipal, TX	0.03
Van Nuys Airport, CA	0.06

*The design value for lead is the maximum value of three-month average concentrations measured at that location.

Two airports have monitored lead concentrations that exceed the lead NAAQS. Fact sheets specific to these airports have been developed and are available at the EPA Region 9 webpage provided below. Supplemental sampling is being conducted at these two airports to evaluate lead concentrations at additional locations at and near the airport. Information from other airports that have previously been studied in greater detail indicates that air lead concentrations decrease within short distances from aircraft emissions.

EPA's Actions Regarding Lead Emissions from Aircraft Operating on Leaded Fuel

EPA is currently conducting the analytical work, including modeling and monitoring, to evaluate under section 231 of the Clean Air Act whether lead emissions from the use of leaded avgas in piston-engine aircraft cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare. Any proposed determination with regard to endangerment would be subject to public notice and comment, and we estimate the final determination will be in mid-to-late 2015. Additional details regarding EPA's evaluation are available in the Advance Notice of Proposed Rulemaking on Lead Emissions From Piston-Engine Aircraft Using Leaded Aviation Gasoline, and the associated public docket (links provided below).

If EPA makes a final positive endangerment finding (i.e., EPA finds that lead emissions from general aviation cause or contribute to air pollution which may reasonably be anticipated to endanger), the agency would initiate rulemaking to establish standards concerning lead emissions from piston-engine aircraft. FAA would then be required to prescribe regulations to insure compliance with such standards, and prescribe standards for the composition of aircraft fuel to control or eliminate certain emissions.

For Additional Information

For more information regarding monitoring at the San Carlos Airport and San Diego airports (McClellan-Palomar and Gillespie Field), please visit:

www.epa.gov/region9/air/airport-lead/

For more information on EPA's actions regarding the endangerment evaluation, please visit:

www.gpo.gov/fdsys/pkg/FR-2010-04-28/pdf/2010-9603.pdf
and
www.epa.gov/otaq/aviation.htm

For access to the rulemaking docket containing documents relevant to EPA's evaluation, please visit:

www.regulations.gov and enter EPA-HQ-OAR-2007-0294

For information on the Federal Aviation Administration's actions to eliminate leaded aviation fuels, please visit:

www.faa.gov/news/

For information on the Federal Aviation Administration's actions to reduce lead concentrations at airports, please visit:

www.faa.gov/airports/environmental/

For more information on how you can reduce your family's risk of lead exposure, please visit:

www.epa.gov/lead/parents.html#

For more information on lead in air, please visit:

www.epa.gov/airquality/lead/

Contact

Marion Hoyer
U.S. Environmental Protection Agency
Office of Transportation and Air Quality
2000 Traverwood Drive
Ann Arbor, MI 48105
734-214-4513,
E-mail: hoyer.marion@epa.gov

Or:

Meredith Pedde
U.S. Environmental Protection Agency
Office of Transportation and Air Quality
2000 Traverwood Drive
Ann Arbor, MI 48105
734-214-4748
E-mail: pedde.meredith@epa.gov