#778

Hemp Oil GRAS Notice

THE SAFETY AND THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF THE PROPOSED USE OF HEMP OIL IN HUMAN FOOD

Submitted By: Fresh Hemp Foods Ltd.

Prepared By: Marc C. Sanchez, Esq. (Contract In-House Counsel and Consultants, LLC d/b/a FDA Atty).

Table of Contents

Section 1
Administrative Information

April 4, 2018

HEMP OIL GRAS NOTICE

Introduction

Fresh Hemp Foods (the "Notifier") has determined that the intended use of its Cold Pressed Hemp Seed Oil (hereinafter "Hemp Oil") derived from whole hemp seeds and/or portion of hemp seeds is Generally Recognized As Safe (GRAS), based on section 201(s) of the Food Drug and Cosmetic Act and provisions of the related regulations (Subpart E of Part 170).

The Hemp Oil is marketed both as a bulk ingredient and as a branded product. Both are intended for use as an ingredient or garnish with conventional foods.

The bulk ingredient and branded product are available as organic or conventional product and they are registered as kosher, halal and non-gmo. Gluten free bulk ingredient is also available in both organic and conventional.

The determination of GRAS status is based on scientific procedures, in accordance with 21 C.F.R. § 170.30(b) and conforms to the guidance issued in § 170.36.

Administrative Information

1.1 Claim Regarding GRAS Status

Fresh Hemp Foods Ltd. is hereby submitting a GRAS notice (the "Notice") in accordance with 21 CFR 170.255 Part 1.

This Notice based on scientific procedures, in accordance with 21 C.F.R. § 170.30(b) and conforms to the guidance issued in § 170.36.

1.2 Name and Address of Notifier

Notifier/Manufacturer	Notifier's Agent
Fresh Hemp Foods Ltd. (d/b/a Manitoba Harvest Hemp Foods, Hemp Oil Canada and Just Hemp Foods) 69 Eagle Drive Winnipeg, MB R2R1V4 Canada	Marc C. Sanchez, Esq. Contract In-House Counsel and Consultants LLC (d/b/a FDA Atty) 1717 Pennsylvania Ave. #1025 Washington, D.C. 20006 Ph: 202.765.4491 E-mail: msanchez@fdaatty.com

1.3 Common or Usual Name of GRAS Substance

The name of the notified substance is Cold Pressed Hemp Seed Oil (herinafter "Hemp Oil").

Cultivar: The Hemp Oil is generally derived from the hemp seeds of Cannabis sativa L and they may be organic or conventional. All cultivars used comply with Health Canada's Healthy Environments and Consumer Safety Branch Industrial Hemp Regulations (Subsection 39(1) of the *Industrial Hemp Regulations*).

1.4 Intended Use

Food additive in various finished conventional foods in human food products (See Section 5 below). The food products are intended for the general population (age 2 and above). It is not intended to be added to any USDA/FSIS regulated products and is not intended to be added to any infant formulas.

Refer to Table 1 for application levels of organic and conventional Hemp Oil for the General Population.

1.5 Basis for GRAS Determination

The Notifier is submitting notification to the FDA that it has concluded the intended use of Hemp Oil as an ingredient in human food products is Generally Recognized as Safe (GRAS) based on scientific procedures as described in 21 C.F.R. § 170.30(b).

The content of this submission, as described herein, demonstrates that Hemp Oil is GRAS for the intended use as a human food and/or food ingredient based on (1) Estimated exposure under the intended conditions of use; (2) Literature pertaining to the safety of plant based oil; (3) Literature pertaining to the safety of Delta 9-tetrahydrocannabinol ((6aR, 10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo [b,d] pyran-1-ol) commonly known as THC (hereinafter, "THC"); (4) Expert interpretation of published literature pertaining to safety of THC (Appendix 1); and, (4) Established identity of Hemp Oil as a substance characterized as meeting Fresh Hemp Food Ltd. specifications and produced in accordance with current Good Manufacturing Practices (cGMP) and Health Canada's Healthy Environments and Consumer Safety Branch Industrial Hemp Regulations.

1.6 Exemption from Food Additive Petition

Based on the information contained herein the Notifier asserts the notified substance, Hemp Oil, is not subject to premarket approval requirements under the Food Additive Amendments of 1958 to the Food Drug and Cosmetic Act on the basis the notified substance is GRAS under the conditions of its intended use.

1.7 Availability of Information for FDA Review

The data and information that serve as the basis for the GRAS conclusion herein are available to the FDA and copies may be made during normal business hours at the Firm's address as provided in Section 1.2 above.

The Firm will provide the FDA a complete and accurate copy of any data or information used to conclude the notified substance is GRAS in an electronic format during the Agency's evaluation of this notice.

1.8 Exemption from Disclosure

The data and information of this GRAS notice are NOT exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552.

1.9 Certification

The undersigned certifies that to the best of their knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to the Firm and pertinent to the evaluation of the safety and GRAS status of the use of the Hemp Oil.

1.10 Name and position of Signatory

Signature	Notifier's Agent
(b) (6)  Digitally signed by Marc C. Sanchez, Esq. Date: 2018.04.09 16:49:13 -04'00' Adobe Acrobat Reader version: 2018.011.20038	Marc C. Sanchez, Esq. Contract In-House Counsel and Consultants LLC (d/b/a FDA Atty) 1717 Pennsylvania Ave. #1025 Washington, D.C. 20006 Ph: 202.765.4491 E-mail: msanchez@fdaatty.com

Section 2
Identity and Specifications

2. Product Identity and Specifications

2.1 Common or Usual Name of the Notified Substance

The name of the notified substance is Cold Pressed Hemp Seed Oil (herinafter "Hemp Oil")

Cultivar: The Hemp Oil is generally derived from the seeds of Cannabis sativa L. All cultivars used comply with Health Canada's Healthy Environments and Consumer Safety Branch Industrial Hemp Regulations.

The Hemp Oil is marketed both as a bulk ingredient and as a branded product. Both are intended for use as an ingredient or garnish with conventional foods. The Hemp Oil bulk ingredient and branded product are available as organic or conventional product and they are registered as kosher, halal and non-gmo. Gluten free bulk ingredient is also available in both organic and conventional format.

Fresh Hemp Foods produces Hemp Oil through mechanical separation of the oil from the whole or parts of seeds using cold pressing.

2.2 Growing information

Fresh Hemp Foods Ltd. abides by the Industrial Hemp Regulations as set by Health Canada (1998).

Delta 9-tetrahydrocannabinol ((6aR, 10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo [b,d] pyran-1-ol) commonly known as THC ("THC") and its precursor THCA are present in the hemp plant at about a 1 to 9 ratio (EIHA 2017). THC is not found in the interior of hemp seed unless there has been physical cross contamination of the seed hull with cannabinoid-containing resins in bracts and leaves during maturation, harvesting and processing. THC is psychoactive but THCA has no psychotropic effect as long as it is not heated.

The Industrial Hemp Regulations ensure that all hemp acres and producers are licensed, indicating that THC levels in the crop are in accordance with regulated limits. Further, as per the Industrial Hemp Regulations, products derived from hemp seeds shall have a maximum allowable THC limit of 10 µg/g.

Fresh Hemp Foods Ltd. is licensed by Health Canada and contracts only licensed hemp seed acres meeting the Industrial Hemp Regulations (Health Canada 1998). Fresh Hemp Foods Ltd. tests hemp seed product at third party accredited laboratories to confirm THC levels are compliant with the regulated limits of not more than 10 µg/g.

Fresh Hemp Foods Ltd. prohibits the use of in-crop herbicides and pesticides as a normal practice for the production of hemp seed grown under contract.

2.3 Identity, Composition and Quality Specifications

Specifications

Refer to Table 2 for specifications applied by Fresh Hemp Foods Ltd. to the organic and conventional Hemp Oil

Nutritional Data

Refer to Table 3 for typical nutritional data for organic and conventional Hemp Oil.

Labeling and Storage Information

Label Declaration: Organic Hemp Oil or Conventional Hemp Oil.

Storage conditions: Should be stored in a cool, dry location and in the original sealed package away from odorous material.

Shelf life: The shelf life is a minimum of 9 months from date of manufacture when stored in the original sealed packaging.

Allergens

Refer to Table 4 for the allergen declaration for organic and conventional Hemp Oil.

Fatty Acid Profile

Refer to Table 5 for the fatty acid profile for organic and conventional Hemp Oil.

2.4 Manufacturing Process

Narrative on Manufacturing Method

All whole hemp seed processed by Fresh Hemp Foods Ltd. is grown from Health Canada approved cultivars of industrial hemp which has been grown by licensed growers who are producing industrial hemp seed under license from Health Canada.

Throughout the planning and growing seasons, company agronomists provide services and guidance to ensure growers implement best management practices for field selection, growth, harvest and storage of hemp seed to ensure safety and quality of the seed.

After harvest and drying, a field harvest sample is requested from the grower to review safety and quality. Prior to processing, the seed is sent to a seed cleaner for mechanical removal of debris, weed seeds and other crop seeds. The seed is then shipped by an approved trucking company to the GFSI (BRC) certified Fresh Hemp Foods Ltd. facility for processing.

The hemp seed is stored in locked bins upon receipt. Representative samples are taken and tested to ensure quality and safety of the seed prior to processing.

The seed is further mechanically cleaned to remove foreign materials prior to pressing. Pressing is a mechanical process. No additives or processing aids are added to the seed during processing. The hemp is crushed (cold pressed) in oil pressing equipment. The oil is filtered through filter paper to improve quality and consistency and remove any sediment/foreign material prior to being packaged in bulk bladders.

Representative samples are taken from each bulk tote and sent to the laboratory for testing. The final product is tested for safety and quality prior to packaging and shipment.

The oil is either shipped bulk or packaged into smaller packages (drums, pails, plastic or glass bottles etc.) and shipped to customers.

List of Products Added During Manufacturing (Raw Materials)
NO products are added during the manufacturing process.

Flow Chart
Refer to Figure 1 for manufacturing Flow Chart for Hemp Oil.

Batch/Lot Analysis
Consistency on Final Product Specifications

To demonstrate conformance to listed product specifications in Table 2, Fresh Hemp Foods Ltd. has provided analysis from multiple lots of Hemp Oil (refer to Tables 6). Although lot to lot variation can occur, all results are within specification indicating consistency in the process and compliance to the product specifications set forward.

Refer to Tables 7 and 8 for representative analytical data confirming conformance with heavy metals and aflatoxin specifications.

The plant *Cannabis sativa L.* is well known to uptake and remove heavy metals from the soil. The distribution is such that the content of the heavy metals is lowest in the seed in comparison to other parts of the plant (roots>stems>leaves>seed) (Angelova et.al. 2004). Therefore, the risk of heavy metal contamination is lowest in seed, which is the plant part used to manufacture the hemp food products produced by Fresh Hemp Foods Ltd. Since the risk is low, heavy metals are not tested per lot and testing is completed at a frequency based on risk.

Aflatoxins are the main potential mycotoxin that can be found in oilseeds (https://www.gov.mb.ca/agriculture/food-safety/at-the-food-processor/mycotoxins.html). Mycotoxins production is more likely to occur when the oilseeds moisture content is 20-25% (Manitoba Agriculture 2017). A requirement of Fresh Hemp Foods Ltd. is that a sample arrives at a Fresh Hemp Foods Ltd. facility immediately after harvest and drying and moisture content must be verified. This moisture content requirement manages the risk of aflatoxin production. Aflatoxins are thus not tested every lot and rather at a lower frequency based on risk.

Pesticide and herbicide residues are not tested since Fresh Hemp Foods Ltd. prohibits the use of in-crop herbicides and pesticides as a normal practice for the production of hemp seed grown under contract.

No products are added during the manufacturing of the Hemp Oil.

There are no known anti-nutritional properties.

Section 3
Dietary Exposure

3. Dietary Exposure

3.1. Overview of Consumption

Hemp has been reconsidered as a valuable industrial crop for both food and fiber in Canada and European countries during at least the last decade. As a result, hempseed and hempseed food products have become available to the general public in a variety of foods including Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil.

Hemp as a food has long been recognized for its nutritional properties and valued as food for humans throughout Asia, India, Russia and Eastern Europe. In China, roasted hempseed is still sold as snacks by street venders. In Russia, 'black' oil has been pressed from hempseed and used as a substitute for more expensive sources of dietary fat, such as butter and hydrogenated margarines. Traditional hempseed foods can be found in Latvia and much of Eastern Europe.

Although this submission does not make a history of use claim for GRAS, there is a long-history and a variety of uses over a widespread geographic area that reinforces the scientific data and recognition by the scientific community of hempseed's safety and utility as a nutritive food.

The Congressional Research Service (CRS) issued a report on March 10, 2017 titled *Hemp as an Agricultural Commodity* (CRS March 2017). CRS cited current industry estimates of nearly $600 million in U.S. hemp sales. Food uses account for over 16% of those sales. The CRS report favorably covers a wide range of hemp food and beverage products currently sold in the US.

3.2. Exposure Estimates

Hemp Oil

Refer to Table 1 for a summary of the anticipated uses and minimum and maximum levels of inclusion of Hemp oil in food products.

USDA NHANES 2013-2014 survey data were used to estimate mean and 90th percentile consumption of Hemp Oil for foods anticipated to be consumed daily which could reasonably be expected to be manufactured using Hemp Oil as an ingredient. Refer to Tables 9 to 13 for estimated exposure to Hemp Oil.

To thoroughly assess the probability of harm from Hemp Oil, a conservative and upper-bound level of intake was modeled. The exposure estimates are then used in Section 5 to compare to levels found in the literature.

There is currently no information available in USDA NHANES survey data specific to consumption of industrial hemp seed products. Therefore, food categories were selected based on how industrial hemp seed materials could be used in typical food products. The following list is not all inclusive. It gives examples of foods captured within the categories selected from the

NHANES 2013-2014 survey data. The examples represent typical applications where it is anticipated that ingredients derived from hemp seed are likely to be used:

1. Hemp Oil would be used in a similar way to canola, cottonseed, olive, flax, safflower, soybean and sunflower oils.
2. Hemp Protein Powder, Hemp Oil, Hulled Hemp Seed based non-dairy milk would be used in a similar way to legume-based, cereal-based or nut- or seed-based non-dairy milks and spreads.

Assumptions and Chain of Contingencies Used to Develop Conservative Level of Intake

The quantity of Hemp oil anticipated to be consumed on a daily basis for individuals aged 2 years and older and children aged 2 to 5 years and 6 to 11 years has been estimated at the lowest, middle and maximum levels based on rates of inclusion specified in Table 1. Refer to Tables 9 to 13. For discussion purposes, the highest level of inclusion and highest levels of consumption have been used to estimate exposure to Hemp Oil.

The intended use of Hemp Oil at the maximum inclusion levels listed in Table 1 will result in mean and 90th percentile intake of 4.11 and 8.22 g/person/day of Hemp Oil from all food categories for the general population ages 2 and older (Table 9). It can be conservatively estimated that maximum inclusions levels would result in mean and 90th percentile intake of Hemp Oil of 2.4 and 4.81 g/person/day for boys aged 2 to 5 years, 2.29 and 4.58 g/person/day for girls aged 2 to 5 years, 3.03 and 6.06 g/person/day for boys aged 6 to 11 years and 3.24 and 6.48 g/person/day for girls aged 6 to 11 years (Tables 9 to 13).

The use of Hemp Oil is not expected to exceed 8.25 grams per day for any of the age groups when used at the maximum level in the food categories in Table 1. The usage level is variable depending on application and is self-limiting due to sensory and functional limitations.

Cumulative Hemp Consumption

Multiple GRAS Notices Used in Conservative Exposure Estimates

Unique to hemp seed, GRAS notifications are split between three (3) separate but interrelated submissions. Those are GRN #### (Hemp Oil), GRN 000765 (Hulled Hemp Seed), and GRN #### (Hemp Protein Powder). All three notified substances are from the same material, hemp seed, but extract or used different components. The exposure estimate below could not look at one without estimating consumption of the others. Therefore, one key assumption in developing an upper-bound exposure estimate is that consumption of one hemp product would likely mean consumption of other hemp products requiring the use and reference of multiple GRAS notifications.

Refer to Tables 14 to 18 for estimated exposure to all Fresh Hemp Foods Ltd. hemp ingredients, including Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil. To thoroughly assess the probability of harm from Hemp Oil and all other hemp products, a conservative and upper-bound

level of intake was modeled. The exposure estimates are then used in Section 6 to compare to levels found in the literature.

USDA NHANES 2013-2014 survey data were used to estimate mean and 90th percentile consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil for foods anticipated to be consumed daily which could reasonably be expected to be manufactured using hemp as an ingredient.

Assumptions and Chain of Contingencies Used to Develop Conservative Level of Intake

The quantity of Fresh Hemp Foods Ltd. hemp ingredients anticipated to be consumed on a daily basis for individuals aged 2 years and older and children aged 2 to 5 years and 6 to 11 years has been estimated at the lowest, middle and maximum levels based on rates of inclusion specified in the respective GRAS Notifications. Refer to Tables 14 to 18 for a summary of the total level of each ingredient anticipated to be consumed by each age group. For discussion purposes, the highest level of inclusion and highest levels of consumption have been used to estimate exposure to each hemp ingredient.

The intended use of each hemp ingredient at the maximum inclusion levels will result in a cumulative mean and 90th percentile intake of 18.05 and 36.12 g/person/day from all food categories for the general population ages 2 and older (Table 14). It can be conservatively estimated that maximum inclusions levels would result in cumulative mean and 90th percentile intake of 14.44 and 28.88 g/person/day for boys aged 2 to 5 years, 12.67 and 25.33 g/person/day for girls aged 2 to 5 years, 15.16 and 30.32 g/person/day for boys aged 6 to 11 years and 15.55 and 31.1 g/person/day for girls aged 6 to 11 years (Tables 14 to 18).

Hemp food products are well established in Europe, especially Germany. It has been estimated by the European Industrial Hemp Alliance (EIHA 2017) that German consumers would be exposed to about 443.81 grams of hemp daily through consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil. EIHA identified similar categories comparable to the ones anticipated in this GRN notice but estimated their level assuming that hemp would be used as a 100% replacement for other materials. This level is not realistic and the authors themselves noted that hemp is unlikely to be used as a full replacement for other standard materials.

The exposure to THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil is dependent upon consumption habits and is self-limiting due to sensory and functional limitations of the hemp ingredients, so it is not expected to exceed 0.1938 mg/person/day when foods from all groups and containing maximum inclusion levels are consumed at the 90th percentile by any individual age 2 years and older (refer to Table 19).

The cumulative total of THC consumed by 2 to 5 years old, 6 to 11 year old and individuals aged 2 years and older is anticipated to be spread over various foods consumed over the course of three main meals in a 24 hour period.

3.3. Dietary Exposure to THC

Refer to Sections 4B.i. and 4.B.ii. for discussion on how much Hemp Oil and cumulative hemp ingredient is anticipated to be consumed by children age 2 to 5 years, 6 to 11 years and all individuals age 2 years and older.

THC has been included in the safety discussion of this GRN since oral consumption of Hemp Oil and foods containing Hemp Oil and/or other hemp ingredients will inadvertently result in the ingestion of small amounts of THC, a psychotropic cannabinoid which naturally occurs in low levels in the seeds of *Cannabis sativa* L.

Hemp Oil

The THC levels in Hemp Oil is controlled through internal Fresh Hemp Foods Ltd. measures in combination with strict enforcement of Health Canada's Industrial Hemp Regulations. All *Cannabis sativa* L seed is grown under license from Health Canada using specific cultivars that have been thoroughly vetted as low THC producing varieties. Fresh Hemp Foods Ltd. ensures that the health risk posed by THC exposure is mitigated by employing a combination of seed cleaning, processing and testing to ensure that all Fresh Hemp Foods Ltd. hemp ingredients (see GRNs filed with this Notice) are compliant with maximum THC limits imposed by Health Canada and Fresh Hemp Foods Ltd.

The Fresh Hemp Foods Ltd specification is not more than 10 µg/g THC for Hemp Oil which is consistent with the maximum limit of not more than 10 µg/g set forth by the Industrial Hemp Regulations. For discussion purposes, THC exposure at the maximum Fresh Hemp Foods Ltd. specification of NMT 10 µg/g will be used to evaluate THC exposure from Hemp Oil.

Upper-Bound Estimation – THC from Hemp Oil
Refer to Table 20. At the maximum level of 10 µg/g THC, it can be conservatively anticipated that individuals age 2 years and older would consume a mean and 90th percentile intake of 0.0411 mg and 0.0822 mg/person/day of THC from Hemp Oil if they consumed all food groups at the maximum level of use shown in Table 1.

Refer to Tables 21 to 24. It can be conservatively estimated that a maximum level of 10 µg/g THC would result in the consumption of a mean and 90th percentile intake of 0.024 and 0.0481 mg THC/person/day for boys aged 2 to 5 years, 0.0229 and 0.0458 mg THC/person/day for girls aged 2 to 5 years, 0.0303 and 0.0606 mg THC/person/day for boys aged 6 to 11 years and 0.0324 and 0.0648 mg THC/person/day for girls aged 6 to 11 years if they consumed Hemp Oil at the maximum level in all food groups.

Upper-Bound Estimation – THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil Using Monte Carlo Modelling
Monte Carlo modelling was also used to estimate THC exposure at the 90th percentile based on the mean THC level detected by historical third party analytical testing. The exposure to THC was estimated at 0.0772 mg THC/person/day for Hemp Protein Powder for individuals age 2

years and older (Figure 8). The estimated 90th percentile is 0.0451 mg THC/person/day for boys aged 2 to 5 years, 0.0431 mg THC/person/day for girls aged 2 to 5 years, 0.0566 mg THC/person/day for boys aged 6 to 11 years and 0.0605 mg THC/person/day for girls aged 6 to 11 years (refer to Figures 16, 24, 32, 40 respectively).

For all age groups, these daily amounts are estimated to be the cumulative total consumption of Hemp Oil over the course of a full 24-hour period and are expected to encompass three meals consumed roughly 4 hours apart.

In the hemp crop and hemp food, THC and THCA are present, often in a 1 to 9 ratio (EIHA 2017) . THCA has no psychotropic effect as long as it is not heated. Transformation of THCA to THC is time and temperature dependent. To fully convert THCA to THC at 115 °C it takes about 2 hours (reported by EIHA 2017). For example, a cake in the oven has an internal temperature of less than 100 °C (as long as water is present). Using an average baking time of 45 min, this would mean, that only about 1/3 of the available THCA is able to be converted into THC. The majority of foods made from hemp seeds are anticipated to be exposed to low temperatures or short duration of heat since hemp ingredients contain high amounts of polyunsaturated fatty acids and hemp oil has a low smoke point that makes it unsuitable for frying.

Cumulative Hemp Consumption

The THC levels in Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil is controlled through internal Fresh Hemp Foods Ltd. measures in combination with strict enforcement of Health Canada's Industrial Hemp Regulations. All *Cannabis sativa* L seed is grown under license from Health Canada using specific cultivars that have been thoroughly vetted as low THC producing varieties. Fresh Hemp Foods Ltd. ensures that the health risk posed by THC exposure is mitigated by employing a combination of seed cleaning, processing and testing to ensure that all Fresh Hemp Foods Ltd. hemp ingredients (see GRNs filed with this Notice) are compliant with maximum THC limits imposed by Health Canada or the tighter limits self-imposed (on specific materials) by Fresh Hemp Foods Ltd.

The Fresh Hemp Foods Ltd specification is not more than 4 µg/g THC for Hemp Protein Powder and Hulled Hemp Seed which is well below the maximum limit of not more than 10 µg/g set forth by the Industrial Hemp Regulations. The Fresh Hemp Foods Ltd specification is not more than 10 µg/g THC for Hemp Oil. For discussion purposes, THC exposure at the maximum Fresh Hemp Foods Ltd. specifications will be used to evaluate THC exposure from all hemp ingredients.

Upper-Bound Estimation – THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil at Maximum Fresh Hemp Foods Ltd. Specification Limits
Refer to Table 19. At the maximum THC level permitted by the Fresh Hemp Foods Ltd. specifications, it can be conservatively anticipated that individuals age 2 years and older would consume a mean and 90th percentile intake of 0.0968 and 0.1938 mg/person/day of THC if they consumed all hemp ingredients at the maximum level of use as indicated in Tables 14 to 18.

Refer to Tables 25 to 28. It can be conservatively estimated that a maximum level of Hemp Ingredients would result in the consumption of a mean and 90th percentile intake of 0.0722 and 0.1444 mg THC/person/day for boys aged 2 to 5 years, 0.0644 and 0.1288 mg THC/person/day for girls aged 2 to 5 years, 0.0788 and 0.1576 mg THC/person/day for boys aged 6 to 11 years and 0.0816 and 0.1633 mg THC/person/day for girls aged 6 to 11 years if they consumed all hemp ingredients at the maximum level of use as indicated in Tables 14 to 18.

For all age groups, these daily amounts are estimated to be the cumulative total consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil over the course of a full 24-hour period and are expected to encompass three meals consumed roughly 4 hours apart.

Upper-Bound Estimation – THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil Using Monte Carlo Modelling

Monte Carlo modelling was used to estimate THC exposure at the 90th percentile based on the mean THC level detected by historical third party analytical testing of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil. The exposure to THC was estimated at 0.1049 mg THC/person/day for individuals age 2 years and older, 0.0698 mg THC/person/day for boys aged 2 to 5 years, 0.0651 mg THC/person/day for girls aged 2 to 5 years, 0.0794 mg THC/person/day for boys aged 6 to 11 years and 0.0834 mg THC/person/day for girls aged 6 to 11 years (refer to Figures 2, 10, 18, 26, 34 respectively).

3.4. Dietary Exposure to Hemp Derived Oil

Cold pressed Hemp Oil is comprised of about 77% polyunsaturated fatty acids and 13% monounsaturated fatty acids (Table 3). Alpha-linolenic acid (ALA, omega-3) and Linoleic Acid (LA, omega-6) make up the majority of the polyunsaturated content although there are notable amounts of Stearidonic Acid (SA) and Gamma-linoleic acid Acid (GLA) present (Table 5). ALA and LA are considered essential fatty acids, meaning that they must be obtained from the diet (Jones 2012).

Intake recommendations for fatty acids and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board of the Institute of Medicine (IOM 2005). When the IOM last reviewed omega-3s, insufficient data was available to establish an Estimated Average Requirement (EAR), so the IOM established Adequate Intakes (AIs) for all ages based on omega-3 intakes in healthy populations. Intake at the AI level is assumed to ensure nutritional adequacy (IOM 2005).

The AI for omega-3 has been set at 0.7 g and 0.9 g for males and females age 1 to 3 years and 4 to 8 years respectively (IOM 2005). For ages 1 and older, the AIs apply only to ALA because ALA is the only omega-3 that is essential. IOM did not establish specific intake recommendations for other long chain omega-3s including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

IOM has set the AI for omega-3 at 1.2 g to 1.6 g and 1 g to 1.1 g for males and females age 9 to 13 and 14 to 18 years respectively. AIs are set at 1.6 g and 1.1 g for males and females age 19 years and older (IOM 2005).

The intended use of Hemp Oil at the maximum inclusion levels listed in Table 1 will result in mean and 90th percentile intake of 4.11 and 8.22 g/person/day of Hemp Oil from all food categories for the general population ages 2 and older (Table 9). Refer to Tables 10 to 13. It can be conservatively estimated that maximum inclusions levels would result in mean and 90th percentile intake of Hemp Oil of 2.4 and 4.81 g/person/day for boys aged 2 to 5 years, 2.29 and 4.58 g/person/day for girls aged 2 to 5 years, 3.03 and 6.06 g/person/day for boys aged 6 to 11 years and 3.24 and 6.48 g/person/day for girls aged 6 to 11 years. Hemp Oil typically contains about 16% ALA, so the AI is not exceeded by the conservative mean and 90th percentile consumption levels estimated by the exposure data.

Hemp Oil is recognized by Food Standards Australia New Zealand as being a useful alternative dietary source of many nutrients and polyunsaturated fatty acids, particularly essential fatty acids LA and particularly ALA (FSANZ 2017). They based their opinion on the contribution of ALA and LA from low THC hemp versus the Nutrient Reference Values for Australia and New Zealand which specify Adequate Intakes (AIs) for the essential fatty acids: LA (men 13 g/day; women 8 g/day) and ALA (men 1.3 g/day; women 0.8 g/day.)

FDA has issued "no questions" letters in response to Generally Recognized As Safe (GRAS) Notifications (GRNs) on novel oil sources Sacha Inchi (GRN 506) and Camelina (642). These sources are similar to Hemp Oil because they are also highly unsaturated but they do not appear to contain SA or GLA (Table 34). Hemp Oil is similar to other commercially available oils like canola, flax, walnut and cottonseed based on the typical proportions of ALA, LA and oleic acid (OA) as reported in government nutrient databases (Table 34)

GRN 506 and 642 each contain reviews of the published safety information regarding the metabolism, toxicology, and human health and safety data for the respective oil sources. Based on these GRAS notifications, FDA currently permits the use of these oils at the use levels indicated in the notifications. The level of use and anticipated exposure to specific fatty acids resulting from consumption of Hemp Oil is similar to the exposure anticipated from the consumption of the oils in these notifications and is also anticipated to be similar to the levels of exposure resulting from general consumption of the commercial oil sources detailed in Table 34.

In accordance with Section 4.B.iii. Multiple GRAS Notices Used in Conservative Exposure Estimates, risk resulting from exposure to hemp derived oil was determined by assessing the cumulative exposure to oil from all Fresh Hemp Foods Ltd. hemp ingredients. Hemp Oil (GRN ####) is almost entirely oil. Hulled Hemp Seed (GRN 000765) and Hemp Protein Powder (GRN ####) contain significant amounts of oil and are included in this evaluation.

Refer to Tables 29 to 33 for the upper bound exposure to hemp oil resulting from the conservative cumulative consumption of oil from Hemp Oil, Hulled Hemp Seed and Hemp Protein Powders. Oil consumption from Hemp Oil alone ranges from the highest value of 8.207

g for individuals age 2 years and older (Table 29) to the lowest value of 4.576 g for females age 2 years to 5 years (Table 23) which is significantly lower than the level of exposure when cumulative exposure from all oil rich sources are considered. Cumulative oil exposure is 17.457 g/day for individuals age 2 and older, 12.631 g/day for males 2 to 5 years, 11.36 g/day for females 2 to 5 years, 14.058 g/day for males 6-11 years and 14.538 g/day for females 6 to 11 years. The oil in Hemp Protein Powder, Hemp Oil and Hulled Hemp Seed is about 19% omega 3 (Table 3). Cumulative consumption of all hemp sources at the levels estimated in this GRN (refer to Tables 29 to 33) would result in an intake of omega 3 which is greater than the AI set by IOM (IOM 2005) thereby providing a valuable source of omega 3 to help ensure nutritional adequacy.

Section 4
Self Limiting Levels of Use

4. Self-Limiting Levels of Use

For discussion purposes, the highest level of inclusion and highest levels of consumption have been used to estimate exposure to Hemp Oil. Hemp Oil sold as a branded product at a serving size of 15 mL is intended as a directly consumed consumer packaged product where consumers mix, sprinkle or garnish within salads, baking, breakfast foods, pasta, smoothies/ blended beverages, non-dairy beverages, meat analogues, crackers, bars and desserts prepared at home.

Hemp Oil is also intended as a food ingredient in conventional foods such as soups, and spreads; beverages and beverage bases; meat and dairy product analogs and plant protein products at levels ranging from 1 to 15%. When used as an ingredient, the level of use of Hemp Oil is variable but is self-limiting due to sensory and functionality limitations so it is not expected to exceed 8.22 grams per serving when used at the maximum level in any of the food categories (refer to Table 14).

The exposure to THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil is dependent upon consumption habits and is self-limiting due to sensory and functional limitations of the hemp ingredients, so it is not expected to exceed 0.1938 mg/person/day when foods from all groups and containing maximum inclusion levels are consumed at the 90th percentile by any individual age 2 years and older (refer to Table 19).

GRAS Based on History
N/A

Section 5 - GRAS Based on History of Use
NOT APPLICABLE

Section 5
GRAS Narrative

5. Basis for Conclusion of GRAS Status (Narrative)

5.1. Introduction to GRAS Conclusion

Hemp Oil is intended for nutritional fortifications of foods. It has high levels of monounsaturated and polyunsaturated fat and is a rich source of omega 3 and 6 fatty acids which make it a desirable addition to human foods.

There is a long history of research and studying into the benefits of hemp seed. Including a report on children during the 1930s and 1940s in Czechoslovakia that emphasized the importance of hempseed protein, the basis of this conclusion of GRAS status is based on scientific procedures, which has led to the relatively recent recognition of safety for human food by Health Canada, Food Standards Australia New Zealand/Australian New Zealand Food Authority, and the European Food Safety Authority. All have looked at the scientific data and found hemp seed safe for human consumption.

Fresh Hemp Foods Ltd. has performed a critical assessment of the publicly available literature on *Cannabis sativa* low THC (industrial hemp) and high THC (marijuana) varieties. Data from both human and animal studies confirm that Hemp Oil produced from Health Canada approved cultivars of low THC industrial hemp which has been produced in accordance with Fresh Hemp Foods Ltd. procedures and specifications is unlikely to result in positive urine THC drug test results and is safe for children, adults and breastfeeding women and their infants when consumed at anticipated levels based on Table 1 and NHANES 2013-2014 food survey data (Tables 9 to 18).

Refer to Table 35 for drug testing programs and recognized limits (Table duplicated below). Fresh Hemp Foods Ltd. has assessed the potential of Hemp Protein Powder to produce positive urine drug test results using the US Department of Defense and Federal Workplace Drug Testing limits of 15 ng/ml.

Table 35 Detection of Cannabinoids in Urine

Drug Testing Program	**Cut Off Limit**
US Department of Defense	15 ng/ml
US Federal Workplace Drug Testing	15 ng/ml
World Anti-Doping Agency	150 ng/ml

Fresh Hemp Foods Ltd. manufacturers multiple ingredients from whole hemp seed. Each ingredient is highly nutritious and is suitable for formulation into human food (refer to GRNs filed with this Notice). Accordingly, an assessment of the safety of the cumulative exposure to these ingredients and the THC resulting from their combined ingestion has been performed. Data from human and animal studies confirms that cumulative exposure to Fresh Hemp Foods Ltd. hemp ingredients (Hulled Hemp Seed, Hemp Oil and Hemp Protein Powders) which have been produced in accordance with Fresh Hemp Foods Ltd. procedures and specifications is unlikely to result in positive urine THC drug test results and is safe for children, adults and breastfeeding women and their infants when consumed at anticipated levels and NHANES 2013-

2014 food survey data (Table 1 and Tables 9 to 18). Fresh Hemp Foods Ltd. has assessed the potential of cumulative hemp consumption to produce positive urine drug test results using the US Department of Defense and Federal Workplace Drug Testing limits of 15 ng/ml.

5.2. Safety Overview

Hemp is different to other varieties of Cannabis sativa which are commonly referred to as marijuana as it contains very low levels of THC (delta 9-tetrahydrocannabinol), the cannabinoid associated with the psychoactive properties of marijuana. Hemp has recognition of safety for human food by Health Canada, Food Standards Australia New Zealand/Australian New Zealand Food Authority, and the European Food Safety Authority. All have looked at the scientific data and found hemp seed safe for human consumption.

Hemp seed derived foods including Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil are safe for human food as they contain minimal amounts of THC because THC may have behavioral and physiological effects. Fresh Hemp Foods Ltd. ensures the safety of its hemp derived ingredients by ensuring that all seed processed is a Health Canada approved low THC variety which has been grown and processed in accordance with the Industrial Hemp regulations. Safety is further ensured by testing at third party accredited laboratories to confirm THC levels are in compliance with the mandatory regulated limits and Fresh Hemp Foods Ltd. corporate limits.

Historical trending of Fresh Hemp Food's third party accredited laboratory testing of THC content for Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil reveals that actual THC levels are consistently below the Fresh Hemp Food specifications. Refer to Figures 2 to 41 for Monte Carlo modelled exposure of THC and to Table 36 (duplicated below) for a summary of daily exposure of THC from all hemp ingredients at maximum THC limits based on specifications versus daily exposure of THC based on Monte Carlo probabilistic model.

Table 36. Daily THC Exposure at Maximum Specification Levels and Monte Carlo Modelling of Daily THC Exposure

	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014)					THC EXPOSURE FROM HEMP MATERIAL CONSUMED AT MAXIMUM FRESH HEMP FOODS LTD. SPECIFICATION LIMITS (mg/Day) *Hulled Hemp Seed = NMT 4 µg/g THC *Hemp Protein Powder = NMT 4 µg/g THC *Hemp Oil = NMT 10 µg/g THC					THC EXPOSURE FROM HEMP MATERIAL CONSUMED USING MONTE CARLO MODEL AND HISTORICAL TEST DATA (mg/Day) *Hulled Hemp Seed = Mean of 0.29 µg/g THC *Hemp Protein Powder = Mean of 0.31 µg/g THC *Hemp Oil = Mean of 4.95 µg/g THC				
	2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years	
	Males & Females	Males	Females	Males	Females	Males & Females	Males	Females	Males	Females	Males & Females	Males	Females	Males	Females
HULLED HEMP SEED GRN XXX	14.07 (Table 14)	11.71 (Table 15)	10.2 (Table 16)	12.12 (Table 17)	12.14 (Table 18)	0.0563 (Table 19)	0.0468 (Table 25)	0.0408 (Table 26)	0.0485 (Table 27)	0.0486 (Table 28)	0.0213 (Figure 4)	0.0178 (Figure 12)	0.0155 (Figure 20)	0.0184 (Figure 28)	0.0184 (Figure 36)
HEMP PROTEIN POWDER GRN XXX	13.84 (Table 14)	12.36 (Table 15)	10.55 (Table 16)	12.14 (Table 17)	12.47 (Table 18)	0.0553 (Table 19)	0.0494 (Table 25)	0.0422 (Table 26)	0.0485 (Table 27)	0.0499 (Table 28)	0.0164 (Figure 6)	0.0147 (Figure 13)	0.0126 (Figure 22)	0.0145 (Figure 30)	0.0149 (Figure 38)
HEMP OIL GRN XXX	8.22 (Table 14)	4.81 (Table 15)	4.58 (Table 16)	6.06 (Table 17)	6.48 (Table 18)	0.0822 (Table 19)	0.0481 (Table 25)	0.0458 (Table 26)	0.0606 (Table 27)	0.0648 (Table 28)	0.0772 (Figure 8)	0.0451 (Figure 17)	0.0431 (Figure 24)	0.0566 (Figure 32)	0.0605 (Figure 40)
CUMMULATIVE	**36.12 (Table 14)**	**28.88 (Table 15)**	**25.33 (Table 16)**	**30.32 (Table 17)**	**31.1 (Table 18)**	**0.1938 (Table 19)**	**0.1444 (Table 25)**	**0.1288 (Table 26)**	**0.1576 (Table 27)**	**0.1633 (Table 28)**	**0.1049 (Figure 2)**	**0.0698 (Figure 10)**	**0.0651 (Figure 18)**	**0.0794 (Figure 26)**	**0.0834 (Figure 34)**

The low levels of THC that would be ingested through oral consumption of Hemp Oil and other hemp ingredients will result in metabolites in the urine. Measurement of the presence of THCCOOH equal to or greater than the threshold value in urine is a standard test used by workplace, military, criminal justice and drug treatment programs to identify use/abuse of Cannabis. Accordingly, an assessment of the potential for Hemp Oil and other hemp ingredients (see other GRNs filed with this Notice) to result in positive urine drug test results has been performed. Fresh Hemp Foods elected to use the tightest current cutoff level of 15 ng/ml as currently used by the US Department of Defense and US Federal Workplace Drug Testing to perform this assessment. The presence of urine metabolites at drug testing cut off levels indicates that THC has been consumed. The THC level consumed may be too low to result in psychological effects, but they are still a significant concern since a failing drug test result has the potential to damage the career and reputation of the individual.

The literature review found no instances of safety discussions outside of THC (delta 9-tetrahydrocannabinol). The overwhelming consensus in the literature and the scientific community is that hemp is a valuable food.

5.3. Safety of THC Exposure – General Population – Hemp Oil and Cumulative Hemp Ingredient Consumption

The exposure to THC from low THC varieties of hemp has recently been evaluated by Food Standards Australia New Zealand/Australian New Zealand Food Authority. Food Standards set their lowest-observable-effect level (LOEL) based on a clinical study assessing impact of oral consumption of THC on the skill performance (standing steadiness, hand to eye coordination, reaction time, numbers test) of young adults (ANZFA Final Assessment Report Inquiry – S.17 Application A360). The participants showed slight but reversible effects on skill performance and no psychotropic effects after consuming 5 mg THC, the lowest level studied. The 2.5 and 5

mg doses evaluated by EIHA and Food Standards are much higher than the 0.0822 mg THC/person/day level anticipated for individuals 2 years and older consuming Hemp Oil at the 90th percentile and maximum level of inclusion (Table 20). It is also much higher than the 0.1288 to 0.1444 and 0.1576 to 0.1633 levels conservatively anticipated for male and female children aged 2 to 5 years and 6 to 11 years respectively (Tables 25 to 28), thereby confirming that the estimated THC exposure resulting from cumulative consumption of hemp ingredients detailed in this GRN is unlikely to result in psychoactive effects and is therefore not a safety concern for the general population.

Law et al 1984 administered 5.0-5.2 mg THC in a meat sandwich to 5 subjects. None of the subjects reported any psychological effects or any reaction associated with cannabis administration. One of 5 subjects had poor pallor and felt faint. It is highly unlikely that individuals would receive the same level of exposure to THC from Hemp Oil since a quantity of about 0.5 kg in a single meal is needed to provide a comparable amount of THC at the maximum permitted levels resulting from the Fresh Hemp Foods Ltd. Specifications (Table 2).

Brenneisen et al 1996 administered 10 mg Marinol (synthetic THC) to Patient A and 15 mg THC to Patient B for four consecutive days. There were improvements in mobility, walking ability and rigidity in both patients, one patient showed no change in concentration and mood, while the other patient showed mixed changes at the higher 15 mg oral dose. It is not anticipated that individuals would experience any changes in concentration and mood or improvements in mobility, walking ability and rigidity at the levels of THC exposure anticipated from the consumption of Hemp Oil or cumulative consumption of hemp ingredients (Table 20).

Since 2013, Nabiximols, an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD in each 100 µL spray was approved in Italy for the treatment of Multiple Sclerosis. Low blood concentrations were produced by Nabiximols administration, more than 10 times lower than the blood concentrations known to produce psychotropic effects (Indorato et al 2016). Blood THC Cmax concentrations after a single 2.7 mg THC oromucosal spray were 0.52 ± 0.30 µg/L. Blood samples from 20 patients treated with Nabiximols for short (28 days) or long-term treatment (60 or 90 days) were analyzed. The quantity of THC expected to be consumed from Hemp Oil and cumulative consumption of all hemp ingredients is 0.0822 mg and 0.1938 mg respectively which is far less than the 2.7 mg dose of Nabiximols studied indicating that consumers would not have psychotropic effects following the consumption of the 90th percentile of THC at the highest recommended level of inclusion (Tables 20 and 19).

Stott et al, 2013 administered single Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses as 2 (5.4 mg THC), 4 (10.8 mg THC), 8 (21.6 mg THC) sprays, or multiple sprays (2, 4 or 8 sprays) for 9 consecutive days. The results demonstrated that low daily THC doses do not appear to accumulate in the blood. There was evidence of dose-proportionality in the single but not the multiple dosing data. The 5 mg THC dose, an amount far exceeding the 0.0822 mg level anticipated from consumption of Hemp Oil (Table 20), was the lowest level studied. It was found to produce Cmax values (<12 µg/L) well below those reported in patients who smoked/inhaled cannabis, which is associated with significant psychotropic effect. In terms of safety, the authors found that THC/CBD spray was well tolerated in all phases of the study, with

no serious adverse events (AEs) or withdrawals due to AEs. All but three AEs were of mild severity, with three of moderate severity. All AEs resolved without sequelae, but most were considered to be related to the study treatment. The most common AEs were dizziness and somnolence. As expected, there was a direct relationship between increasing doses of THC/CBD spray and the frequency of AEs, with all subjects receiving eight sprays of THC/CBD spray experiencing at least one AE.

These data illustrate that the number of adverse events are low and of minor or moderate severity at much higher THC doses than would be expected from the 0.1938 mg THC consumption from all hemp ingredients at the 90% percentile at maximum inclusion levels for all age groups (Table 19).

Perez Reyes et al, 1973 administered 35 mg oral THC (containing 50 µc tritium THC) in five different vehicles (ethanol, sesame oil, 5.5% sodium glycholate, 5.5% sodium glycholate and ethanol, and Tween-80) to 40 individuals after fasting showing that the speed and bioavailability of absorption was highly dependent upon the vehicle utilized. Plasma, urine and feces were analyzed over 72 h. Total radioactivity of thin layer chromatography bands were used to quantify results. The vehicles providing the highest concentrations in plasma were from highest to lowest bioavailability were 5.5% sodium glycholate, sesame oil, Tween-80, ethanol and combined glycholate and ethanol, with peak concentrations between 1-2 h. In addition, with the same vehicle and dose, a large 4.8 inter-individual variability in peak plasma THC concentrations was observed. Factors determining individual response to oral administration of cannabis include the dose of total THC and THC precursor acid, the degree of conversion of THC precursor acid to THC prior to ingestion, the rate of absorption of THC from the gastrointestinal system that is influenced by the vehicle used, and degree of first-pass THC metabolism. Perez-Reyes et al. 1973 reported that the speed and degree of absorption of THC are greatly influenced by the vehicle used for administration and based on cumulative urinary excretion data over 72 h, the rate of absorption of THC was affected by the nature of the vehicle and not the degree of absorption.

Ohlsson et al 1980, 1981, Wall and Perez 1981, Hollister et al, 1981 and Ohlsson et al 1985 administered 20 mg oral THC in a chocolate cookie, 10 mg smoked THC, and 5 mg intravenous (IV) THC in 95% ethanol over 2 min to 11 males. Plasma was analyzed from 3 to 240 min (4 h) for smoked and IV doses and from 30 to 360 min (6 h) after oral dosing. THC was analyzed by GC-MS. Maximum plasma THC concentrations (Cmax) after the 20 mg oral dose were 4.4-11 µg/L with time of peak concentration (Tmax) between 60 and 300 min. Compared to the IV dose, bioavailability of the oral dose was 6 ± 3% (4-12%), with slow and irregular absorption. The results indicate that an oral dose of 20 mg THC would produce a measurable effect although the likelihood of such an occurrence happening because of consumption of Hemp Oil or other hemp ingredients is highly unlikely since the individual would need to consume about 2 kilograms of Hemp Oil to be exposed to 20 mg THC.

Wall et al 1983 compared oral and intravenous bioavailability of THC. A mean of 2.2 mg THC was intravenously administered over 15 to 25 min to six women and 4.0 mg to 6 men laced with tritium-labeled THC. Women received 15 mg and men 20 mg oral THC in sesame oil in

capsules. Cumulative urinary excretion for cannabinoids was 15.9±3.6 and 13.4±2% of the dose in women and men, respectively. After oral dosing, total cannabinoid excretion in feces was 48±6 and 53±19% of the dose. After the oral route of administration, approximately 13-16% of the dose was excreted in urine by 72 h, while about 50% of the dose was found in the feces. There were no differences between women and men. The bioavailability of THC in the oral dose compared to an IV dose was 10.9% for women and 19% for men. Overall, there were no significant differences between sexes in THC metabolism, disposition and kinetics.

Sadler et al 1984 evaluated oral bioavailability of THC by simultaneously administering 0.141 mg/123 µCi ^{3}H THC intravenous tracer and 20 mg oral THC in sesame oil to 6 males. After 72 h, 21±1% of the tracer was in the urine and 40±2% was in the feces. A low bioavailability of 13% was found which was attributed to an extensive first pass effect in the liver.

Goodwin et al 2005 evaluated the pharmacokinetics and pharmacodynamics of oral THC through a controlled cannabinoid administration study of THC-containing hemp oils and dronabinol. Up to 14.8 mg THC was ingested by six volunteers each day in three divided doses with meals for five consecutive days. There was a 10-day washout phase between each of the five dosing sessions. THC was quantified in plasma by GC/MS. THC and 11-OH-THC were not detected in plasma following the two lowest doses of 0.39 and 0.47 mg/day THC, while peak plasma concentrations of < 6.5 µg/L THC, < 5.6 µg/L 11-OH-THC, and < 43.0 µg/L THCCOOH were achieved after the two highest THC doses of 7.5 and 14.8 mg/day. The findings of Goodwin et at. 2005 indicate that THC and 11-OH-THC would not be expected to be detected in plasma following consumption of 0.0822 mg or 0.1938 mg THC, the estimated THC exposure from Hemp Oil and cumulative consumption of all hemp ingredients at the 90th percentile and maximum inclusion level (Tables 20 and 19).

5.4. Safety of THC Exposure – Children – Hemp Oil and Cumulative Hemp Ingredient Consumption

THC's receptor-mediated mode of action appears to provide an additional margin of safety from undesirable health effects. This is particularly true for children. The severity of a toxic effect for most harmful chemicals is a function of exposure concentration and duration (Gaylor 2000). Thus, the no observed adverse effect level (NOAEL) correspondingly decreases with the duration of exposure. This is not the case with THC since the effect of a given exposure level decreases with time, likely due to the development of tolerance to THC by its receptors.

Children are considered particularly sensitive to many harmful chemicals resulting in higher safety factors being chosen to provide adequate protection. However, there are clinical studies that indicate that children are less sensitive to the effects of THC (Abrahamov et al. 1995, Dalzell et al. 1986), although this point is considered controversial.

The body surface of children would suggest a greater impact of THC on children. Clinical studies have shown that children tolerate higher doses of THC than adults before psychotropic side effects become significant (Abrahamov et al. 1995, Dalzell et al. 1986). Eight children age 3 to 10 who were undergoing chemotherapy were given 18 mg delta-8-THC per square meter of body surface, four times daily. Each child received an average of 60 doses. Two of the six children experienced mild psychotropic side effects. Extrapolating this same dosing to adults with an assumed body surface of 1.8 square meters, corresponds to single doses of 30 mg and a daily dose of about 120 mg THC. Delta-8-THC is assumed to be approximately 75% as psychotropic as delta-9-THC so a 30 mg dose is equivalent to about 23 mg of delta-8-THC, an amount which usually produces significant psychotropic effects in adults. Children between the ages of 2 and 11 years can be conservatively estimated to be exposed to between 0.1288 mg (Table 26) to 0.1633 mg (Table 28) of THC depending on their age and gender if they consume all hemp ingredients at the maximum level of inclusion at the 90th percentile level of consumption. These levels are over 100 times less than the 23 mg quantity shown to produce mild psychotropic effects in 2 of the 6 children studied.

5.5. Safety of THC Exposure – Breastfeeding Population – Hemp Oil and Cumulative Hemp Ingredient Consumption

A thorough literature search for data related to transfer of THC from the mother to the infant during breastfeeding was performed. There is a surprising lack of information related to this question in the published literature, and most focused on THC transfer during the perinatal period that included transfer during gestation and breastfeeding.

The lack of controlled THC administration studies is obvious due to ethical and medical concerns with unnecessarily exposing the fetus and neonate to an exogenous compound. After extensive searching, data relating to the ingestion of a known amount of THC by the mother and resultant breast milk THC concentrations was identified. Neither are there controlled studies of THC administration to the infant and resultant infant plasma or urine THC concentrations. There are data estimating the volume of daily breast milk ingested by neonates and infants, effects on

the fetus following in utero THC exposure and on the neonate following THC breast milk exposure. In addition, there are many reports advising for or against breastfeeding if the mother uses cannabis.

Maximum cumulative THC exposure estimates for individuals over the age of two were based on the individual using the maximum amount of all products in a single day (Refer to Table 36). These data were used as mean and maximum exposures for the lactating woman to assess the safety of cumulative THC exposure from Fresh Hemp Foods, Ltd hemp products including Hulled Hemp Seed, Hemp Protein Powders (including protein concentrate) and Hemp Oil in the breastfeeding population (see GRNs filed with this notice). The THC calculations are based on the Fresh Hemp Foods, Ltd specifications for maximum THC content (refer to Table 19). These values were used in determining daily THC intake if the recommended dose of all products were consumed each day.

Preclinical data

Reisner et al 1983 reported that only 0.2% of a labeled THC dose to squirrel monkeys appeared in their breast milk as hydrophilic & lipophilic metabolites within 24 hours; 0.01% of the dose appeared in the squirrel monkeys' offspring's urine. In lactating ewes, milk contained less radiolabel than their feces or urine, with radiolabel being detected 4 and 96 hours after THC injection (Mourh and Rowe 2017). Endocrine and behavioral changes were noted in suckling rodents after THC exposure in breast milk. THC acted as an in vivo weak competitor of the estrogen receptor, producing a primary estrogen effect in male & female rats (Warner et al 2014). In addition, THC was shown to reduce trophoblast cell proliferation and inhibit placenta development. In some studies, THC also produced hormonal changes reducing fertility. In animal models, THC crossed the placenta resulting in fetal plasma concentrations approximately 10% of maternal plasma concentrations after acute exposure; however, significantly higher fetal concentrations were observed after repetitive exposures (American College of Obstetricians & Gynecologists' Committee on Obstetric Practice 2015). Furthermore, these clinicians noted that although animal models may be poor surrogates for the human condition, endocannabinoids played key roles in normal fetal brain development, including neurotransmitter systems, and neuronal proliferation, migration, differentiation, and survival.

Battista et al 2014 noted that the endocannabinoid-CB1 receptor system is important for milk suckling, and in growth and development early in life. It was suggested that increased endocannabinoids and/or cannabinoids in milk might have relevant effects on breastfed newborns.

Murphy et al 1998 showed that THC inhibited gonadotropin, prolactin, growth hormone and thyroid-stimulating hormone release and stimulated release of corticotropin, inhibiting the quantity and reducing the quality of breast milk. In a recent review, Mourh and Rowe 2017 demonstrated that animals exposed to THC in milk had decreased prolactin concentrations and motor, neurobehavioral, & developmental effects. Lactating rats and non-pregnant rhesus monkeys displayed lower prolactin concentrations following THC injections, with maximum reductions of 74% (in male monkeys) and 85% (in female monkeys) over the first 30-90 minutes. There was a >70% reduction in prolactin from baseline after 1.25 mg/kg THC and >90%

reduction following a 4 mg/kg dose over 30-60-min. In addition, lactating rats displayed lower blood oxytocin concentrations following THC dosing. THC prevented suckling-induced oxytocin secretion by the posterior pituitary, leading to a longer delay in initial ejection of milk and between successive ejections. Additional effects seen in monkeys & rats included lethargic behavior, reduced maternal care, and anxiety.

In milk samples from buffalos eating cannabis plants, 50% contained cannabinoids (Ahmad and Ahmad 1990). Consumers of the contaminated milk were passively exposed to THC and metabolites were detectable in at least 30% of children up to the age of 3 years. Mouse pups whose mothers consumed food containing hashish during lactation weighed significantly less (by 10– 14%) than control pups from day 11 onward. The endocannabinoids play key roles in normal fetal brain development, including neuronal proliferation, migration, differentiation, & survival (The American College of Obstetricians & Gynecologists' Committee on Obstetric Practice 2015), suggesting that this occurred due to malnutrition (which could be the result of poorer milk production in the mothers or the direct influence of THC on the pups).

The degree to which we can correlate effects of THC exposure in breast milk in animals and humans, especially neurobehavioral changes, is unclear. Also, the animal doses were frequently greater than those in human studies and were usually administered intravenously, making comparison of pharmacokinetics difficult. Exposure to cannabis includes exposure to numerous other cannabinoids, terpenes and polyaromatic hydrocarbons and might have different effects than synthetic IV THC.

Clinical data & recommendations

All drugs may pass into breast milk depending upon the drug's molecular weight and size, protein binding, amount of free drug in the blood, the lipophilicity of the drug, and the drug's pKa. Berlin and Briggs describe the transport of compounds across the mammary alveolar cells as primarily due to transcellular diffusion, in which small molecules (molecular weight 100-200) pass through with the flow of water due to hydrostatic or osmotic pressure differences. Larger molecular weight compounds may enter milk through intercellular diffusion, explaining the presence in breast milk of maternal proteins such as cow milk antigen and antibodies. The 3-dimensional shape of the molecule also may be a determinant in transfer to breast milk. Ionophore diffusion facilitates charged ions transfer and carrier proteins transfer other substances. THC is a highly lipophilic compound and transfers readily into breast milk.

Perez-Reyes and Wall reported that cannabis & metabolites pass into breast milk in concentrations dependent upon the amount of drug ingested by the mother. These authors published the one and only breast milk/plasma THC ratio data (one single paired sample) as the primary source for THC concentrating in breast milk, and many recommendations to not breastfeed if the mother continues to use marijuana. Breast milk from two chronic frequent cannabis users were studied. There were no data on the amount of THC ingested by the women, thus, there are no data on maternal THC intake per event or per day. Woman #1 reported smoking cannabis once per day and woman #2 reported smoking approximately seven times per day. A single matched plasma and breast milk sample was collected from woman #2, as described as under steady state conditions. THC concentrations in the plasma were 7.2 µg/L

THC, 2.5 µg/L 11-OH-THC, and 19 µg/L THCCOOH, and 60.3, 1.1, and 1.6 µg/L THC, 11-OH-THC and THCCOOH concentrations in the breast milk, respectively. These are the sole data supporting a human THC breast milk/plasma ratio of 8.4, indicating that THC is concentrated up to 8-fold in breast milk compared to maternal plasma. At these concentrations, it was estimated that the infant's daily THC exposure was 0.01 to 0.1 mg THC/day. There were no observable side effects in the infant receiving this amount of THC (Hale 2012). Concentrations in woman #1's breast milk were 105 µg/L THC, with no detectable 11-OH-THC and THCCOOH. Marcei et al 2011 reported cannabinoid concentrations in breast milk from one lactating woman of 86 µg/L THC and 5 µg/L 11-OH-THC, but maternal plasma was not tested. Also, the duration of THC in the breast milk after cessation of use is unknown (Wang 2016). The evidence is unclear if breastfeeding benefits (nutrition, immune protective factors, sudden infant death syndrome (SIDS), bonding, etc.) outweigh potential THC breast milk exposure risks.

There are so few data on THC in human breast milk and the effects of this exposure, that most experts refer to the effects of in utero cannabis exposure as a means of evaluating potential adverse developmental outcomes. Furthermore, most women who use cannabis during pregnancy continue use during breastfeeding, making it difficult to assign causation to one source of exposure. There does not appear to be a need to discuss in utero drug exposure. Clearly, use of cannabis during pregnancy is contra-indicated.

Reported cannabis use prevalence rates in pregnancy vary from 3-34% (Metz & Stickrath 2015), with cannabis the most common illicit drug taken during gestation. Sixty percent of women who used cannabis in the year prior to pregnancy continued to use more than 10 joints per week, indicating that many women continue use throughout pregnancy. Identification of cannabis use in the mother at birth does not differentiate the amount of use and designation of occasional or chronic frequent use. The American College of Obstetricians & Gynecologists' Committee on Obstetric Practice (2015) estimate that 48–60% of cannabis users continue use during pregnancy, with many women believing that it is relatively safe to use during pregnancy & less expensive than tobacco. Colorado's largest local Tri-County health department serves >26 % of the population (Wang 2016). Their Women's Infants & Children (WIC) Program survey revealed 7.4% of mothers aged <30 years & 4% of mothers >30 years are current cannabis users. Of all cannabis users (past, ever, current), 35.8% said they used at some point during pregnancy, 41% since the baby was born & 18% while breastfeeding.

Breast milk samples (N=109) from lactating women were analyzed for cannabinoids and questionnaires were completed about their drug use during pregnancy and while breastfeeding (Mourh & Rowe 2017). Of 19 women reporting drug use, 1 had 20 µg/L THC in her breast milk, with no detectable cannabinol or cannabidiol, and her urine was positive for cannabinoids. Another woman not reporting drug use had 31 µg/L THC in her breast milk with no detectable cannabidiol. Infant THC exposure was estimated as 2 and 3.1 µg THC/100 mL breast milk. Using 12% oral THC bioavailability, infant exposure was estimated at 0.24 & 0.37 µg THC. Maternal THC dose and dosing time in relation to breast milk collection were unknown.

Astley & Little 1990 suggested that cannabis use by the breastfeeding mother during the first month of life could impair neurodevelopment. Glial and myelin formation in the infant brain

continues after birth during breastfeeding and might lead to sedation and weakness. Other disadvantages include the possibility that THC in breast milk may decrease the production, volume, composition & ejection of breastmilk, resulting in poor feeding patterns (Liston 1998).

The American Academy Pediatrics Committee on Drugs 2001 noted that there were no reported adverse effects of cannabis in published studies.

In the WHO Breastfeeding 1997 Report, it was estimated that in one feeding the infant will ingest 0.8% of the weight-adjusted maternal intake of 1 joint (Garry et al 1990). The authors suggest that mothers who use cannabis must stop breastfeeding, or ask for medical assistance to stop cannabis use, to provide their babies with all the benefits of human milk. THC in breast milk could sedate the infant and result in growth delays.

Liston 1998 suggested that infants exposed to marijuana via breast milk show signs of sedation, reduced muscular tonus, & poor sucking. Two studies evaluated the effects of cannabis use by the lactating mother on their child's development. The first study found no significant differences in terms of weaning, growth, and mental or motor development with regard to age. The second study found that cannabis exposure via the mother's milk during the first month postpartum appeared to be associated with a decrease in infant motor development at one year of age. Infants exposed to cannabis for more than half of the days during the 1st trimester of gestation or 1st month of lactation had significantly lower mean Psychomotor Development. Other factors come into play like cannabis exposure during pregnancy, passive exposure to cannabis smoke in ambient air, or the quality of the mother-child relationship. There are no studies relating to the long-term effects of marijuana exposure through breast milk. There are almost no studies of lactation exposure only; the infant was usually prenatally exposed and almost all of their mothers continued use after birth (Reece-Stremtan et. al 2015).

Despite preclinical studies suggesting that THC exposure during breastfeeding can reduce the quality and quantity of breast milk, these effects have not been confirmed in humans (Sharma et al 2012). According to Warner et al 2014, the identification of side effects in the lactation-exposed infant are inconsistent and there are no long-term outcome studies. Hotham and Hotham 2015 stated that the most commonly used drugs are relatively safe for breastfed babies. Drugs contraindicated during breastfeeding include anticancer drugs, lithium, oral retinoids, iodine, amiodarone & gold salts. Estimated breastmilk intake by an exclusively breastfed baby is 150 mL/kg/d.

Hale 2012 placed cannabis in highest risk category, L5 or Hazardous, stating that using cannabis during breastfeeding clearly outweighs the benefits of breastfeeding; however, many lactation experts disagree with this conclusion. Jansson et al 2015 noted the importance of active, passive (from maternal side stream smoke) and cumulative exposures to breastfed infants must be considered. THC delivered via lactation to the infant may affect the ontogeny of various neurotransmitter systems, leading to changes in neurobiological functioning. The recent new recommendation by the Academy of Breastfeeding Medicine was described as erroneous & disappointing. It is unclear why a recommendation would err on the side of breastfeeding with

potentially toxic exposures and other risk factors that could portend short- & long-term infant harm.

Most adverse effects of drugs in breast milk occurred in newborns under 2 months and rarely in those older than 6 months (Jansson et al 2015). A follow-up study of 1-year-old breastfed infants of mothers who used cannabis found some impairment in motor development, although researchers found it difficult to determine whether in utero exposure or breastfeeding was the greater influence. Women should be encouraged to stop using cannabis & avoid exposure of the baby to second-hand smoke.

In a survey of mothers by lactation experts, 15% of women reported using cannabis during breastfeeding (Bergeria and Heil 2015). Forty-four percent of the lactation experts reported that their recommendations were based on marijuana use factors like the severity of maternal use. Another 41% reported recommending continued breastfeeding because benefits outweigh harms, and the remaining 15% recommended that a woman should stop breastfeeding if she cannot stop using marijuana. Infants whose mothers used marijuana during lactation (n = 27) had similar growth outcomes, mental & motor development, & weaning ages compared with infants of non-using mothers (n=35). In contrast in a larger study, significant deficits in motor development was found at 1 year of age among exposed infants (n = 68) versus matched controls (n = 68), however, marijuana exposure occurred during the first trimester of pregnancy & the first month of lactation, making it difficult to determine which period of exposure had a stronger influence on infant motor development.

The American College of Obstetricians & Gynecologists Committee on Obstetric Practice released new recommendations on breastfeeding and marijuana use in 2015. Obstetricians and gynecologists should be discouraged from prescribing or suggesting marijuana use for medicinal purposes during preconception, pregnancy, & lactation. There are insufficient data to evaluate effects of marijuana use on infants during lactation & breastfeeding; thus, marijuana use is discouraged. In animal models, THC crossed the placenta, producing fetal plasma levels that were approximately 10% of maternal levels after acute exposure. Significantly higher fetal concentrations were observed after repetitive exposures. Animal models demonstrate that endocannabinoids play key roles in normal fetal brain development, including in neurotransmitter systems, & neuronal proliferation, migration, differentiation, & survival. Breastfeeding women should be informed that the potential risks of exposure to marijuana metabolites are unknown & should be encouraged to discontinue marijuana use.

The strongest determinant of breast milk medication concentration is the non-protein bound maternal plasma drug concentration (Newton & Hale 2015). THC is a highly bound drug that should result in lower breast milk concentration; however, THC has a large volume of distribution (Vd) in maternal compartments, with especially rapid tissue sequestration that will reduce maternal free drug concentrations. THC is a highly lipid soluble drug that passes through the alveolar cells more easily and is sequestered in milk. Marijuana is an example of a highly lipid soluble drug with higher concentrations in breastmilk based on a single paired maternal plasma and breast milk sample. THC's pKa is 10.2, leading to ion trapping in milk due to the higher ionization at lower pH. The relative infant dose (RID) is amount of the drug dose to the

breastfeeding infant. The infant dose (mg/kg/d) is divided by the mother's dose (mg/kg/d). An RID <10% is considered acceptable in a healthy postnatal infant. The bioavailability of the drug in the infant must be known. THC's oral bioavailability is low- estimated to be about 6% in adults. Premature, term or ill neonates may have higher absorption rate than adults. The ultimate measure of drug in breast milk is the infant's plasma blood concentrations but none have been published. Mothers are advised to choose drugs with a low M/P ratio and to avoid drugs with a long half-life (12-24 h).

The Academy of Breastfeeding Medicine "A recommendation of abstaining from any marijuana use is warranted. At this time, although the data are not strong enough to recommend not breastfeeding with any marijuana use, we urge caution (Foeller & Lyell 2017).

We included the data for marijuana use during breastfeeding because no data are available for oral THC dose and breastfeeding; however, maternal blood THC concentrations following maternal cannabis smoking or vaporization can be as high as 200-300 ng/mL, while blood THC concentrations after oral THC from ingestion of Fresh Hemp foods is expected to be very low.

Based on the studies administering known quantities of THC and blood/plasma/serum concentrations, we can estimate the blood concentrations that would result from a mean intake of 0.0968 mg to a 90th percentile intake of 0.1938 mg oral THC (refer to Table 21). Stott et al 2013 administered two Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses (total 5.4 mg THC) to adults. There are no infant THC administration data. The mean plasma Cmax was <1.2 µg/L THC and <2 µg/L 11-OH-THC. The mean daily amount (0.0968 mg) and 90th percentile (0.1938 mgk) of THC exposure from ingesting all Fresh Hemp Foods, Ltd. Products is 55- and 27-fold lower than this exposure, respectively (Table 19). These data would estimate the plasma Cmax in the breastfeeding mother assuming a 0.0968 mg daily dose as <0.02 µg/L THC and <0.035 µg/L 11-OH-THC, and if the highly conservative 0.1938 mg THC dose is assumed, plasma Cmax in the mother of <0.04 µg/L THC and <0.07 µg/L 11-OH-THC. Refer to Table 37 for a summary of estimated infant THC exposure.

Furthermore, based on the Monte Carlo simulation, the maximum daily THC exposure at the 90th percentile was estimated at 0.1049 mg 99.9% of the time based on cumulative ingestion of all hemp ingredients (refer to Figure 3). This amount is 51 times lower than the 5.4 mg THC Stott et al dose, estimating a maximum THC concentration of <0.02 µg/L and <0.04 µg/L.

In a single maternal plasma and breast milk pair, the THC plasma to breast milk ratio was 8.4 (Hale 2012). Based on this ratio and the mean-90% maternal plasma THC concentrations the maximum THC concentration in the breast milk would be between 0.17-0.34 µg/L. There are no data on breast milk/plasma ratios, but if one assumed a similar distribution for 11-OH-THC into breast milk, maximum 11-OH-THC concentrations in breast milk would be 0.34-0.59 µg/L.

The estimate of daily breast milk intake is 150 mL/kg/day. Our estimates of maximum THC concentration in breast milk and daily intake would suggest THC intake of 0.05 – 0.09 µg/kg/day THC. As 11-OH-THC is equipotent to THC, assuming the breast milk to plasma ratio is also 8.4, the total active cannabinoids exposure for the infant is estimated to be <0.08-0.14 µg/kg/day.

Gustafson et al 2014 administered 0.39 and 0.47 mg THC per day for 5 days, resulting in non-detectable THC concentrations in human plasma. These doses are 2-4 times the dose a breastfeeding mother would consume with all hemp products. This low-level exposure is not expected to produce adverse developmental outcomes in the infant whose mother consumes the maximum amount of all hemp ingredients at the maximum inclusion level per day.

Furthermore, Stott et al 2013 also administered the 5.4 mg THC/day dose for 9 consecutive days and showed that THC and 11-OH-THC concentrations did not accumulate over time. This also demonstrates that daily use of the 3 Fresh Hemp Foods, Ltd hemp ingredients that provide THC at a much lower level than the 5.4 mg Stott dose should not accumulate. At birth, a 10 lb. (4.55 kg) infant would receive about 0.14-0.23 µg/day THC and 0.23-0.41 µg/day 11-OH-THC. The total active cannabinoid dose would be approximately 0.37-0.64 µg/day. The oral bioavailability of THC and 11-OH-THC is low, estimated to be 6-12% in adults; bioavailability could be different in the infant although first pass metabolism would still reduce active cannabinoid exposure. This low concentration of active cannabinoids should not produce adverse developmental effects.

5.6. Safety of THC Exposure – Urine Analysis and Drug Testing – Hemp Oil and Cumulative Hemp Ingredient Consumption

Fresh Hemp Foods Ltd. evaluated publicly available clinical studies to assess the potential for food products containing Hemp Protein Powder to produce positive urine drug test results (refer to summary in Table 38). The cut off level of not more than 15 ng/ml was applied to the assessment in accordance with US Federal Workplace Drug Testing and US Department of Defense requirements (Table 35).

Hemp Oil

The exposure to THC was estimated at the mean and 90th percentile based on consumption of maximum levels of Hemp Oil containing THC at maximum permitted specification levels of 10 µg/g in all food categories identified. Refer to Tables 20 to 24. The estimated mean and 90th percentile is 0.0411 mg and 0.0822 mg/person/day for individuals age 2 years and older, 0.024 and 0.0481 mg THC/person/day for boys aged 2 to 5 years, 0.0229 and 0.0458 mg THC/person/day for girls aged 2 to 5 years, 0.0303 and 0.0606 mg THC/person/day for boys aged 6 to 11 years and 0.0324 and 0.0648 mg THC/person/day for girls aged 6 to 11 years.

Monte Carlo modelling was also used to estimate THC exposure at the 90th percentile based on the mean THC level detected by historical third party analytical testing. The exposure to THC was estimated at 0.0772 mg THC/person/day for Hemp Oil for individuals age 2 years and older (Figure 8). The estimated 90th percentile is 0.0451 mg THC/person/day for boys aged 2 to 5 years, 0.0431 mg THC/person/day for girls aged 2 to 5 years, 0.0566 mg THC/person/day for boys aged 6 to 11 years and 0.0605 mg THC/person/day for girls aged 6 to 11 years (refer to Figures 16, 24, 32, 40 respectively).

The estimated THC exposure levels resulting from consumption of Hemp Oil at the maximum level of THC permitted by the specifications is not expected to screen positive for THCCOOH in urine at 15 µg/L cutoff concentrations. Furthermore, the Monte Carlo probabilistic modelling of THC exposure from Hemp Oil provides further support that Fresh Hemp Foods Ltd. Hemp Oil is unlikely to produce positive urine test results at the 15 ng/ml testing limit. These conclusions are based on the upper bound estimated quantity of THC anticipated to be consumed in contrast to the findings of the comprehensive literature review of publicly available data (refer to Table 38) as well as specific studies that were found highly relevant to this GRN Notification (Bosy and Cole 2000, Leson et. al. 2001, Gustafson et. al. 2003).

Cumulative Hemp Ingredients

Refer to Table 38 for a tabular summary of the publicly available clinical data.

Bosy & Cole 2000 had 7 daily administered doses of hemp oils between 0.10 and 1.8 mg/day and tested random urine specimens for up to 7 days after the last dose. Peak THCCOOH concentrations in the participants' urine ranged from 1.8 to 48.7 µg/L. There were no positive urine specimens ≥15 µg/L following the 0.10, 0.17, 0.32, and 0.55 mg THC/d for 7 daily doses. The 0.54 mg and 1.8 mg THC/d doses produced positive urine specimens ≥15 µg/L. Subjects ingesting low doses of THC (0.10 & 0.17) mg THC/d had no positive immunoassay results, while the 1 subject ingesting 0.32 mg THC/d had 11 of 18 results ≥ 50-µg/L immunoassay positive cutoff, but none were positive by GC/MS. Subjects ingesting medium doses of THC in hemp oil (0.54 & 0.55 mg THC/d) produced positive immunoassay screen results on the third and fourth days of ingestion. These two subjects had negative immunoassays within 24 h after ingestion ceased. The subject ingesting a high dose (1.8 mg THC/d) screened positive on the first day and was immunoassay negative within 72 h after last ingestion. No psychotropic effects were experienced by any of the subjects during the course of the experiment.

Leson et al 2001 reported results from 15 adults ingesting 10 daily THC doses of 0.09, 0.19, 0.29, and 0.45 mg THC. Urine specimens were collected prior to the first ingestion of oil, on days 9 and 10 of each of the four 10-day study periods, and 1 and 3 days after the last ingestion. All specimens were confirmed for THCCOOH by GC–MS and analyzed for creatinine to identify dilute specimens. There were no positive screening results and no positive GC-MS results ≥15 µg/L for doses below 0.60 mg THC/d. Only one specimen screened positive at the 50 µg/L cutoff at a daily THC dose of 0.6 mg. The highest THCCOOH concentration was 5.2 µg/L, well below the 15 ng/ml confirmation cutoff of federal drug testing programs.

Gustafson et al 2003 determined urinary THCCOOH excretion by GC/MS analysis in 4381 urine specimens collected before, during, and after 5 oral daily 0.39, 0.47, 7.5, and 14.8 mg THC/day doses to 7 participants. All urine voids were collected over the 10-week study. At the federally mandated immunoassay cutoff (50 µg/L), mean detection rates were <0.2% during ingestion of the two low doses typical of current hemp oil THC concentrations. These low dose data are representative of the daily THC concentrations present in Fresh Hemp Food products and suggest that the possibility of positive urine THCCOOH tests following ingestion of 0.39 mg THC from hemp foods is low but measurable. Only four of 7 participants produced a mean of 3.1

positive urine THCCOOH specimens after the 0.39 mg/day and 2 of 7 had a mean of 2.4 positive samples during and for the 10 days following 5 daily doses, range 0-13 total specimens). Positive cannabinoid urine tests ≥15 µg/L occurred as early as 14.6 h and as late as 110.5 h after the start of 5 daily doses. Mean detection rate for the 0.39 mg THC/d was 2.6% positive tests with a range of 0 to 10.3% positive tests at ≥15 µg/L. Mean detection rate for the 0.47 mg THC/d was 2.3% positive tests with a range of 0 to 8.7% positive tests at ≥15 µg/L. Maximum metabolite concentrations were 5.4 – 38.2 µg/L for the low THC/day doses.

The results of these three studies are not consistent. Bosy and Cole found no positive urine tests after 7 daily doses of 0.10, 0.17, and 0.32 mg THC and testing urine samples up to 6 h after dosing and daily for 7 days. However, dosing 0.54 and 0.55 mg THC per day produced different results, with some urine samples positive after the 0.54 mg regimen and no samples positive after the 0.55 mg regimen. Only a single individual was administered each dose. Leson et al found no positive GC/MS results ≥15 µg/L following 4 daily up to 0.6 mg THC per day doses, but all urine specimens were not collected and analyzed. Gustafson et al administered 5 daily doses of 0.39 and 0.47 mg THC per day to 7 individuals and all urine specimens were collected and analyzed. Less than 0.2% of urine specimens screened positive at a 50 µg/L cutoff; however, in one subject receiving the 0.39 mg regimen, up to 10.3% of urine specimens were positive for THCCOOH ≥15 µg/L. It is apparent that the vehicle is important for absorption, as a 0.47 mg THC per day hemp oil produced fewer positive urine specimens than the 0.39 mg THC per day dose in Gustafson et al.

Literature Review

Refer to Table 38 for a tabular summary of the publicly available clinical data.

Bosy & Cole 2000 had 7 daily administered doses of hemp oils between 0.10 and 1.8 mg/day and tested random urine specimens for up to 7 days after the last dose. Peak THCCOOH concentrations in the participants' urine ranged from 1.8 to 48.7 µg/L. There were no positive urine specimens ≥15 µg/L following the 0.10, 0.17, 0.32, and 0.55 mg THC/d for 7 daily doses. The 0.54 mg and 1.8 mg THC/d doses produced positive urine specimens ≥15 µg/L. Subjects ingesting low doses of THC (0.10 & 0.17) mg THC/d had no positive immunoassay results, while the 1 subject ingesting 0.32 mg THC/d had 11 of 18 results ≥ 50-µg/L immunoassay positive cutoff, but none were positive by GC/MS. Subjects ingesting medium doses of THC in hemp oil (0.54 & 0.55 mg THC/d) produced positive immunoassay screen results on the third and fourth days of ingestion. These two subjects had negative immunoassays within 24 h after ingestion ceased. The subject ingesting a high dose (1.8 mg THC/d) screened positive on the first day and was immunoassay negative within 72 h after last ingestion. No psychotropic effects were experienced by any of the subjects during the course of the experiment.

Leson et al 2001 reported results from 15 adults ingesting 10 daily THC doses of 0.09, 0.19, 0.29, and 0.45 mg THC. Urine specimens were collected prior to the first ingestion of oil, on days 9 and 10 of each of the four 10-day study periods, and 1 and 3 days after the last ingestion. All specimens were confirmed for THCCOOH by GC–MS and analyzed for creatinine to identify dilute specimens. There were no positive screening results and no positive GC-MS

results ≥15 µg/L for doses below 0.60 mg THC/d. Only one specimen screened positive at the 50 µg/L cutoff at a daily THC dose of 0.6 mg. The highest THCCOOH concentration was 5.2 µg/L, well below the 15 ng/ml confirmation cutoff of federal drug testing programs.

Gustafson et al 2003 determined urinary THCCOOH excretion by GC/MS analysis in 4381 urine specimens collected before, during, and after 5 oral daily 0.39, 0.47, 7.5, and 14.8 mg THC/day doses to 7 participants. All urine voids were collected over the 10-week study. At the federally mandated immunoassay cutoff (50 µg/L), mean detection rates were <0.2% during ingestion of the two low doses typical of current hemp oil THC concentrations. These low dose data are representative of the daily THC concentrations present in Fresh Hemp Food products and suggest that the possibility of positive urine THCCOOH tests following ingestion of 0.39 mg THC from hemp foods is low but measurable. Only four of 7 participants produced a mean of 3.1 positive urine THCCOOH specimens after the 0.39 mg/day and 2 of 7 had a mean of 2.4 positive samples during and for the 10 days following 5 daily doses, range 0-13 total specimens). Positive cannabinoid urine tests ≥15 µg/L occurred as early as 14.6 h and as late as 110.5 h after the start of 5 daily doses. Mean detection rate for the 0.39 mg THC/d was 2.6% positive tests with a range of 0 to 10.3% positive tests at ≥15 µg/L. Mean detection rate for the 0.47 mg THC/d was 2.3% positive tests with a range of 0 to 8.7% positive tests at ≥15 µg/L. Maximum metabolite concentrations were 5.4 – 38.2 µg/L for the low THC/day doses.

The results of these three studies are not consistent. Bosy and Cole found no positive urine tests after 7 daily doses of 0.10, 0.17, and 0.32 mg THC and testing urine samples up to 6 h after dosing and daily for 7 days. However, dosing 0.54 and 0.55 mg THC per day produced different results, with some urine samples positive after the 0.54 mg regimen and no samples positive after the 0.55 mg regimen. Only a single individual was administered each dose. Leson et al found no positive GC/MS results ≥15 µg/L following 4 daily up to 0.6 mg THC per day doses, but all urine specimens were not collected and analyzed. Gustafson et al administered 5 daily doses of 0.39 and 0.47 mg THC per day to 7 individuals and all urine specimens were collected and analyzed. Less than 0.2% of urine specimens screened positive at a 50 µg/L cutoff; however, in one subject receiving the 0.39 mg regimen, up to 10.3% of urine specimens were positive for THCCOOH ≥15 µg/L. It is apparent that the vehicle is important for absorption, as a 0.47 mg THC per day hemp oil produced fewer positive urine specimens than the 0.39 mg THC per day dose in Gustafson et al.

5.7. Safety of THC Exposure – THC Exposure Based on Body Weight

Hemp Oil

The upper bound estimate of THC exposure based on body weight has been determined. using anticipated THC exposure based on 90th percentile consumption of all food products containing maximum levels of Hemp Oil at maximum Fresh Hemp Foods Ltd. THC specification limits. Refer to Tables 19 to 23 for THC values and to Table 39 (duplicated below) for summary of exposure based on body weight for all hemp ingredients and age groups. It is estimated that males and females age 2 years and older would be exposed to THC at 0.925 and 1.075 µg/kg body weight respectively. Exposure is estimated to be 3.387 µg/kg body weight for boys age 2

to 5 years, 3.444 µg/kg body weight for girls age 2 to 5 years and 2.536 µg/kg body weight for boys age 6 to 11 years and 2.723 µg/kg body weight for girls aged 6 to 11 years.

Table 39. Upper Bound Estimate of THC Exposure Based on Body Weight

	THC EXPOSURE BASED ON BODY WEIGHT AT MAXIMUM SPECIFICATION LEVELS (µg/kg Body Weight)[1,2] *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014) *Hulled Hemp Seed = NMT 4 µg/g THC *Hemp Protein Powder = NMT 4 µg/g THC *Hemp Oil = NMT 10 µg/g THC						THC EXPOSURE BASED ON BODY WEIGHT USING MONTE CARLO MODELLING FROM FIGURES 2 to 41 (µg/kg Body Weight)[1,2] *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014) *Hulled Hemp Seed = Mean of 0.29 µg/g THC *Hemp Protein Powder = Mean of 0.31 µg/g THC *Hemp Oil = Mean of 4.95 µg/g THC						TOLERABLE DAILY INTAKE RECOGNIZED BY OTHER REGULATORY AUTHORITIES (µg/kg Body Weight)					
	2 Years & Older		2 to 5 Years		6 to 11 Years		2 Years & Older		2 to 5 Years		6 to 11 Years		Germany	Switzerland	Australia	New Zealand	Canada	Austria
	Males (Mean BW = 88.8 kg)	Females (Mean BW = 76.4 kg)	Males (Mean BW = 14.2 kg)	Females (Mean BW = 13.3 kg)	Males (Mean BW = 23.9 kg)	Females (Mean BW = 23.8 kg)	Males (Mean BW = 88.8 kg)	Females (Mean BW = 76.4 kg)	Males (Mean BW = 14.2 kg)	Females (Mean BW = 13.3 kg)	Males (Mean BW = 23.9 kg)	Females (Mean BW = 23.8 kg)						
Hulled Hemp Seed GRN XXX	0.634 (Table 41)	0.737 (Table 41)	3.299 (Table 42)	3.067 (Table 43)	2.029 (Table 44)	2.041 (Table 45)	0.240	0.279	1.254	1.165	0.770	0.773						
Hemp Protein Powder GRN XXX	0.623 (Table 41)	0.724 (Table 41)	3.482 (Table 42)	3.172 (Table 43)	2.031 (Table 44)	2.096 (Table 45)	0.185	0.215	1.035	0.947	0.607	0.626	5	7	6	6	Not Set	1-2
Hemp Oil GRN XXX	0.925 (Table 41)	1.075 (Table 41)	3.387 (Table 42)	3.444 (Table 43)	2.536 (Table 44)	2.723 (Table 45)	0.869	1.010	3.176	3.241	2.368	2.542						
CUMMULATIVE	**2.182 (Table 41)**	**2.536 (Table 41)**	**10.168 (Table 42)**	**9.684 (Table 43)**	**6.596 (Table 44)**	**6.86 (Table 45)**	**1.181**	**1.373**	**4.915**	**4.895**	**3.322**	**3.504**						
[1] Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States. 2011-2014. National center for Health Statistics. Vital Health Stats 3(39). 2016																		
[1] Assumes that children would eat all the same foods as an adult.																		

A more realistic assessment of THC exposure is achieved by using the daily THC exposure predicted by Monte Carlo modelling using historical third-party THC testing data for Hemp Oil to calculate THC µg/kg body weight. Refer to Tables 39 for a summary of the THC exposure at the 90th percentile for each hemp ingredient and all age groups and the corresponding exposure based on body weight.

It can be realistically estimated that males and females age 2 years and older would be exposed to 0.869 and 1.01 µg/kg body weight respectively, while exposure for children is estimated to be 3.176 µg/kg body weight for boys age 2 to 5 years, 3.241 µg/kg body weight for girls age 2 to 5 years and 2.368 µg/kg body weight for boys age 6 to 11 years and 2.542 µg/kg body weight for girls aged 6 to 11 years. The Monte Carlo estimates are anticipated to be more realistic but are still considered to be relatively conservative because they predict THC exposure at 90th percentile consumption of all food products containing maximum levels of Hemp Oil.

Cumulative Hemp Consumption

The upper bound estimate of THC exposure based on body weight has been determined. using anticipated THC exposure based on 90th percentile consumption of all food products containing maximum levels of Hulled Hemp Seed, Hemp Protein Powders and Hemp Oil at maximum Fresh Hemp Foods Ltd. THC specification limits. Refer to Tables 25 to 28 for THC values and to Table 39 for summary of exposure based on body weight for all hemp ingredients and age groups. Using anticipated cumulative THC exposure based on 90th percentile consumption of all food products containing maximum levels of all hemp ingredients at maximum Fresh Hemp Foods Ltd. THC specification limits, the upper bound estimate is that males and females age 2 years and older would be exposed to 2.182 and 2.636 µg/kg body weight respectively while

children would have a higher per kg exposure based on their lower body weight. Exposure calculated based on body weight is conservatively estimated to be 10.168 for boys age 2 to 5 years, 9.684 µg/kg body weight for girls age 2 to 5 years and 6.596 for boys age 6 to 11 years and 6.86 µg/kg body weight for girls aged 6 to 11 years. These THC exposure levels are highly conservative since they are calculated using the maximum THC levels based on Fresh Hemp Foods Ltd. specifications.

A more realistic assessment of THC exposure is achieved by using the daily THC exposure predicted by Monte Carlo modelling using historical third-party THC testing data for the three Fresh Hemp Foods Ltd. hemp ingredients to calculate THC µg/kg body weight. Refer to Tables 36 and 39 for a summary of the THC exposure at the 90th percentile for each hemp ingredient and all age groups and the corresponding exposure based on body weight.

Refer to Table 39. It can be realistically estimated that males and females age 2 years and older would be exposed to 1.181 and 1.373 µg/kg body weight respectively, while exposure for children is estimated to be 4.915 µg/kg body weight for boys age 2 to 5 years, 4.895 µg/kg body weight for girls age 2 to 5 years and 3.322 µg/kg body weight for boys age 6 to 11 years and 3.504 µg/kg body weight for girls aged 6 to 11 years. The Monte Carlo estimates are anticipated to be more realistic but are still considered to be relatively conservative because they predict THC exposure at 90th percentile consumption of all food products containing maximum levels of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil.

Refer to summary Table 39 for a comparison of the THC exposure from Hulled Hemp Seed and cumulative hemp consumption versus the Tolerable Daily Intake (TDI) recognized by other international regulatory authorities. The THC exposure estimated in this GRAS notification is similar to these other standards. For instance, New Zealand and Australia legalized low THC hemp foods for human consumption in 2017. Through their clinical review, the TDI was set at 6 µg/kg body weight (Food Standards 2017). The estimated µg/kg body weight exposure for children using maximum THC levels based on Fresh Hemp Foods ltd. specifications is higher than this TDI, whereas the estimates obtained by using historical data are in line with this and other TDI identified by regulatory bodies which have performed similar assessment of the safety of THC from low hemp foods.

Food Standards 2017 based their TDI on a study assessing impact of oral consumption of THC on the skill performance (standing steadiness, hand to eye coordination, reaction time, numbers test) of young adults (ANZFA Final Assessment Report Inquiry – S.17 Application A360). The participants showed slight but reversible effects on skill performance and no psychotropic effects after consuming 5 mg THC, the lowest level studied. A 5 mg THC dose was equivalent to 60 mcg/kg BW for this study. ANZFA applied an uncertainty factor of 10 to this lowest-observable-effect level (LOEL) in order to derive an overall TDI of 6 mcg/kg BW.

The European Industrial Hemp Association (EIHA 2017) proposed, after an extensive review of the literature on the topic of THC consumption and effects, a Lowest Observed Effect Level (LOEL) of 2.5 mg of THC intake per person twice daily (Sarmento et al. 2015). A total daily intake of 5 mg THC (2 x 2.5 mg) results in a LOEL of 0.07 mg THC/kg body weight (BW) per

day assuming a body weight of 70 kg. The conclusions were based on the findings regarding the minimal effective THC doses described in the studies by Chesher (1990), Petro & Ellenberger (1981), Beal (1995, 1997), Strasser (2006), and Zajicek (2003, 2005). According to these scientific studies, a single dose of 2.5 mg of THC may usually be regarded as a placebo dose, since comparable minimal effects were also seen with the placebo. EIHA therefore also concluded that a single 2.5 mg dose could be considered the NO(A)EL (EIHA 2017).

EIHA used an uncertainty value of 10 and a LOEL (and NOAEL) of 0.07 mg/kg BW to determine the Acute Reference Dose (ARfD) of 7 µg THC/kg BW. This ARfD is similar to the conclusions made by the Australia and New Zealand's Food Standards as well as the assessment of the health risks of THC in foods performed by the Swiss Federal Office of Public Health (1995). The Swiss authority recognized a lowest observable physiological effect level of orally administered THC of 5 mg per adult and applied an uncertainty factor of 10 to determine that the provisional tolerable daily intake is 7 µg /kg BW (reported by EIHA 2017).

This GRN notice calculated the THC exposure based on body weight using the 90th percentile level of consumption of all foods anticipated to contain Hemp Oil, Hemp Protein Powder and Hulled Hemp Seed at the maximum level of inclusion (*See*, accompanying GRNs filed with this Notice). It is reasonable to anticipate that the estimated THC exposure for individuals 2 years and older and especially for children ages 2 to 5 and 6 to 11 is greatly over estimated since this upper bound estimate assumes that all hemp containing foods will be eaten and that the maximum level of hemp will be used in these foods. The likelihood of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil completely replacing all comparable existing non-hemp materials in the foods identified is unlikely. Furthermore, anticipating that THC will be consistently present at the maximum limits allowed by the specifications in Table 2 is highly conservative and greatly over estimates actual THC exposure for all ages. Refer to Table 39 for a summary contrasting Tolerable Daily Intake (TDI) levels recognized by other international regulatory bodies versus the exposure anticipated from 90th percentile of Hemp Oil and cumulative hemp consumption.

5.8. Allergenicity

The simplest definition of an allergen is a substance that causes an allergic reaction, broadly speaking, a hypersensitivity immune response, but usually refers to a type I– or immunoglobulin E (IgE)–mediated hypersensitivity response (Masilamani et. al. 2012). This definition allows for both principal and proximate causes. Allergens are generally recognized by IgE response from patients. Some allergens are not very potent inducers of primary allergic immune responses, so they are weak allergenic immunogens; but they can trigger an effector response if IgE capable of binding them is present (possibly because of cross-reactivity with a strong immunogen).

Some allergens are considered complete allergens because they can induce sensitization and trigger reactions. Ara h 2 from peanut is an example of a complete allergen. Other allergens are considered incomplete because they trigger reactions by being cross-sensitive to other dominant allergens but are themselves not actually an immunogen. Food allergens, are generally considered to be protein that are recognized by IgE and found in the diet. They may or may not

be complete allergens. The clinical manifestations of a cannabis allergy can vary from mild to life-threatening and is often dependent on the route of exposure. Sensitization to cannabis allergens can trigger various secondary cross-allergies, mostly for plant-derived food. This secondary cross-allergy has been designated as the "cannabis-fruit/vegetable syndrome" and it might also imply cross-reactivity with tobacco, latex and plant-food derived alcoholic beverages (Decuyper et. al. 2015). The cannabis-fruit/vegetable syndrome has mainly been described in Europe and appears to result from cross-reactivity between non-specific lipid transfer proteins or thaumatin-like proteins present in *Cannabis sativa* and their homologues that are ubiquitously distributed throughout plant kingdom (Decuyper et. al. 2015).
About 65% of the plant food allergens belongs to one of the following classes of structurally related protein super families: (1) the prolamin superfamily; (2) the cupin super-family; and (3) the pathogenesis-related proteins (PR-10) family, of which Bet v 1 is the best known (Mills et. al. 2003 and Jenkins et. al. 2007). The prolamin superfamily includes seed storage proteins of cereals, lipid transfer proteins (LTPs), alpha-amylase/protein inhibitors and 2S albumins. A 10-kDa protein (2S albumin) has been isolated from hemp seed and shown to consist of two polypeptide chains (small and
large) with 27 and 61 amino acid residues respectively (Odani and Odani 1998). This 2S hemp protein is thought to be a prolamin.

Structural features, such as stability during thermal processing and digestion, seem to be obvious factors in determining allergenic potency of ingested molecules. PR-10 sensitization, a food-pollen syndrome, is a good example since the structural instability of these proteins correlates with the observation that cooking destroys allergenicity and that ingestion of any form is rarely if ever associated with systemic reactions (Masilamani et. al. 2012). However, digestibility, by itself, produces mixed results when tested as a predictor of food allergenicity (Astwood et. al 1996, Bannon 2004, Fu et. al. 2002, Herman et. al. 2007). There are multiple potential explanations for the weak correlation between digestibility and food allergenicity, including limitations of in vitro systems used to mimic digestion, food matrix effects that are lost when assessing purified proteins, alteration of protein structure during protein preparation, relative abundance of proteins in whole food, and others (Masilamani et. al. 2012). However, whatever the explanation, it is believed that IgE-mediated activation of effector cells requires cross-linking and, therefore, interaction with multivalent ligands that possess a complex structure. Food allergens must therefore either survive or bypass digestion in sufficient amounts to provoke immune responses (Masilamani et. al. 2012). Hemp seed protein including the protein in the Hulled Hemp Seed and Hemp Protein Powders has a lack of trypsin inhibitory activity (Aluko 2017) and has been shown to be highly digestible through use of a rat bioassay (House et. al. 2010).

Various routes of exposure and sensitization can lead to primary cannabis allergy. Exposure through oral ingestion of the seeds and resulting sensitization or allergic response is not well represented in the literature since the published data focusses on marijuana and tends to document exposure via the leaves, stems, flowers and buds (all materials outside the scope of this GRN). There is one published case of a male experiencing anaphylaxis after orally consuming a meal containing hulled hemp seed (Stadmauer et. al. 2003) and there is a published case series of five patients with anaphylaxis to hemp seed ingestion (Bortolin et. al. 2016). In the

case study reported by Stadmauer et. al. 2003, the patient was administered epinephrine and antihistamine, which are treatments typically used for an IgE-mediated reaction. The Bortolin et. al. 2016 case series involved four male and one female patient ranging in age from 13-40 years (mean age 25 years). 80% of patients were atopic and all presented to an emergency room with anaphylaxis shortly after ingestion of hempseed. 60% of patients received isolated antihistamine, 20% received isolated epinephrine, and 20% received both treatments. All were prescribed an epinephrine autoinjector and they all had positive SPTs to fresh hemp seed, with an average wheal size of 10.3mm (3/5 patients). Bortolin et. al. 2016 concluded that allergy to hemp seed appears to manifest later in life as anaphylaxis.

Primary cannabis allergy may occur by people becoming sensitized by inhalation of cannabis allergen through active smoking and/or vaporizing, cutaneous contact and sensitization via chewing, ingestion or intravenous use of marijuana. Sensitization to marijuana pollen is also possible since *Cannabis sativa* is an anemophilous plant and the male plants produce a wind-borne pollen which is capable of being transported over long distances (reported in Decuyper et. al. 2015). Secondary cannabis allergy might result from cross-reactivity with allergenic compounds such as non-specific lipid transfer proteins (ns-LTPs) or thaumatin-like proteins (TLPs) present in other plants from closely or more distantly related origin (Larramendi et al. 2013).

The allergenic composition of *Cannabis sativa* is incompletely characterized. Six different bands with a molecular weight of 10-, 14-, 20-, 35-, 38- and 60-kDa that were recognized by the individual patients' sera have been identified (Larramendi et al. 2013). The 10-kDa band binds IgE and is believed to be Can s 3, a ns-LTP (Gamboa et al. 2007) that belongs to the pathogenesis-related proteins (PR)-14 group (Van Loon 1999). In a European study involving patients with a primary Cannabis allergy, sensitization to the purified cannabis ns-LTP was observed in 124 out of 130 patients (Armentia et. al. 2014). The 38-kDa band corresponds with a thaumatin like protein, which belongs to the PR-5 family previously seen in fruit allergens with cross-reactivity to apple, tomato, gold kiwi and cypress (Larramendi et al. 2013). The 14 kDa band is speculated to be a profilin although no homology was found between it and any known allergen (de Larramendi et al. 2008).

Multiple IgE-binding proteins have been observed, the most prominent of which are 23-kDa and 50-kDa, which appear to have the binding ability even after deglycosylation, suggesting that the IgE-binding epitopes do not reside in the carbohydrate moiety of the glycoprotein allergens (Nayak et al. 2013). The 23-kDa band was identified as "oxygen-evolving enhancer protein 2", an enzyme involved in the photosynthesis and the 50-kDa band corresponds with the heavy chain subunit of ribulose-1,5-biphosphate carboxylase/oxygenase (RuBisCo). Nayak et. al. 2013 observed that ubiquitously distributed cross-reactive carbohydrate determinants might also be the cause of some IgE reactivity. They also identified other possible allergens which are glyceraldehyde-3-phosphate and adenosine triphosphate (ATP) synthase. Most interestingly, Nayak et. al. 2013 observed no IgE-binding sequences of the pan allergen ns-LTP in their American/Canadian proteomics study even though IgE reactivity at approximately 10-kDa was observed in two patients. This contrasts to the European studies since

most of the Canadian patients apparently did not suffer from a cannabis-related cross-reactivity syndrome. It is unknown whether this indicates cannabis allergic patients display geographically different sensitization profiles.

Patients with IgE-mediated cannabis allergy can display distinct sensitization profiles such as sensitization to ns-LTP (Can s 3), a pan allergen which is ubiquitously present throughout the plant kingdom including fruits and vegetables (Egger et al. 2010). Sensitization to Can s 3 could be an explanation for the high variety of secondary plant-derived food allergies which have been documented in European patients with a cannabis allergy. This cross-reactivity between cannabis and plant-derived food has been described by Ebo et al. (2013) and was recently designated as the "cannabis-fruit/vegetable syndrome" by Van Gasse et al. (2014). Ebo et. al. 2013 found that 10 out of 12 patients with a documented cannabis allergy were sensitized to different ns-LTPs including Pru p 3, the ns-LTP of peach (*Prunus persica*). The food allergies most commonly implicated in the cannabis-fruit/vegetable syndrome were allergies to peach, banana, apple, cherry, nuts, tomato and occasionally citrus fruits such as orange and grapefruit (Ebo et. al. 2013). In general, the allergic reactions were more severe than the oral allergy syndrome that is generally observed in food allergy related to sensitization to Bet v 1, the major birch pollen allergen (Ebo and Stevens 2001) and may be partially explained by resistance of ns-LTP to gastroduodenal proteolysis and thermal processing. Sensitization to Can s 3 might also explain cross-reactions to *Hevea latex* (Beezhold et al. 2003; Faber et al. 2015b; Quadri and Nasserullah 2001; Rihs et al. 2006), alcoholic beverages such as beer and wine (Asero et al. 2001; Jegou et al. 2000) and tobacco (*Nicotinia tabaccum*) (Carnes et al. 2013; Faber et al. 2015a).

The clinical data relating to primary and secondary cannabis allergy is not extensive. The sensitizing potential of hemp proteins in humans is unknown, and it is unclear if patients that show allergic reactions upon consuming hemp seed have been sensitized by hemp-proteins or that hemp proteins mainly cross-react in patients allergic to other allergens.
It appears that exposure to the plant leaves, stems, flowers, buds and pollen does result in sensitization for some individuals and that there is the potential for individuals to be sensitized to the proteins in the seed, albeit at a very low reported level of incidence. Secondary allergy through cannabis-fruit/vegetable syndrome cross-reactivity between ns-LTP or TLP present in *Cannabis sativa* and their homologues which are widely distributed throughout the plant kingdom is also a possibility.

5.9. Nutritional Benefits of Hemp as Food

Hemp seeds and hemp seed products are considered of particular important nutritional value due to their "almost perfect" balance of the omega-3 and omega-6 essential fatty acids which includes the presence of stearidonic acid (SDA) and gamma linoleic acid (GLA) (Journal of Agriculture and Food; Manku 1990; Ross 1996; Science Daily 2014; Parker et al. 2003; Erasmus 1999; Simopoulos 2002; Ross et al. 2000; Lachenmeier and Walch 2005; Karimi and Hayatghaibi 2006; Gibb et al. 2005; Leizer et al. 2000, Callaway 2004, Callaway and Pate 2009).

Hemp seeds and its milled seed cake flour contain a high quality protein. As mentioned above, it is easily digestible, and contains all essential amino acids needed by humans (Amerio 1998; Gibb et al. 2005; Erickson 2007; Hessle, Erik- son and Turner 2008; Callaway and Pate 2009, House et. al. 2010).

Protein digestibility-corrected amino acid score (PDCAAS) measurements, using a rat bioassay for protein digestibility and the FAO/WHO amino acid requirement for children 2 to 5 years of age as reference have been conducted on Fresh Hemp Food's Hulled Hemp Seed (House et. al. 2010). The study determined that the protein is highly digestible and that the PDCAAS is positioned higher than some grains such as whole wheat and is in the same range as major pulse protein sources such as lentils and pinto beans.

The safety and efficacy of hemp seed protein has been evaluated and is recognized by Health Canada's Non-Prescription and Natural Health Products Directorate (NNHPD) which has assessed the totality of evidence and has determined that hemp protein concentrate, and hemp protein isolate are safe and effective sources of protein for use in human natural health products (NNHPD Workout Supplements Monograph 2016).

5.10. Toxicology

The literature review found no instances of safety discussions outside of THC (delta 9-tetrahydrocannabinol).

5.11. Pharmacology/Metabolism/Half-Life

THC, the primary psychoactive component of cannabis, is rapidly absorbed into the bloodstream following inhalation and is extensively metabolized in the liver into multiple metabolites. The equipotent metabolite 11-hydroxy-THC (11-OH-THC) of THC is further oxidized to THCCOOH and THCCOOH-glucuronide and sulfate (Huestis et. al. 2011). THC is extensively metabolized to multiple other alcohols and acids, but THCCOOH has been selected as the analyte monitored in urine for virtually all drug-testing programs, including workplace, military, criminal justice and drug treatment programs. After alkaline hydrolysis of urine to free THCCOOH from its conjugates, THCCOOH is the most abundant urinary marker of cannabis use (Huestis et. al. 2011).

When ingested, peak concentrations are much lower and peak later than after smoking. Less euphoria is experienced and exposure to the more toxic ingredients produced from burning cannabis is avoided (Huestis et. al. 2011). After oral exposure, THC is slowly and incompletely absorbed from the gastrointestinal tract (EFSA 2015). The oral ingestion of THC shows distinct differences compared to intraperitoneal, intravenous and inhalation administration with regard to metabolism and time course of plasma level. Compared to inhalation, oral ingestion of the same dose will cause less toxicity because of the lower systemic bioavailability. Ingestion may also result in less toxicity compared to inhalation of a dose producing the same bioavailability, due to a less pronounced THC plasma peak. THC detection after oral ingestion is not reached until approximately 2 hours after ingestion (Holler 2008). In addition, bioavailability of THC through

oral ingestion is only 6-18% compared to 18-50% via smoking (Holler 2008). The literature points to the THC degradation in the acidic environment of the stomach and first-pass metabolism in the liver as the reasons for lower bioavailability.

THC is a pharmacologically highly active substance with dose-dependent effects on several organ systems and body functions. The most conspicuous effects are those on the central nervous and the cardiovascular systems. THC produces an increased heart rate, reddened eyes, and a dry mouth. As for psychotropic effects, a mild euphoria, an enhanced sensory perception, fatigue, and eventually dysphoria together with anxiety have been observed. Brenneisen et al. (1996) administered single oral doses of 10 or 15 mg THC to two patients and measured no change to physiologic parameters (heart rate) and psychological parameters (concentration, mood) as a result of the administration. In contrast, Chesher et. al. (1990) dosed healthy people with 5 mg, 10 mg and 15 mg followed by a light breakfast and found no difference in the subjective level of intoxication at 5 mg, a slight difference at 10 mg and 15 mg and a marked difference at 20 mg relative to placebo controls. At the lowest administered oral dose of 5 mg, a minor decrease in several psychomotoric performance scores, primarily related to standing steadiness, reaction time, and arithmetic performance were observed. Findings by other researchers suggest that even doses of 10 or 15 mg of orally administered THC generally result in minor psychomotoric effects (Brenneisen et al. 1996).

These findings relative to the production of effects by THC indicate that the psychotropic threshold of THC is in the range of 0.2–0.3 mg THC per kg body weight for a single oral dose and corresponds to an administration of 10 to 20 mg THC to an adult. A single dose of 5 mg THC can be regarded as a placebo dose or the NOAEL for psychotropic effects and certain physical effects. It can also be considered as the lowest observed adverse effect level (LOAEL) for the slight reduction in psychomotoric performance.

More than 100 metabolites of THC have been identified. The predominant acid metabolite, 11-nor-9-carboxydelta-9-THC (THC-COOH) is commonly used to identify prior use of marijuana in urine tests. Oral consumption results in higher amounts of THC-COOH being formed more rapidly compared to inhalation or intravenous administration (Wall et al. 1983) which has been attributed to the first-pass effect of orally ingested THC through initial metabolism by the liver. There is large variability in the time course of plasma levels of THC and its metabolites amongst individuals after oral consumption. The composition and timing of meals ingested prior to oral THC consumption is one of the factors that influences the time course of plasma level of THC and subjective response. This is believed to be due to the impact on THC absorption. Oral THC intake via hemp containing food is comparable to the repeated intake of smaller doses over the course of a day since it is likely that hemp containing foods would be eaten throughout the waking hours of the day. This pattern causes broader and lower THC levels in plasma over time, compared to higher single or multiple doses.

5.12. Expression Patterns

THC at high concentrations can cause physiological effects. The most common are those on mood and cognition (euphoria, fear, reduced cognitive functions) as well as

on the cardiac circulation system (increase in cardiac frequency, changes in blood pressure) (Nova Institute 2015). None of these physiological effects are serious threat or pose a risk of injury or death.

It is also important to note THC differs from non-specifically acting harmful chemicals in food in that it acts on compound-specific binding sites (cannabinoid receptors) on the surface of body cells. This expression provides additional assurances of safety. This is due to the effect of repeated ingestion of THC which can lead to tolerance by cannabinoid receptors (Nova Institute 2015). Additionally, children have a significantly lower density of cannabinoid receptors sites which means the psychotropic effects occur only at much higher THC doses (Nova Institute 2015).

5.13. Benefits of Consumption

A review of the toxicology of THC would be imbalanced absent a discussion of the beneficial effects of low doses of THC. Studies have observed antiemesis, immune-stimulating and neuroprotective effects from low doses of THC (Sides 2015).

This body of research again points to THC at the low levels in industrial hemp ingredients not being a toxicology risk or safety concern.

5.14. Other Regulatory Bodies

Refer to Table 40 for a summary of standards adopted by other regulatory bodies for cumulative THC exposure from uses of industrial hemp.

Fresh Hemp Foods Ltd. is licensed by Health Canada and contracts only licensed hemp seed acres meeting the Industrial Hemp Regulations. Fresh Hemp Foods Ltd. tests Hulled Hemp Seed at third party accredited laboratories to confirm THC levels do not exceed internal specifications for THC content (not more than 4 µg/g).

Hemp varieties grown in the European Union (EU) have a THC content of less than 0.2% (measured in the upper third of the plant) (Matthäus 2008). In Germany, the Federal Institute for Risk Assessment (BfR) estimated a provisional tolerable THC intake of 1–2 mg/kg/day, and from this estimation a precautionary guidance value for THC in hemp seed oil of 5000 µg/kg was defined in the year 2000 (Nova Institute 2015). In contrast, Switzerland has set their maximum limits at 10,000 µg/kg for hulled hempseed and 20,000 µg/kg for oil and Australia and New Zealand has set 5000 µg/kg for Hulled Hemp Seed, 10,000 µg/kg for oil and 5,000 µg/kg for protein powders.

Australia and New Zealand have set their TDI for THC in low hemp foods at 6 mcg/kg BW. This is similar to the provisional TDI of 7 mcg/kg BW set by the Swiss Federal Office of Public Health (1995). In both cases the TDI was determined using the results of studies that found no psychoactive effect at 2.5 mg THC once to twice daily. This THC level and TDI are greater than

the THC exposure anticipated from the consumption of Fresh Hemp Foods Ltd Hulled Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil.

5.15. Human Studies

Cannabis is one of the most well studied plants. This interest in research extends to hempseeds and oral consumption of THC. Several clinical studies including large-scale studies have been conducted on oral THC or oral cannabis extracts with high concentrations of THC (see, e.g. Zajicek et al. 2003, 2005; Wade et al. 2004;
Rog et al. 2005; Strasser et al. 2006; Collin et al. 2007; Narang et al. 2008; Novotna et al. 2011). These studies and others in the literature expound on the effects of THC in the body. None have raised any questions of safety.

Hemp seeds and hemp seed products are considered of particular important nutritional value due to their "almost perfect" balance of the omega-3 and omega-6 essential fatty acids which includes the presence stearidonic acid (SDA) and gamma linoleic acid (GLA) (Journal of Agriculture and Food; Manku 1990; Ross 1996; Science Daily 2014; Parker et al. 2003; Erasmus 1999; Simopoulos 2002; Ross et al. 2000; Lachenmeier and Walch 2005; Karimi and Hayatghaibi 2006; Gibb et al. 2005; Leizer et al. 2000, Callaway 2004, Callaway and Pate 2009).

Hemp seeds and its milled seed cake flour contain a high quality protein. As mentioned above, it is easily digestible, and contains all essential amino acids needed by humans (House et. al. 2010, Amerio 1998; Gibb et al. 2005; Erickson 2007; Hessle, Erik- son and Turner 2008; Callaway and Pate 2009).

5.16. Animal Studies

There have been numerous experimental animal studies on the effect of THC in hemp foods. Studies have found acute exposure doses up to 3,000 and 9, 000 mg Δ9-THC/kg in dogs and monkeys, respectively, were not lethal (EFSA 2015 and Thompson et. al. 1973).

The EFSA conducted an animal feed analysis. It reported the oral LD50 for rats and mice were 666 mg THC/kg and 482 mg THC/kg, respectively (EFSA 2011).

5.17. Conclusion

The daily THC consumption even by extensive users of hemp foods is expected to remain below the LOAEL for oral THC. It is not expected to cause any acute or chronic adverse health impacts because it is below the psychoactive threshold for THC and it is below the level clinically shown to potentially result in positive urine drug test results. The daily THC intake level for all population groups estimated by this GRN for both Hemp Oil and cumulative intake of hemp ingredients is consistent with the TDI identified by other recognized regulatory bodies which have performed similar assessments regarding the safety of low THC hemp foods.

The consensus in the scientific literature is clear – hemp seeds, including Hulled Hemp Seed is safe for consumption. Overwhelming evidence shows hemp seeds and hemp seed products are considered of important nutritional value due to their nutritional profile which includes a balance of the omega-3 and omega-6 essential fatty acids which includes the presence of alpha linolenic acid (ALA) and gamma linoleic acid (GLA).

Section 6
References and Tables

6. References and List of Tables, Figures and Supporting Data

List of Tables

List of Figures

Table 1 Application Levels for the General Population

(applicable to organic and conventional)

Food Category	Level (%)
Prepared food (e.g. ready-to eat meals, soups, spreads, dressings, snacks, vegetarian meals etc.)	1 to 15
Beverages and Beverage Bases	1 to 5
Ready to drink beverages, soups, nutritional beverages (protein fortified smoothies, fruit juices, vegetable based soups etc.)	1 to 10
Smoothies	1 to 5
Non-dairy products/Milk alternatives	1 to 10
Dairy imitation products (dairy free milk, dairy free cheeses, dairy free spreads, dairy free creamers, dairy free desserts, dairy free dips, dairy free whipped toppings)	1 to 15
Salad Dressings, table oils, soups, spreads, antipasto and sauces	1 to 15
Meat Analogs (imitation meat products, fake meat)	1 to 15
Extruded product (crisps)	1 to 5

Table 2 Specifications for Hemp Oil

(applicable to organic and conventional)

Parameter	Specifications	Method of analysis
Sensory Characteristics		
Appearance	Translucent, light green oil	Visual
Taste	Nutty	Organoleptic
Odor	Nutty	Organoleptic
Heavy Metals[1]		
Lead	≤ 3ppm	ICP-MS
Cadmium	≤ 1ppm	ICP-MS
Mercury	≤ 0.1ppm	ICP-MS
Arsenic	≤ 1ppm	ICP-MS
THC		
THC	≤ 10 µg/g	Industrial Hemp Technical Manual, Health Canada[2]
Microbiological		
Standard plate count	<10,000 cfu/g	3 M Petrifilm
Total coliforms	<100 cfu/g	3 M Petrifilm
Yeast and Mold	<1000 cfu/g	3 M Petrifilm
Salmonella	Negative in 25g	3 M Petrifilm
Escherichia coli	Negative (<10 cfu/g)	3 M Petrifilm
Aflatoxin[1]		
Aflatoxin	< 0.5 ppb	ELISA

[1]Heavy metals and aflatoxins are not routinely reported on COAs.

[2]Basic Analytical Procedure For The Determination Of Delta-9-tetrahydrocannabinol (thc) In Industrial Hemp, Industrial Hemp Technical Manual - Standard Operating Procedures for Sampling, Testing and Processing Methodology. Accessed February 22, 2018.

Table 3 Nutritional Data for Organic and Conventional Hemp Oil

(Average values for 100 g of commercial product)

Nutrient	Tolerance	Amount per 100 g
Total Fat	Average	99.9 g
Monounsaturated Fat	Average	13 g
Saturated Fat	Average	9.8 g
Trans Fat	Average	0.2 g
Polyunsaturated Fat	Average	76.8 g
Omega 3	Average	19.2 g
Omega 6	Average	58.9 g
Protein	Average	0
Cholesterol	Average	0
Carbohydrates	Average	0
Ash	Average	0
Moisture	Average	0
Calories	Average	820 Kcal

Table 4 Allergen Declaration for Organic and Conventional Hemp Oil

Component	Present in the Product?	Component	Present in the Product?
1. Barley, Rye, Oats	NO	13. Soybean (not including oil)	NO
2. Celery (not including seeds)	NO	14. Sulphites	NO
3. Corn	NO	15. Tree Nuts	NO
4. Egg or egg product	NO	16. Wheat or wheat products	NO
5. Fish	NO	17. Gluten < 10 ppm	NO
6. Milk & Milk by-product	NO	17. Yellow 5 (Tartrazine)	NO
7. Monosodium Glutamate (MSG)	NO	18. Animal Fat	NO
8. Peanuts or peanut products	NO	19. Grains containing gluten	NO
9. Seeds (Poppy, Sunflower, Cottonseed)	NO	20. Mustard/Canola	NO
10. Sesame Seeds	NO	21. Lupin	NO
11. Shell Fish & Crustaceans	NO	22. Lactose	NO
12. Soybean Oil (excluding refined soy oil)	NO		

Table 5 Fatty Acid Profile for Organic and Conventional Hemp Oil

(Average values for commercial product)

Fatty Acid	Quantity (g/100 g)
Linoleic acid	50.9
Alpha linolenic acid	16.7
Oleic acid	9.4
Palmitic acid	5.3
Gamma linolenic acid	3.6
Stearic acid	2.1
Stearidonic Acid	1.2
Arachidic acid	0.7
Conjugated linoleic acid	0.4
Behenic acid	0.3
C20:1 cis -11-eicosenoic	0.2
Lignoceric acid	0.1
Myristic acid	0.1

* Method of analysis = Schuster, J. Chromatogr., 431:271-284; Henderson et al., Agilent Publications, 2000; Barkholt and Jensen, Anal. Biochem., 177: 318-322; AOAC 988.15

Table 6 Product Specifications and Representative Analytical Data for Organic and Conventional Hemp Oil

Parameter	ANBE45NC	BRSK16NO	KRMA15FC	NABR16FO	BEME15NC
Appearance	Clear, light green	Clear, light green	Clear, light green	Clear, light green	Clear, light green
Standard Plate Count	<1,000 cfu/g	<1,000 cfu/g	<1,000 cfu/g	<1,000 cfu/g	<1,000 cfu/g
Total Coliforms	<10 cfu/g	<10 cfu/g	<10 cfu/g	<10 cfu/g	<10 cfu/g
Yeast	<100 cfu/g	<100 cfu/g	<100 cfu/g	<100 cfu/g	<100 cfu/g
Mold	<100 cfu/g	<100 cfu/g	<100 cfu/g	<100 cfu/g	<100 cfu/g
E.coli	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)
Salmonella	Negative	Negative	Negative	Negative	Negative
Free Fatty Acids	0.56 %	0.15 %	1.02 %	0.39 %	0.33 %
Peroxide Value	0.9 meq/Kg	0.7 meq/Kg	0.6 meq/Kg	0.5 meq/Kg	0.9 meq/Kg
THC	<4 ppm	<4 ppm	<4.0 ppm	<4.0 ppm	<4 ppm

Table 7 Lot Analysis for Heavy Metals - Organic and Conventional Hemp Oil

Lot Code	Arsenic (ppm)	Cadmium (ppm)	Mercury (ppm)	Lead (ppm)
BRAN16FO	<0.05	<0.01	<0.05	<0.01
LAMA16FO	0.06	<0.01	<0.05	<0.01
NABR16FO	<0.05	<0.01	<0.05	<0.01
PGAM16NO	0.08	<0.01	<0.05	0.02
ROSE56FO	<0.05	<0.01	<0.05	<0.01

Table 8 Lot Analysis for Aflatoxin - Organic and Conventional Hemp Oil

Lot Code	Aflatoxin (ppb)
SHCH26NO	<5
DAMA15XC	<5
ANBE15NC	<5
DABR24FO	<5
MAEN75XC	<5

Table 9 Conservative Estimation of Consumption Based on Intended Use Levels and Serving Size, All Individuals 2 Years and Older - Organic or Conventional Hemp Oil

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Ages 2 and Over		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Maximum Use Levels (g/kg)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %									Mean	90th %	Mean	90th %	Mean	90th %
Total Oils	Includes fats naturally present in seafood, nuts, seeds, olives, avocados, and the following: Almond oil, Canola oil, Corn oil, Cottonseed oil, Fish oil, Flaxseed oil, Olive oil, Peanut oil, Rapeseed oil, Safflower oil, Sesame oil, Spreads, Soybean oil, Sunflower oil, Vegetable oil, Walnut oil, Wheat germ oil	25.40	50.80	1.00	7.00	15.00	0.30	2.10	4.50	150.00	30.00	0.25	0.51	1.78	3.56	3.81	7.62
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	1.98	3.97	1.00	7.00	15.00	0.55	3.85	8.25	150.00	55.00	0.02	0.04	0.14	0.28	0.30	0.60
											Total (g/person/day)	0.27	0.55	1.92	3.83	4.11	8.22

[1]Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AJ. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3]Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5]90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985). "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6]Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp oil would direct replace oils in oil products.

[7]Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 10 Conservative Estimation of Consumption Based on Intended Use Levels and Serving Size, Males 2 to 5 Years - Organic or Conventional Hemp Oil

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Males 2 - 5 Years		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Maximum Use Levels (g/kg)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %									Mean	90th %	Mean	90th %	Mean	90th %
Total Oils	Includes fats naturally present in seafood, nuts, seeds, olives, avocados, and the following: Almond oil, Canola oil, Corn oil, Cottonseed oil, Fish oil, Flaxseed oil, Olive oil, Peanut oil, Rapeseed oil, Safflower oil, Sesame oil, Spreads, Soybean oil, Sunflower oil, Vegetable oil, Walnut oil, Wheat germ oil	15.18	30.36	1.00	7.00	15.00	0.30	2.10	4.50	150.00	30.00	0.15	0.30	1.06	2.13	2.28	4.55
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	0.85	1.70	1.00	7.00	15.00	0.55	3.85	8.25	150.00	55.00	0.01	0.02	0.06	0.12	0.13	0.26
											Total (g/person/day)	0.16	0.32	1.12	2.24	2.40	4.81

[1]Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AJ. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3]Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5]90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6]Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp oil would direct replace oils in oil products.

[7]Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 11 Conservative Estimation of consumption Based on Intended Use Levels and Serving Size, Females 2 to 5 Years - Organic or Conventional Hemp Oil

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Females 2 - 5 Years		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Maximum Use Levels (g/kg)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %									Mean	90th %	Mean	90th %	Mean	90th %
Total Oils	Includes fats naturally present in seafood, nuts, seeds, olives, avocados, and the following: Almond oil, Canola oil, Corn oil, Cottonseed oil, Fish oil, Flaxseed oil, Olive oil, Peanut oil, Rapeseed oil, Safflower oil, Sesame oil, Spreads, Soybean oil, Sunflower oil, Vegetable oil, Walnut oil, Wheat germ oil	14.42	28.84	1.00	7.00	15.00	0.30	2.10	4.50	150.00	30.00	0.14	0.29	1.01	2.02	2.16	4.33
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	0.85	1.70	1.00	7.00	15.00	0.55	3.85	8.25	150.00	55.00	0.01	0.02	0.06	0.12	0.13	0.26
											Total (g/person/day)	0.15	0.31	1.07	2.14	2.29	4.58

[1]Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AJ. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3]Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5]90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6]Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp oil would direct replace oils in oil products.

[7]Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 12 Conservative Estimation of Consumption Based on Intended Use Levels and Serving Size, Males 6 to 11 Years - Organic or Conventional Hemp Oil

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Males 6-11 Years		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %								Mean	90th %	Mean	90th %	Mean	90th %
Total Oils	Includes fats naturally present in seafood, nuts, seeds, olives, avocados, and the following: Almond oil, Canola oil, Corn oil, Cottonseed oil, Fish oil, Flaxseed oil, Olive oil, Peanut oil, Rapeseed oil, Safflower oil, Sesame oil, Spreads, Soybean oil, Sunflower oil, Vegetable oil, Walnut oil, Wheat germ oil	19.07	38.14	1.00	7.00	15.00	0.30	2.10	4.50	30.00	0.19	0.38	1.33	2.67	2.86	5.72
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	1.13	2.27	1.00	7.00	15.00	0.55	3.85	8.25	55.00	0.01	0.02	0.08	0.16	0.17	0.34
										Total (g/person/day)	0.20	0.40	1.41	2.83	3.03	6.06

[1]Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AI. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3]Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5]90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6]Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp oil would direct replace oils in oil products.

[7]Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 13 Conservative Estimation of Consumption Based on Intended Use and Serving Size, Females 6 to 11 Years - Organic or Conventional Hemp Oil

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Females 6-11 Years		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %								Mean	90th %	Mean	90th %	Mean	90th %
Total Oils	Includes fats naturally present in seafood, nuts, seeds, olives, avocados, and the following: Almond oil, Canola oil, Corn oil, Cottonseed oil, Fish oil, Flaxseed oil, Olive oil, Peanut oil, Rapeseed oil, Safflower oil, Sesame oil, Spreads, Soybean oil, Sunflower oil, Vegetable oil, Walnut oil, Wheat germ oil	19.90	39.80	1.00	7.00	15.00	0.30	2.10	4.50	30.00	0.20	0.40	1.39	2.79	2.99	5.97
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	1.70	3.40	1.00	7.00	15.00	0.55	3.85	8.25	55.00	0.02	0.03	0.12	0.24	0.26	0.51
										Total (g/person/day)	0.22	0.43	1.51	3.02	3.24	6.48

[1]Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AI. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3]Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5]90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6]Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp oil would direct replace oils in oil products.

[7]Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 14 Cumulative Daily Intake of Hemp, All Individuals Age 2 Years and Older - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1]		Mid-Point Daily intake (g/person)[1]		Maximum Daily intake (g/person)[1]	
	Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	0.52	1.04	3.26	6.51	7.03	14.07
Protein Powders (inc. concentrate)	0.27	0.53	3.32	6.65	6.91	13.84
Oil	0.27	0.55	1.92	3.83	4.11	8.22
TOTAL	**1.06**	**2.12**	**8.49**	**17.00**	**18.05**	**36.12**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 15 Cumulative Daily Intake of Hemp, Males 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1] Males 2-5 Yrs		Mid-Point Daily intake (g/person)[1] Males 2-5 Yrs		Maximum Daily intake (g/person)[1] Males 2-5 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	0.43	0.85	2.71	5.43	5.86	11.71
Protein Powders (inc. concentrate)	0.28	0.55	2.95	5.91	6.18	12.36
Oil	0.16	0.32	1.12	2.24	2.40	4.81
TOTAL	**0.86**	**1.72**	**6.79**	**13.58**	**14.44**	**28.88**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 16 Table 16 Cumulative Daily Intake of Hemp- Females Age 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1] Females 2-5 Yrs		Mid-Point Daily intake (g/person)[1] Females 2-5 Yrs		Maximum Daily intake (g/person)[1] Females 2-5 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.37	0.75	2.36	4.73	5.10	10.20
Protein Powders (inc. concentrate)	0.23	0.46	2.52	5.04	5.28	10.55
Oil	0.15	0.31	1.07	2.14	2.29	4.58
TOTAL	**0.76**	**1.51**	**5.95**	**11.91**	**12.67**	**25.33**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 17 Cumulative Daily Intake of Hemp - Males Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1] Males 6-11 Yrs		Mid-Point Daily intake (g/person)[1] Males 6-11 Yrs		Maximum Daily intake (g/person)[1] Males 6-11 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	0.45	0.90	2.81	5.61	6.06	12.12
Protein Powders (inc. concentrate)	0.26	0.52	2.90	5.81	6.07	12.14
Oil	0.20	0.40	1.41	2.83	3.03	6.06
TOTAL	**0.91**	**1.82**	**7.12**	**14.25**	**15.16**	**30.32**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 18 Cumulative Daily Intake of Hemp - Females Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1] Females 6-11 Yrs		Mid-Point Daily intake (g/person)[1] Females 6-11 Yrs		Maximum Daily intake (g/person)[1] Females 6-11 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.44	0.89	2.81	5.63	6.07	12.14
Protein Powders (inc. concentrate)	0.24	0.49	3.00	5.99	6.24	12.47
Oil	0.22	0.43	1.51	3.02	3.24	6.48
TOTAL	**0.90**	**1.81**	**7.32**	**14.65**	**15.55**	**31.10**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 19 Cumulative Daily Intake of THC, All Individuals Age 2 Years and Older - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	4.00	0.0021	0.0042	0.0130	0.0261	0.0281	0.0563
Protein Powders (inc. concentrate)	4.00	0.0011	0.0021	0.0133	0.0266	0.0276	0.0553
Oil	10.00	0.0027	0.0055	0.0192	0.0383	0.0411	0.0822
TOTAL		**0.0059**	**0.0118**	**0.0455**	**0.0910**	**0.0968**	**0.1938**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 20 Conservative Daily Intake of THC, All Individuals Aged 2 Years and Older - Organic or Conventional Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mcg/person)[1]		Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %
Oil	10.00	2.74	5.48	0.0027	0.0055	0.0192	0.0383	0.0411	0.0822

Table 21 Conservative Daily Intake of THC, Males Age 2 to 5 Years - Organic or Conventional Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Oil	10.00	0.0016	0.0032	0.0112	0.0224	0.0240	0.0481

Table 22 Conservative Daily Intake of THC, Females Age 2 to 5 Years - Organic or Conventional Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Oil	10.00	0.0015	0.0031	0.0107	0.0214	0.0229	0.0458

Table 23 Conservative Daily Intake of THC, Males Age 6 to 11 Years - Organic or Conventional Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Oil	10.00	0.0020	0.0040	0.0141	0.0283	0.0303	0.0606

Table 24 Conservative Daily Intake of THC, Females Age 6 to 11 Years - Organic or Conventional Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Oil	10.00	0.0022	0.0043	0.0151	0.0302	0.0324	0.0648

Table 25 Cumulative Daily Intake of THC, Males 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	4.00	0.0017	0.0034	0.0109	0.0217	0.0234	0.0468
Protein Powders (inc. concentrate)	4.00	0.0011	0.0022	0.0118	0.0236	0.0247	0.0494
Oil	10.00	0.0016	0.0032	0.0112	0.0224	0.0240	0.0481
TOTAL		**0.0044**	**0.0088**	**0.0339**	**0.0678**	**0.0722**	**0.1444**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 26 Cumulative Daily Intake of THC, Females 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seed	4.00	0.0015	0.0030	0.0094	0.0189	0.0204	0.0408
Protein Powders (inc. concentrate)	4.00	0.0009	0.0018	0.0101	0.0202	0.0211	0.0422
Oil	10.00	0.0015	0.0031	0.0107	0.0214	0.0229	0.0458
TOTAL		**0.0039**	**0.0079**	**0.0302**	**0.0605**	**0.0644**	**0.1288**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 27 Cumulative Daily Intake of THC, Males 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seed	4.00	0.0018	0.0036	0.0112	0.0224	0.0242	0.0485
Protein Powders (inc. concentrate)	4.00	0.0010	0.0021	0.0116	0.0232	0.0243	0.0485
Oil	10.00	0.0020	0.0040	0.0141	0.0283	0.0303	0.0606
TOTAL		**0.0048**	**0.0097**	**0.0370**	**0.0740**	**0.0788**	**0.1576**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 28 Cumulative Daily Intake of THC, Females 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seed	4.00	0.0018	0.0035	0.0113	0.0225	0.0243	0.0486
Protein Powders (inc. concentrate)	4.00	0.0010	0.0020	0.0120	0.0240	0.0249	0.0499
Oil	10.00	0.0022	0.0043	0.0151	0.0302	0.0324	0.0648
TOTAL		**0.0049**	**0.0098**	**0.0384**	**0.0767**	**0.0816**	**0.1633**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 29 Cumulative Daily Intake of Oil, All Individuals Age 2 Years and Older - Organic or Conventional Hemp Oil, Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Oil Content (%)	Minimum Daily Oil Intake (g/person)		Mid-Point Daily Oil Intake (g/person)		Maximum Daily Oil Intake (g/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	51	0.265	0.531	1.660	3.322	3.586	7.174
Hemp Protein Powders (including Hemp Protein Concentrate)	15	0.040	0.080	0.498	0.998	1.037	2.075
Hemp Oil	99.9	0.274	0.547	1.915	3.830	4.103	8.207
TOTAL		**0.579**	**1.158**	**4.073**	**8.150**	**8.726**	**17.457**

Table 30 Cumulative Daily Intake of Oil, Males Age 2 to 5 Years - Organic or Conventional Hemp Oil, Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Oil Content (%)	Minimum Daily Oil Intake (g/person)		Mid-Point Daily Oil Intake (g/person)		Maximum Daily Oil Intake (g/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	51	0.218	0.435	1.384	2.769	2.986	5.973
Hemp Protein Powders (including Hemp Protein Concentrate)	15	0.041	0.083	0.443	0.886	0.927	1.854
Hemp Oil	99.9	0.160	0.320	1.121	2.242	2.402	4.804
TOTAL		**0.419**	**0.838**	**2.948**	**5.896**	**6.315**	**12.631**

Table 31 Cumulative Daily Intake of Oil, Females Age 2 to 5 Years - Organic or Conventional Hemp Oil, Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Oil Content (%)	Minimum Daily Oil Intake (g/person)		Mid-Point Daily Oil Intake (g/person)		Maximum Daily Oil Intake (g/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	51	0.191	0.381	1.205	2.410	2.600	5.201
Hemp Protein Powders (including Hemp Protein Concentrate)	15	0.034	0.069	0.378	0.757	0.791	1.582
Hemp Oil	99.9	0.153	0.305	1.068	2.136	2.288	4.576
TOTAL		**0.378**	**0.755**	**2.651**	**5.302**	**5.680**	**11.360**

Table 32 Cumulative Daily Intake of Oil, Males Age 6 to 11 Years - Organic or Conventional Hemp Oil, Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Oil Content (%)	Minimum Daily Oil Intake (g/person)		Mid-Point Daily Oil Intake (g/person)		Maximum Daily Oil Intake (g/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	51	0.229	0.458	1.431	2.862	3.090	6.182
Hemp Protein Powders (including Hemp Protein Concentrate)	15	0.039	0.077	0.436	0.872	0.910	1.820
Hemp Oil	99.9	0.202	0.404	1.413	2.826	3.028	6.055
TOTAL		**0.469**	**0.939**	**3.279**	**6.560**	**7.028**	**14.058**

Table 33 Cumulative Daily Intake of Oil, Females Age 6 to 11 Years - Organic or Conventional Hemp Oil, Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Oil Content (%)	Minimum Daily Oil Intake (g/person)		Mid-Point Daily Oil Intake (g/person)		Maximum Daily Oil Intake (g/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	51	0.226	0.452	1.435	2.871	3.097	6.193
Hemp Protein Powders (including Hemp Protein Concentrate)	15	0.037	0.073	0.449	0.899	0.935	1.871
Hemp Oil	99.9	0.216	0.432	1.510	3.021	3.237	6.474
TOTAL		**0.478**	**0.956**	**3.395**	**6.791**	**7.269**	**14.538**

Table 34 Fatty Acid Comparison - Organic or Conventional Hemp Seed Oil

Fatty Acid	Hempseed Oil (g/100 g oil)	Sacha Inchi Oil GRN 506 (g/100 g oil)	Camelina Oil GRN 642 (g/100 g oil)	Soybean Oil CNF 419[1] (g/100 g oil)	Canola Oil CNF 451[1] (g/100 g oil)	Flax Oil CNF 5497[1] (g/100 g oil)	Olive Oil CNF 422[1] (g/100 g oil)	Walnut Oil CNF 439[1] (g/100 g oil)	Avocado Oil CNF 450[1] (g/100 g oil)	Cottonseed Oil CNF 430[1] (g/100 g oil)
Alpha Linolenic Acid, ALA, 18:3, Omega-3	16.70	32.50	32.50	6.80	9.10	53.40	0.80	10.40	1.00	0.20
Oleic Acid, OA, 18:1, Omega-9	9.40	28.00	28.00	22.60	61.70	18.30	71.20	22.20	67.90	17.00
Stearidonic Acid, SA, 18:4, Omega - 3	1.20	N/R	N/R	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Linoleic Acid, LA, 18:2, Omega-6	50.90	21.70	21.70	51.00	19.00	14.30	9.80	52.90	12.50	51.50
Gamma Linoleic Acid, GLA, 18:3, Omega-6	3.63	N/R	N/R	0.00	0.00	0.00	0.00	0.00	0.00	0.00

1 CNF, Canadian Nutrient File. https://food-nutrition.canada.ca/cnf-fce/index-eng.jsp Accessed October 26, 2017.

Table 35 Detection of Cannabinoids in Urine

Drug Testing Program	Cut Off Limit
US Department of Defense	15 ng/ml
US Federal Workplace Drug Testing	15 ng/ml
World Anti-Doping Agency	150 ng/ml

Table 36 Daily THC Exposure at Maximum Specification Levels and Monte Carlo Modelling of Daily THC Exposure - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014)					THC EXPOSURE FROM HEMP MATERIAL CONSUMED AT MAXIMUM FRESH HEMP FOODS LTD. SPECIFICATION LIMITS (mg/Day) *Hulled Hemp Seed = NMT 4 µg/g THC *Hemp Protein Powder = NMT 4 µg/g THC *Hemp Oil = NMT 10 µg/g THC					THC EXPOSURE FROM HEMP MATERIAL CONSUMED USING MONTE CARLO MODEL AND HISTORICAL TEST DATA (mg/Day) *Hulled Hemp Seed = Mean of 0.29 µg/g THC *Hemp Protein Powder = Mean of 0.31 µg/g THC *Hemp Oil = Mean of 4.95 µg/g THC				
	2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years	
	Males & Females	Males	Females	Males	Females	Males & Females	Males	Females	Males	Females	Males & Females	Males	Females	Males	Females
HULLED HEMP SEED GRN XXX	14.07 (Table 14)	11.71 (Table 15)	10.2 (Table 16)	12.12 (Table 17)	12.14 (Table 18)	0.0563 (Table 19)	0.0468 (Table 25)	0.0408 (Table 26)	0.0485 (Table 27)	0.0486 (Table 28)	0.0213 (Figure 4)	0.0178 (Figure 12)	0.0155 (Figure 20)	0.0184 (Figure 28)	0.0184 (Figure 36)
HEMP PROTEIN POWDER GRN XXX	13.84 (Table 14)	12.36 (Table 15)	10.55 (Table 16)	12.14 (Table 17)	12.47 (Table 18)	0.0553 (Table 19)	0.0494 (Table 25)	0.0422 (Table 26)	0.0485 (Table 27)	0.0499 (Table 28)	0.0164 (Figure 6)	0.0147 (Figure 13)	0.0126 (Figure 22)	0.0145 (Figure 30)	0.0149 (Figure 38)
HEMP OIL GRN XXX	8.22 (Table 14)	4.81 (Table 15)	4.58 (Table 16)	6.06 (Table 17)	6.48 (Table 18)	0.0822 (Table 19)	0.0481 (Table 25)	0.0458 (Table 26)	0.0606 (Table 27)	0.0648 (Table 28)	0.0772 (Figure 8)	0.0451 (Figure 17)	0.0431 (Figure 24)	0.0566 (Figure 32)	0.0605 (Figure 40)
CUMMULATIVE	**36.12 (Table 14)**	**28.88 (Table 15)**	**25.33 (Table 16)**	**30.32 (Table 17)**	**31.1 (Table 18)**	**0.1938 (Table 19)**	**0.1444 (Table 25)**	**0.1288 (Table 26)**	**0.1576 (Table 27)**	**0.1633 (Table 28)**	**0.1049 (Figure 2)**	**0.0698 (Figure 10)**	**0.0651 (Figure 18)**	**0.0794 (Figure 26)**	**0.0834 (Figure 34)**

Table 37 Estimated Infant THC Exposure

Estimated THC food daily intake mg	Maternal THC plasma Cmax µg/L	Maternal 11-OH-THC plasma Cmax µg/L	Breast Milk THC Cmax µg/L B/P 8.4	Breast Milk 11-OH-THC Cmax µg/L B/P 8.4	Infant THC Exposure µg/kg/day[3]	Infant 11-OH-THC Exposure µg/kg/day
0.0968	<0.02	<0.04	<0.17	<0.34	<0.03	<0.05
0.1938	<0.04	<0.07	<0.34	<0.59	<0.05	<0.09
0.1025	<0.02	<0.04	<0.17	<0.34	<0.03	<0.05
5.4[1]	<1.2	<2	<10.1	<16.8	<1.5	<2.5
0.39[2]	ND	ND				
0.47[2]	ND	ND				

[1]Stott et al 2013 oral mucosa THC dose; [2]Gustafson et al 2014 oral THC dose
[3]150 mL/kg/day infant breast milk dose

Table 38 Literature Review – Oral THC Administration, Urine THCCOOH Excretion Data, Blood/Plasma/Serum THC Concentrations and Effects

Amount of THC dosed (mg/dose)	# Doses per Day (d)	Total THC per Day (mg/day)	Delivery Form	Study Duration (# Days)	# Subjects (S)	Urine Cmax (µg/L)	Urine Cutoff Level (µg/L)	# Pos Subjects; % pos urine ≥ 15µg/L	# Days Subject Tested Positive at Cutoff	Reference
NA	NA	NA	Oral hemp oil	2	7	<1.8-78.6 8h post	15	3	2 of 5 participants pos 2 d	Costantino 1997
15	1	15.0	Marinol	6	4	189 - 362	15	4; 44-54%	2 to 5 d	ElSohly 2001
16.5	1	16.5	Oral hemp oil	6	3	Up to 431	15	6 for 2.5d; 2 for 5.5d; no%given	2.5-5.5	Lehmann 1997
33	1	33.0	Oral hemp oil	6	3	Up to 378	15	See above; doses not separated	2.5-5.5	Lehmann 1997
20	1	20.0	Marinol & oral hemp oil	3	18	NA	50 screen & 15 confirm	18; 60%	NA NA	Grauwiler 2008
22.4	1	22.4	Brownie	Until negative urine	5	~325	5	5	Mean 6 d	Cone 1988
44.8	1	44.8	Brownie	Until negative urine	5	~436	5	5	Mean 6.5 d	Cone 1988
50.6	1	50.6	Brownie	2.5	9 O	116 - 667	5	9; median 84.6% (27.3-100%)	2	Huestis 135
50.6	1	50.6	Brownie	2.5	7O	181 - 766	5	7; median 88.9 (50-100)%	2	Huestis 135-5
50.6	1	50.6	Brownie	3	11 F	243 - 2010	5	11: median 100%	3	Huestis 135
50.6	1	50.6	Brownie	3	8 F	133 – 736	5	8; median 100%	3	Huestis 135-5
0.09 d X 10d	1	0.09	Oral hemp & canola oil	10	15	<5.2	50 screen & 15 confirm	0;0%	0	Leson 2001
0.19 X 10d	1	0.19	Oral hemp & canola oil	10	15	<5.2	50 screen & 15 confirm	0;0%	0	Leson 2001
0.29 X 10d	1	0.29	Oral hemp & canola oil	10	15	<5.2	50 screen & 15 confirm	0;0%	0	Leson 2001
0.45 X 10d	1	0.45	Oral hemp & canola oil	10	15	<5.2	50 screen & 15 confirm	0;0%	0	Leson 2001
0.60 X 10d	1	0.6	Oral hemp & canola oil	10	2	<5.2	15	0;0%	0	Leson 2001
0.10 d X 7d	1	0.10	Oral hemp oil capsules	14	1	5.2	15	0;0%	0	Bosy & Cole 2000
0.17 d X 7d	1	0.17	Oral hemp oil	14	1	1.8	15	0;0%	0	Bosy & Cole 2000
0.32 d X 7d	1	0.32	Oral hemp oil	14	1	13.9	15	0;0%	0	Bosy & Cole 2000
0.54 d X 7d	1	0.54	Oral hemp oil	14	1	21.1	15	1;5.3%	1d after last dose	Bosy & Cole 2000
0.55 d X 7d	1	0.55	Oral hemp oil	14	1	13.1	15	0%	0	Bosy & Cole 2000
1.8 d X 7d	1	1.8	Oral hemp oil	14	1	48	15	1; 50% in 14 d	2d after last dose	Bosy & Cole 2000
0.39 d X 5d	1	0.39	Oral hemp oil	15	7	Mean 19.8; (7.3-38.2)	15	4; mean 2.6%	1.5 mean	Gustafson 2003
0.47 d X 5d	1	0.47	Oral hemp oil	15	7	Mean 12.2; (5.4-31.0)	15	2; mean 2.3%	0.5 mean	Gustafson 2003
7.5 d X 5d	1	7.5	Marinol	15	7	Mean 146; (26.0-436)	15	7; mean 37.8%	2.5	Gustafson 2003
14.8 d X 5d	1	14.8	Oral hemp oil	15	7	Mean 116; (19.0-264)	15	7; mean 31.9%	2.5	Gustafson 2003
Unknown	2	Unknown	Oral hemp oil	7.4	1	68	15	1; most during dosing	5	Struempler 1997
2.7	6	16.2	Sativex	Dosed 30 d	8	61.3 ± 27.5	25	8; 1 urine each month	NA	Indorato 2016
2.7	6	16.2	Sativex	Dosed 90 d	12	59.8±23.6 @ 1 mo, 62.6±25.2 @2 mo, 63.2±24.8 @ 3 mo	25	12; 1 urine each month	NA	Indorato 2016

Table 39 Upper Bound Estimate of THC Exposure Based on Body Weight

	THC EXPOSURE BASED ON BODY WEIGHT AT MAXIMUM SPECIFICATION LEVELS (µg/kg Body Weight)[1,2] *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014) *Hulled Hemp Seed = NMT 4 µg/g THC *Hemp Protein Powder = NMT 4 µg/g THC *Hemp Oil = NMT 10 µg/g THC						THC EXPOSURE BASED ON BODY WEIGHT USING MONTE CARLO MODELLING FROM FIGURES 2 to 41 (µg/kg Body Weight)[1,2] *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014) *Hulled Hemp Seed = Mean of 0.29 µg/g THC *Hemp Protein Powder = Mean of 0.31 µg/g THC *Hemp Oil = Mean of 4.95 µg/g THC						TOLERABLE DAILY INTAKE RECOGNIZED BY OTHER REGULATORY AUTHORITIES (µg/kg Body Weight)					
	2 Years & Older		2 to 5 Years		6 to 11 Years		2 Years & Older		2 to 5 Years		6 to 11 Years		Germany	Switzerland	Australia	New Zealand	Canada	Austria
	Males (Mean BW = 88.8 kg)	Females (Mean BW = 76.4 kg)	Males (Mean BW = 14.2 kg)	Females (Mean BW = 13.3 kg)	Males (Mean BW = 23.9 kg)	Females (Mean BW = 23.8 kg)	Males (Mean BW = 88.8 kg)	Females (Mean BW = 76.4 kg)	Males (Mean BW = 14.2 kg)	Females (Mean BW = 13.3 kg)	Males (Mean BW = 23.9 kg)	Females (Mean BW = 23.8 kg)						
Hulled Hemp Seed GRN XXX	0.634 (Table 41)	0.737 (Table 41)	3.299 (Table 42)	3.067 (Table 43)	2.029 (Table 44)	2.041 (Table 45)	0.240	0.279	1.254	1.165	0.770	0.773	5	7	6	6	Not Set	1-2
Hemp Protein Powder GRN XXX	0.623 (Table 41)	0.724 (Table 41)	3.482 (Table 42)	3.172 (Table 43)	2.031 (Table 44)	2.096 (Table 45)	0.185	0.215	1.035	0.947	0.607	0.626						
Hemp Oil GRN XXX	0.925 (Table 41)	1.075 (Table 41)	3.387 (Table 42)	3.444 (Table 43)	2.536 (Table 44)	2.723 (Table 45)	0.869	1.010	3.176	3.241	2.368	2.542						
CUMMULATIVE	**2.182 (Table 41)**	**2.536 (Table 41)**	**10.168 (Table 42)**	**9.684 (Table 43)**	**6.596 (Table 44)**	**6.86 (Table 45)**	**1.181**	**1.373**	**4.915**	**4.895**	**3.322**	**3.504**						

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States. 2011-2014. National center for Health Statistics. Vital Health Stats 3(39). 2016

[1]Assumes that children would eat all the same foods as an adult.

Table 40 Summary of Standards Adopted by Other Regulatory Bodies for Cumulative THC Exposure from Uses of Industrial Hemp[1]

Country	Recognized Tolerable Daily Intake (µg/kg Body Weight)	Regulated THC Limit - Hulled Hemp Seed (µg /g)	Regulated THC Limit - Hemp Protein Powder (µg /g)	Regulated THC Limit - Hemp Oil (µg /g)
Germany	5	No specific guidance	No specific guidance	5
Switzerland	7	1	No specific guidance	2
Australia	6	5	No specific guidance	10
New Zealand	6	5	No specific guidance	10
Canada	Not set	10	10	10
Austria	1-2	Not to exceed 1-2 µg/kg bw/day	Not to exceed 1-2 µg /kg bw/day	Not to exceed 1-2 µg/kg bw/day

[1] Prepared using information from the report by Nova Institute titled, *Scientifically Sound Guidelines for THC in Food in Europe* July 2015 (available at http://eiha.org/media/2015/08/15-07-24-Report-Scientifically-Safe-Guidelines-THC-Food-nova-EIHA.pdf (last visited February 26, 2018)).

Table 41 Daily Intake of THC Based on Body Weight, All Individuals Age 2 Years and Older - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]				Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]				Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]			
	Male - Adult 20 Years and Older Mean BW = 88.8 kg		Female - Adult 20 Years and Older Mean BW = 76.4 kg		Male - Adult 20 Years and Older Mean BW = 88.8 kg		Female - Adult 20 Years and Older Mean BW = 76.4 kg		Male - Adult 20 Years and Older Mean BW = 88.8 kg		Female - Adult 20 Years and Older Mean BW = 76.4 kg	
	Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.02344	0.24775	0.02725	0.28796	0.14664	0.29339	0.17043	0.34101	0.31671	0.63367	0.36812	0.73652
Protein Powders (inc. concentrate)	0.01200	0.24775	0.01395	0.28796	0.14968	0.29962	0.17397	0.34825	0.31135	0.62324	0.36188	0.72440
Oil	0.03083	0.24775	0.03584	0.28796	0.21583	0.43175	0.25086	0.50182	0.46250	0.92517	0.53757	1.07533
TOTAL	**0.06627**	**0.74324**	**0.07703**	**0.86387**	**0.51214**	**1.02475**	**0.59527**	**1.19107**	**1.09056**	**2.18208**	**1.26757**	**2.53624**

[1]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD).

[2]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 42 Daily Intake of THC Based on Body Weight, Males Age 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]	
	Male 2 years[2] Mean BW = 14.2 kg		Male 2 years[2] Mean BW = 14.2 kg		Male 2 years[2] Mean BW = 14.2 kg	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.1202	0.2405	0.7646	1.5292	1.6494	3.2989
Protein Powders (inc. concentrate)	0.0775	0.1549	0.8317	1.6635	1.7408	3.4820
Oil	0.1129	0.2258	0.7902	1.5804	1.6933	3.3866
TOTAL	**0.3106**	**0.6212**	**2.3865**	**4.7732**	**5.0835**	**10.1675**

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016

[2]Highly conservative - assumes a person would consume all sources of hemp per day and assumes a child would consume same foods as an adult.

Table 43 Daily Intake of THC Based on Body Weight, Females Age 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]	
	Female 2 years[2] Mean BW = 13.3 kg		Female 2 years[2] Mean BW = 13.3 kg		Female 2 years[2] Mean BW = 13.3 kg	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.1124	0.2249	0.7105	1.4212	1.5334	3.0672
Protein Powders (inc. concentrate)	0.0691	0.1381	0.7588	1.5169	1.5868	3.1720
Oil	0.1148	0.2296	0.8037	1.6074	1.7222	3.4444
TOTAL	**0.2963**	**0.5926**	**2.2730**	**4.5455**	**4.8423**	**9.6836**

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016

[2]Highly conservative - assumes a person would consume all sources of hemp per day and assumes a child would consume same foods as an adult.

Table 44 Daily Intake of THC Based on Body Weight, Males Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]	
	Male 6 years[2] Mean BW = 23.9 kg		Male 6 years[2] Mean BW = 23.9 kg		Male 6 years[2] Mean BW = 23.9 kg	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.0751	0.1502	0.4695	0.9393	1.0142	2.0287
Protein Powders (inc. concentrate)	0.0432	0.0864	0.4860	0.9724	1.0152	2.0311
Oil	0.0845	0.1691	0.5917	1.1836	1.2680	2.5362
TOTAL	**0.2028**	**0.4056**	**1.5473**	**3.0952**	**3.2974**	**6.5960**

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016

[2]Highly conservative - assumes a person would consume all sources of hemp per day and assumes a child would consume same foods as an adult.

Table 45 Daily Intake of THC Based on Body Weight, Females Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

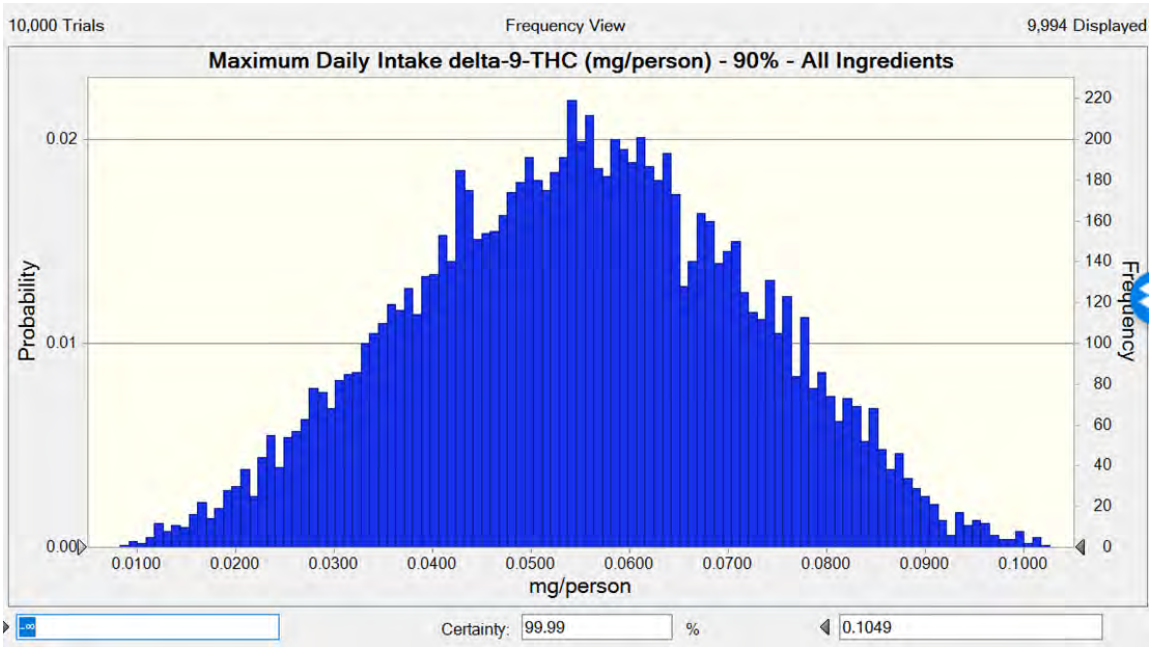
Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]	
	Female 6 years[2] Mean BW = 23.8 kg		Female 6 years[2] Mean BW = 23.8 kg		Female 6 years[2] Mean BW = 23.8 kg	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.0744	0.1488	0.4730	0.9461	1.0205	2.0410
Protein Powders (inc. concentrate)	0.0410	0.0819	0.5035	1.0071	1.0481	2.0961
Oil	0.0908	0.1815	0.6353	1.2706	1.3613	2.7227
TOTAL	**0.2062**	**0.4123**	**1.6119**	**3.2238**	**3.4299**	**6.8598**

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016

[2]Highly conservative - assumes a person would consume all sources of hemp per day and assumes a child would consume same foods as an adult.

Figure 1 Manufacturing Flow Chart

Figure 2 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – All Individuals Age 2 Years and Older

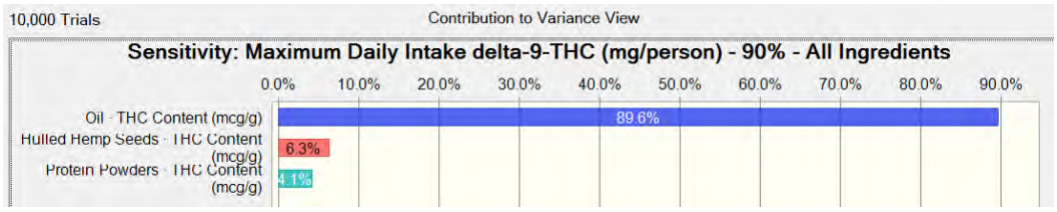


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.1049 mg/person/day.

Figure 3 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile - All Individuals Age 2 Years and Older

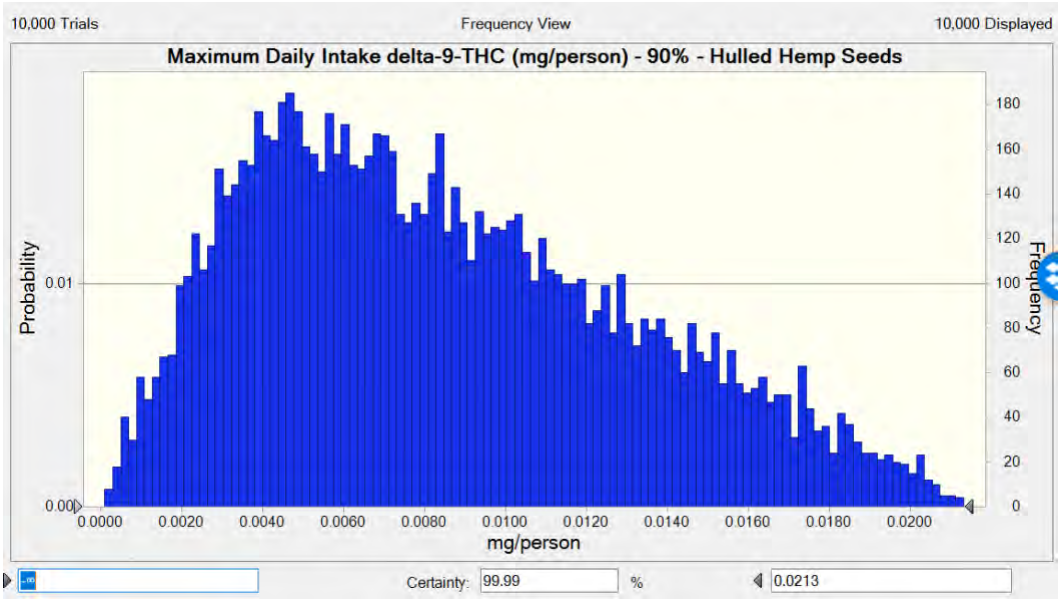
Statistic	Forecast values
Trials	10,000
Base Case	0.0490
Mean	0.0550
Median	0.0552
Mode	---
Standard Deviation	0.0170
Variance	0.0003
Skewness	-0.0190
Kurtosis	2.55
Coeff. of Variation	0.3093
Minimum	0.0063
Maximum	0.1061
Mean Std. Error	0.0002

Percentile	Forecast values
0%	0.0063
10%	0.0323
20%	0.0400
30%	0.0456
40%	0.0507
50%	0.0552
60%	0.0597
70%	0.0642
80%	0.0701
90%	0.0775
100%	0.1061



Variability in THC within Hemp Oil makes up 89.6% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 6.3% and Protein Powders make up 4.1%

Figure 4 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – All Individuals Age 2 Years and Older



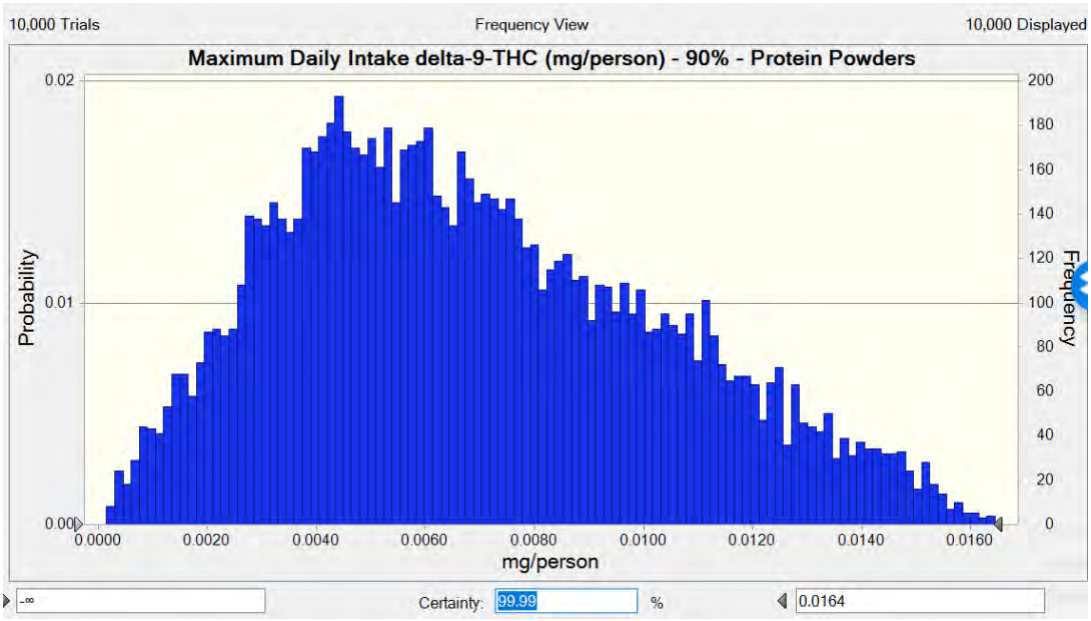
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0213 mg/person/day.

Figure 5 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile - All Individuals Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0041
Mean	0.0085
Median	0.0078
Mode	---
Standard Deviation	0.0047
Variance	0.0000
Skewness	0.4952
Kurtosis	2.42
Coeff. of Variation	0.5508
Minimum	0.0001
Maximum	0.0213
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0029
20%	0.0042
30%	0.0053
40%	0.0065
50%	0.0078
60%	0.0092
70%	0.0108
80%	0.0128
90%	0.0154
100%	0.0213

Figure 6 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – All Individuals Age 2 Years and Older



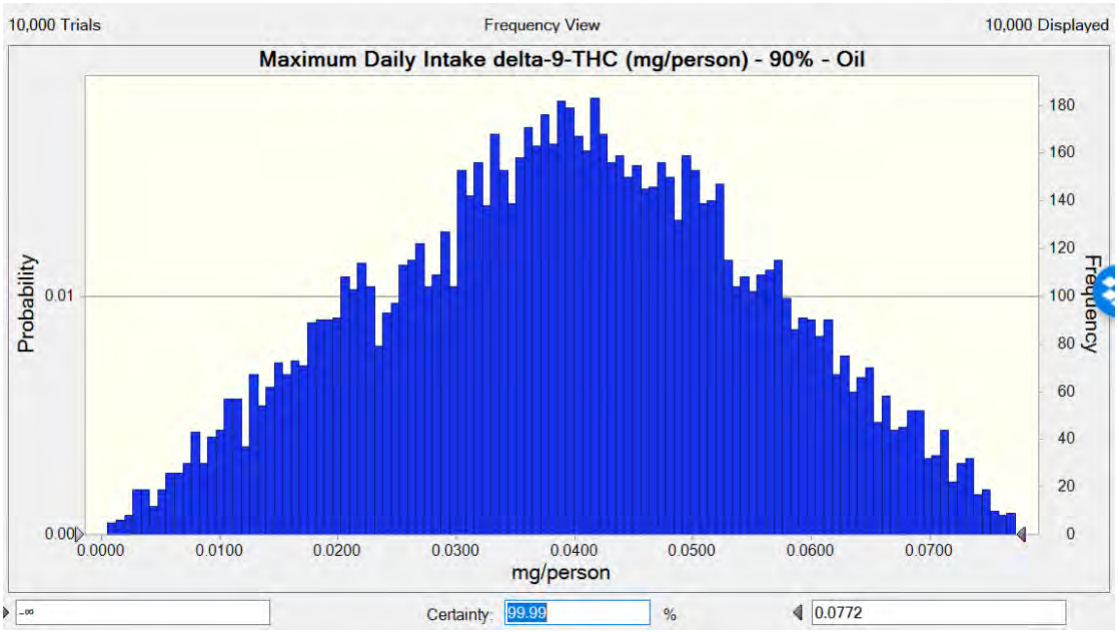
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0164 mg/person/day.

Figure 7 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile - All Individuals Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0043
Mean	0.0069
Median	0.0064
Mode	---
Standard Deviation	0.0035
Variance	0.0000
Skewness	0.4205
Kurtosis	2.44
Coeff. of Variation	0.5019
Minimum	0.0001
Maximum	0.0164
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0027
20%	0.0038
30%	0.0046
40%	0.0055
50%	0.0064
60%	0.0074
70%	0.0086
80%	0.0101
90%	0.0119
100%	0.0164

Figure 8 Monte Carlo Model – Hemp Oil - THC Exposure at 90th Percentile – All Individuals Age 2 Years and Older



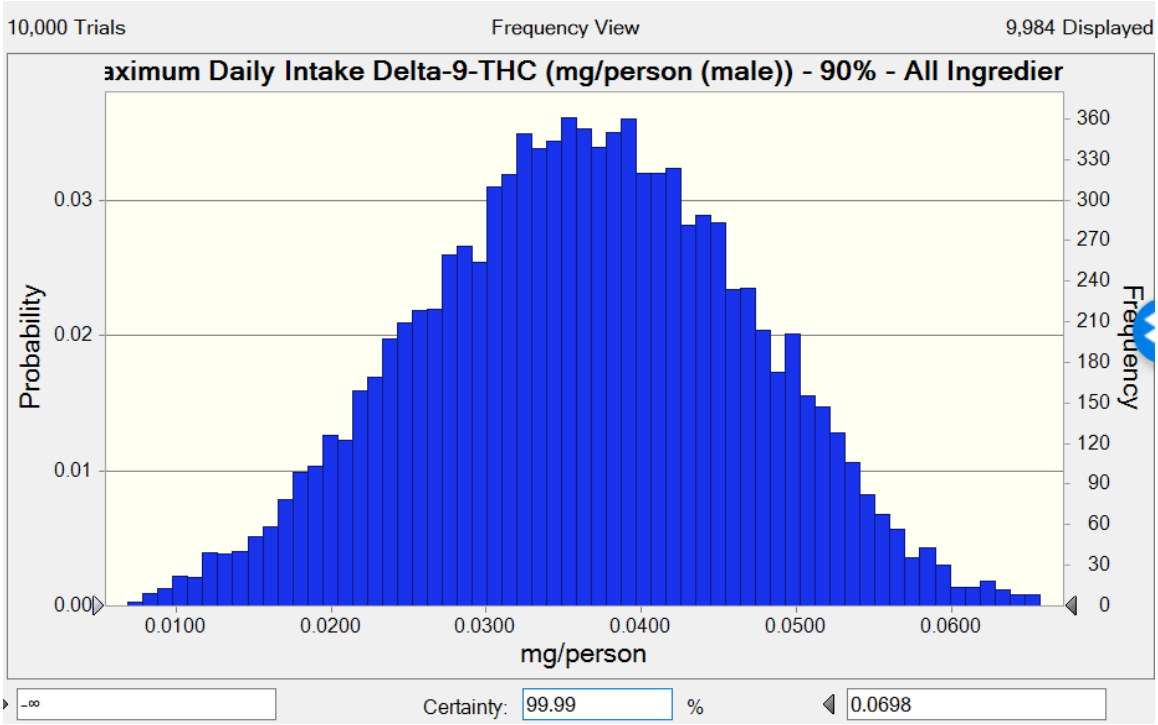
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0772 mg/person/day.

Figure 9 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile - All Individuals Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0407
Mean	0.0396
Median	0.0398
Mode	---
Standard Deviation	0.0160
Variance	0.0003
Skewness	-0.0429
Kurtosis	2.39
Coeff. of Variation	0.4029
Minimum	0.0005
Maximum	0.0772
Mean Std. Error	0.0002

Percentile	Forecast values
0%	0.0005
10%	0.0178
20%	0.0251
30%	0.0310
40%	0.0357
50%	0.0398
60%	0.0440
70%	0.0488
80%	0.0538
90%	0.0609
100%	0.0772

Figure 10 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years

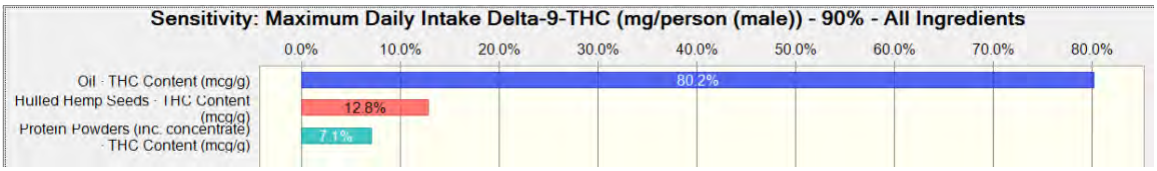


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.0698 mg/person/day.

Figure 11 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile – Males Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0310
Mean	0.0363
Median	0.0364
Mode	---
Standard Deviation	0.0105
Variance	0.0001
Skewness	-0.0238
Kurtosis	2.68
Coeff. of Variation	0.2891
Minimum	0.0048
Maximum	0.0724
Mean Std. Error	0.0001

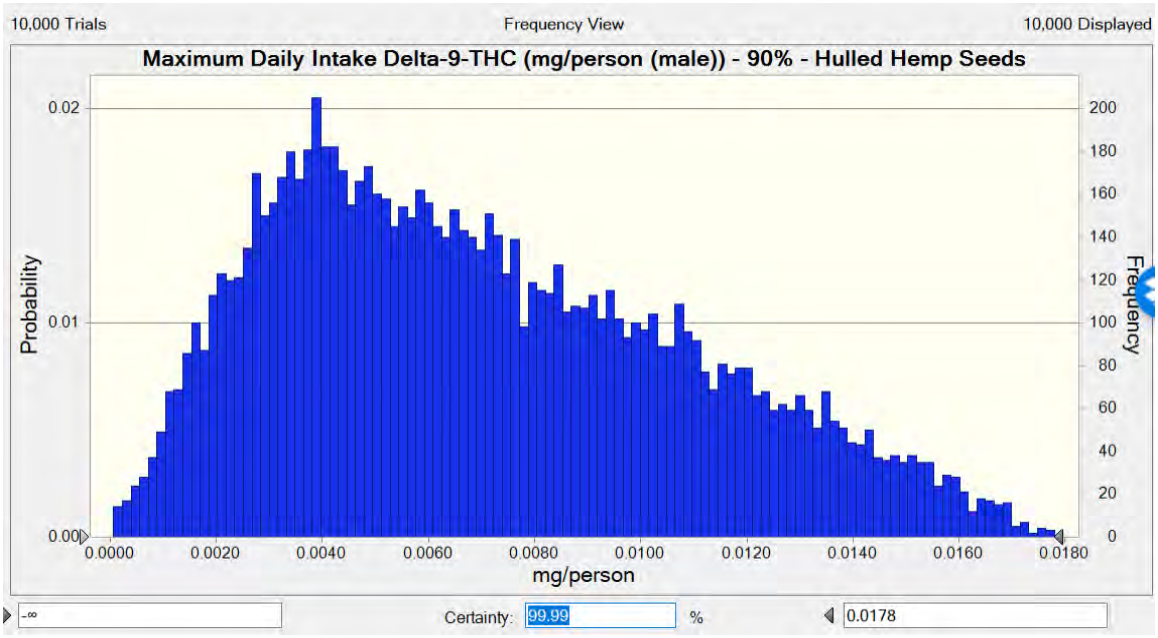
Percentile	Forecast values
0%	0.0048
10%	0.0225
20%	0.0272
30%	0.0307
40%	0.0336
50%	0.0364
60%	0.0392
70%	0.0421
80%	0.0454
90%	0.0499
100%	0.0724



Variability in THC within Hemp Oil makes up 80.2% of the variability in our Maximum Daily

Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 12.8% and Protein Powders make up 7.1%

Figure 12 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years



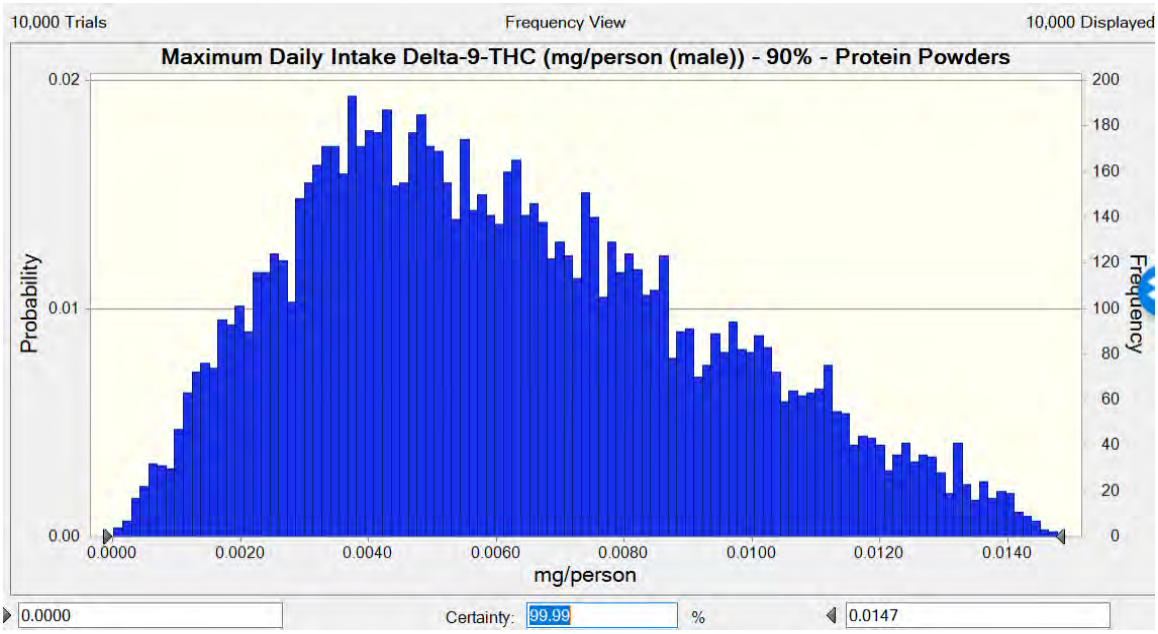
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0178 mg/person/day.

Figure 13 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile – Males Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0034
Mean	0.0070
Median	0.0064
Mode	---
Standard Deviation	0.0039
Variance	0.0000
Skewness	0.4921
Kurtosis	2.40
Coeff. of Variation	0.5487
Minimum	0.0001
Maximum	0.0178
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0024
20%	0.0035
30%	0.0044
40%	0.0054
50%	0.0064
60%	0.0076
70%	0.0090
80%	0.0107
90%	0.0128
100%	0.0178

Figure 14 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years



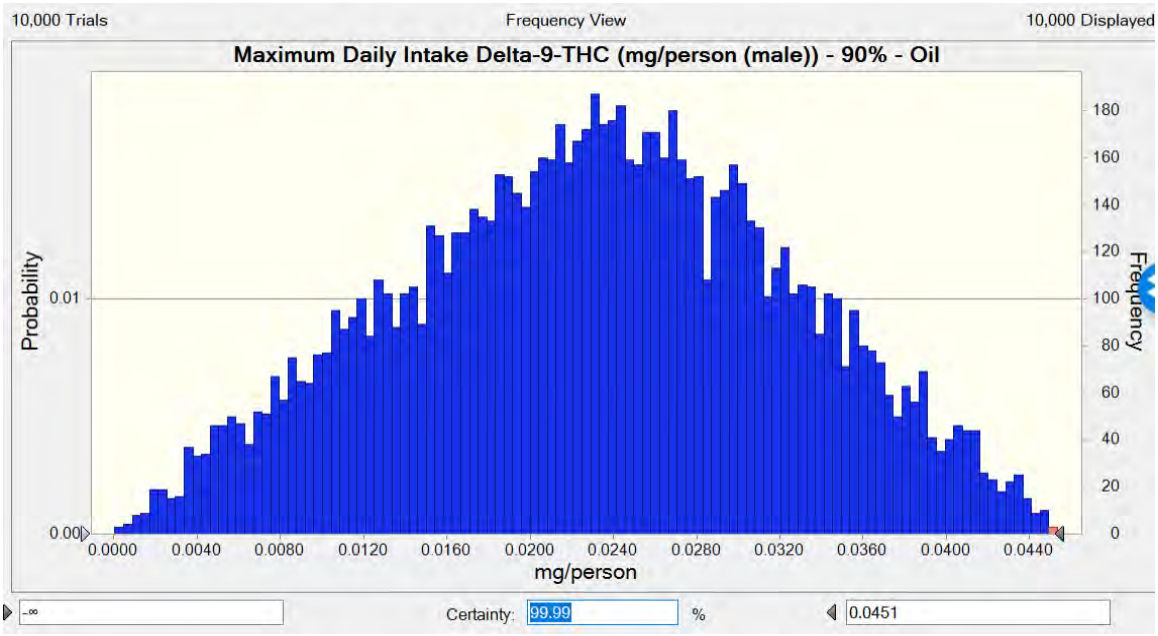
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0147 mg/person/day.

Figure 15 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile – Males Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0038
Mean	0.0062
Median	0.0058
Mode	---
Standard Deviation	0.0031
Variance	0.0000
Skewness	0.4352
Kurtosis	2.46
Coeff. of Variation	0.5051
Minimum	0.0000
Maximum	0.0148
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0000
10%	0.0024
20%	0.0033
30%	0.0041
40%	0.0049
50%	0.0058
60%	0.0067
70%	0.0077
80%	0.0090
90%	0.0107
100%	0.0148

Figure 16 Monte Carlo Model – Hemp Oil Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years



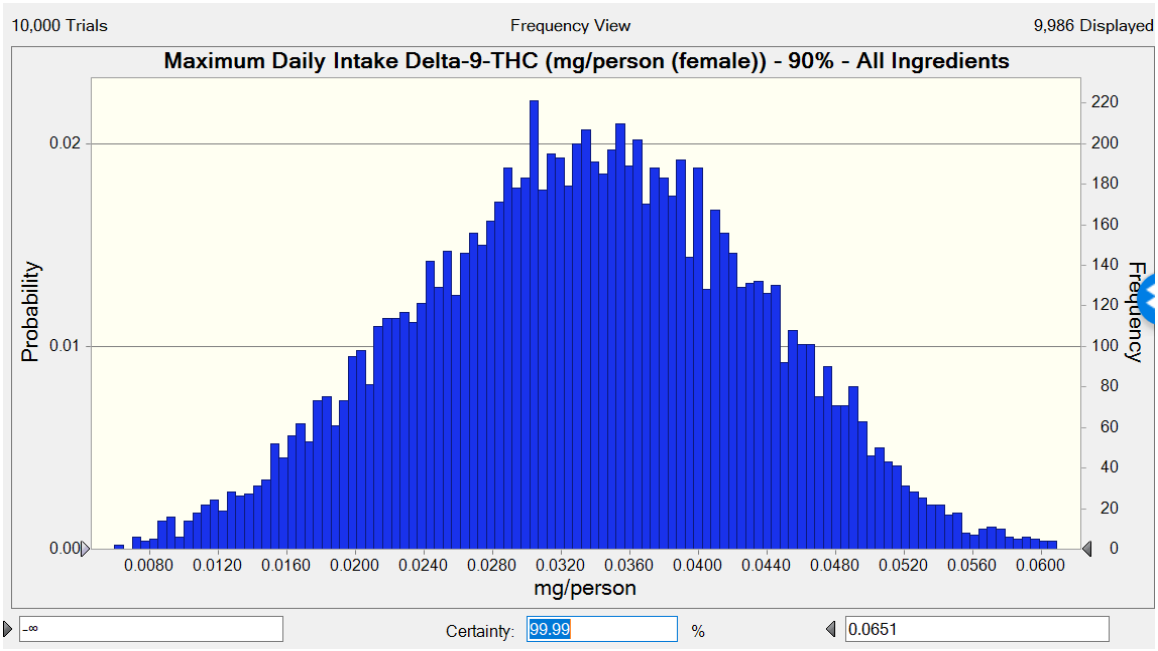
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0451 mg/person/day.

Figure 17 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile – Males Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0238
Mean	0.0231
Median	0.0233
Mode	---
Standard Deviation	0.0093
Variance	0.0001
Skewness	-0.0540
Kurtosis	2.41
Coeff. of Variation	0.4026
Minimum	0.0001
Maximum	0.0453
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0001
10%	0.0104
20%	0.0147
30%	0.0181
40%	0.0208
50%	0.0233
60%	0.0257
70%	0.0283
80%	0.0313
90%	0.0355
100%	0.0453

Figure 18 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – Females Age 2 to 5 Years

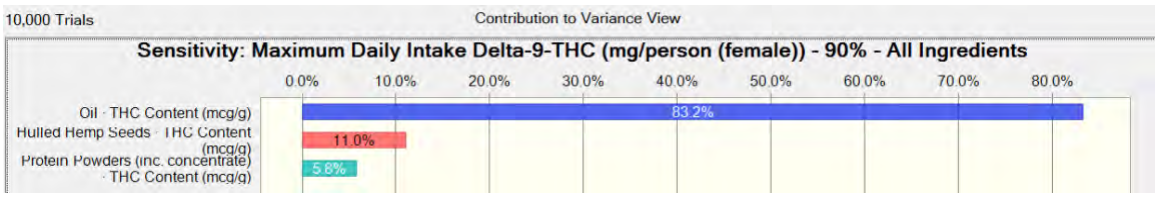


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.0651 mg/person/day.

Figure 19 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile – Females Age 2 to 5 Years

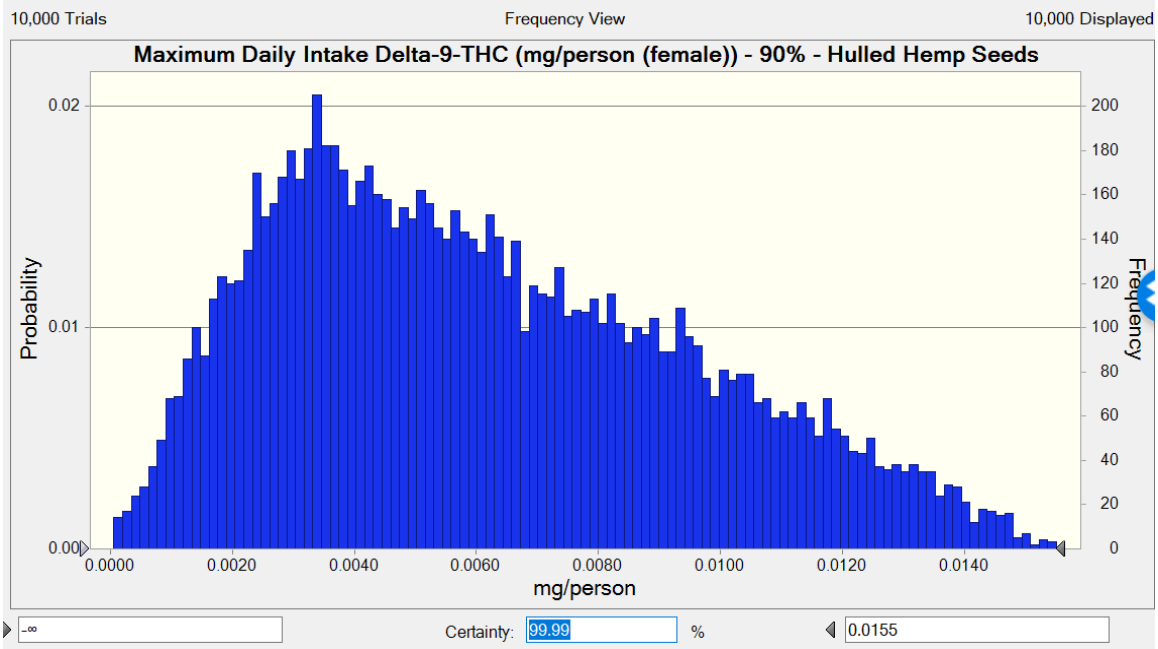
Statistic	Forecast values
Trials	10,000
Base Case	0.0289
Mean	0.0334
Median	0.0335
Mode	---
Standard Deviation	0.0098
Variance	0.0001
Skewness	-0.0324
Kurtosis	2.65
Coeff. of Variation	0.2935
Minimum	0.0042
Maximum	0.0663
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0042
10%	0.0203
20%	0.0248
30%	0.0282
40%	0.0309
50%	0.0335
60%	0.0361
70%	0.0388
80%	0.0420
90%	0.0462
100%	0.0663



Variability in THC within Hemp Oil makes up 83.2% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 11% and Protein Powders make up 5.8%

Figure 20 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – Females Age 2 to 5 Years



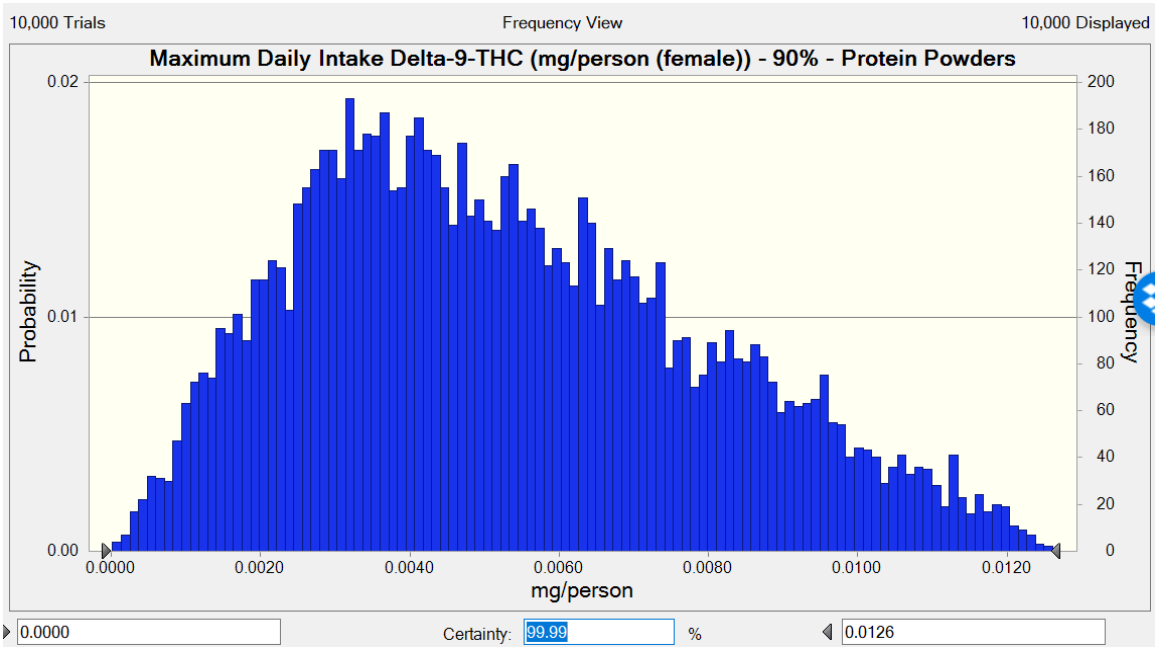
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0155 mg/person/day.

Figure 21 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile – Females Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0030
Mean	0.0061
Median	0.0056
Mode	---
Standard Deviation	0.0034
Variance	0.0000
Skewness	0.4921
Kurtosis	2.40
Coeff. of Variation	0.5487
Minimum	0.0001
Maximum	0.0155
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0021
20%	0.0030
30%	0.0038
40%	0.0047
50%	0.0056
60%	0.0066
70%	0.0079
80%	0.0093
90%	0.0111
100%	0.0155

Figure 22 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – Females Age 2 to 5 Years



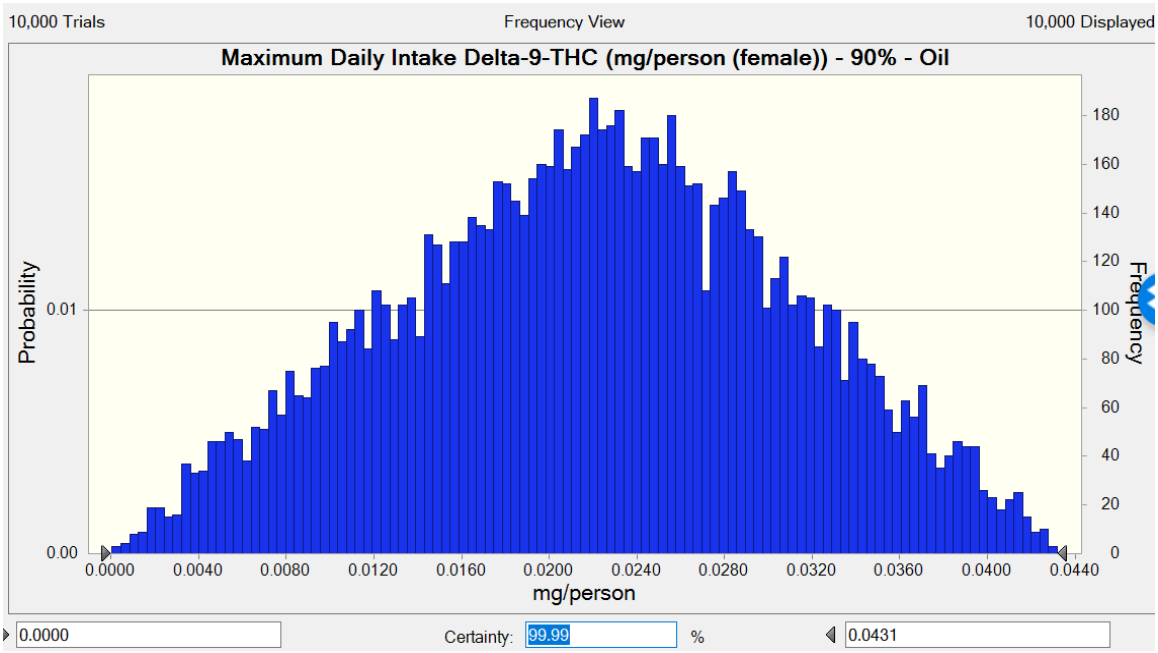
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0126 mg/person/day**.**

Figure 23 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile – Females Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0033
Mean	0.0053
Median	0.0049
Mode	---
Standard Deviation	0.0027
Variance	0.0000
Skewness	0.4352
Kurtosis	2.46
Coeff. of Variation	0.5051
Minimum	0.0000
Maximum	0.0126
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0000
10%	0.0020
20%	0.0029
30%	0.0035
40%	0.0042
50%	0.0049
60%	0.0057
70%	0.0066
80%	0.0077
90%	0.0091
100%	0.0126

Figure 24 Monte Carlo Model – Hemp Oil Consumption - THC Exposure at 90th Percentile – Females Age 2 to 5 Years



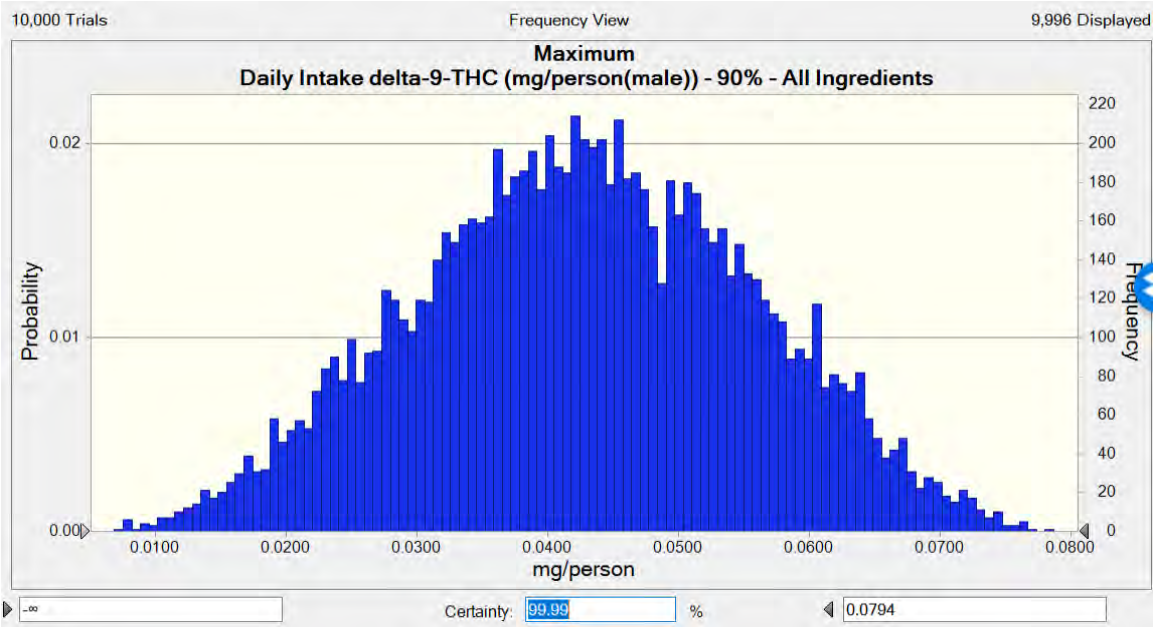
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0431 mg/person/day.

Figure 25 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile – Females Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0227
Mean	0.0220
Median	0.0222
Mode	---
Standard Deviation	0.0089
Variance	0.0001
Skewness	-0.0540
Kurtosis	2.41
Coeff. of Variation	0.4026
Minimum	0.0000
Maximum	0.0432
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0000
10%	0.0099
20%	0.0140
30%	0.0172
40%	0.0198
50%	0.0222
60%	0.0245
70%	0.0269
80%	0.0298
90%	0.0338
100%	0.0432

Figure 26 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years

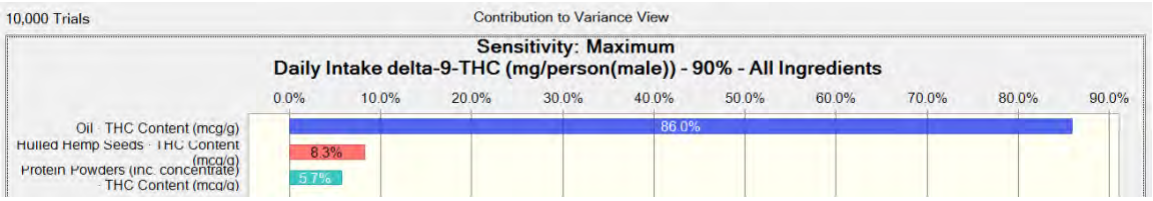


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.0794 mg/person/day.

Figure 27 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile – Males Age 6 to 11 Years

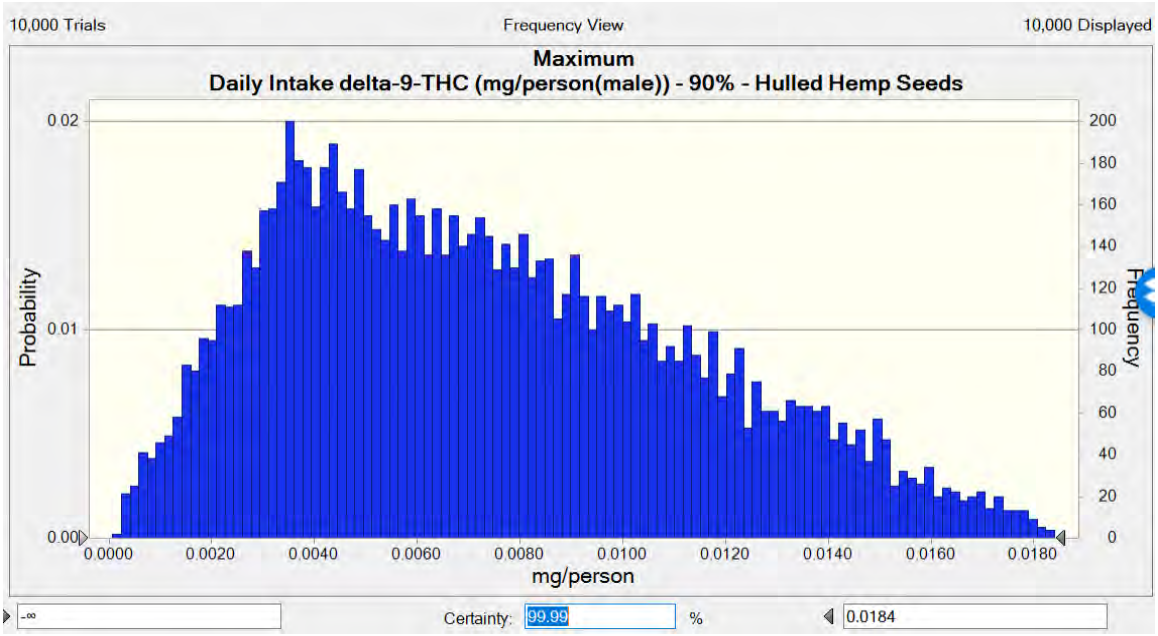
Statistic	Forecast values
Trials	10,000
Base Case	0.0373
Mean	0.0428
Median	0.0427
Mode	---
Standard Deviation	0.0128
Variance	0.0002
Skewness	-0.0172
Kurtosis	2.54
Coeff. of Variation	0.2998
Minimum	0.0048
Maximum	0.0804
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0048
10%	0.0256
20%	0.0316
30%	0.0358
40%	0.0393
50%	0.0427
60%	0.0461
70%	0.0500
80%	0.0542
90%	0.0599
100%	0.0804



Variability in THC within Hemp Oil makes up 86% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 8.3% and Protein Powders make up 5.7%.

Figure 28 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years



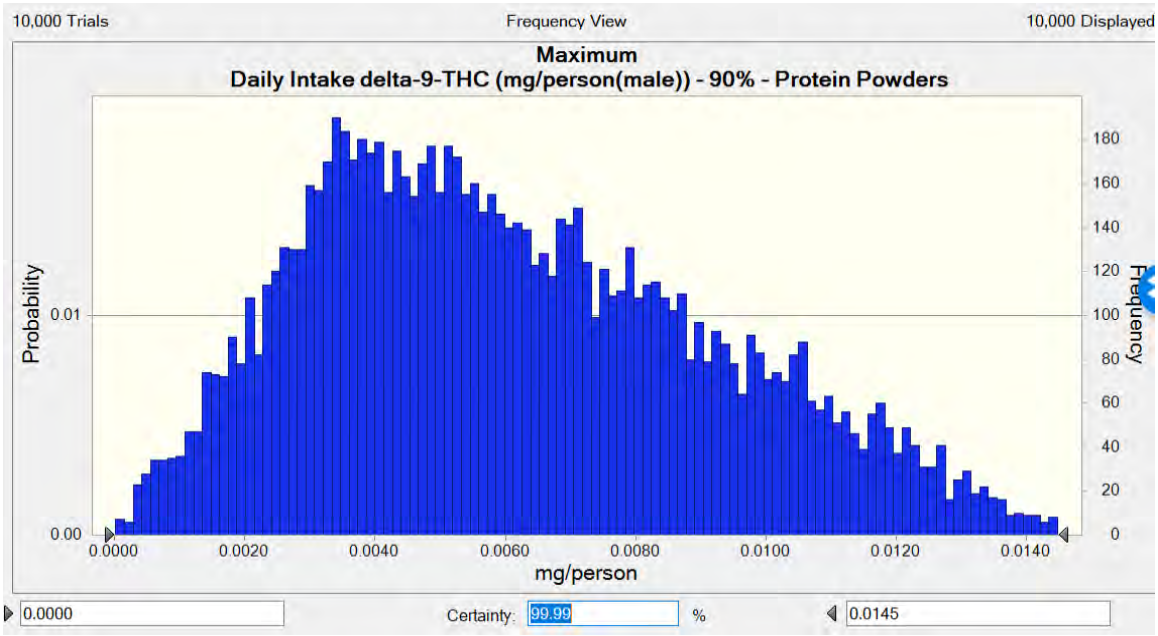
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0184 mg/person/day.

Figure 29 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0035
Mean	0.0074
Median	0.0069
Mode	---
Standard Deviation	0.0040
Variance	0.0000
Skewness	0.4788
Kurtosis	2.44
Coeff. of Variation	0.5382
Minimum	0.0001
Maximum	0.0184
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0026
20%	0.0037
30%	0.0046
40%	0.0057
50%	0.0069
60%	0.0080
70%	0.0094
80%	0.0110
90%	0.0132
100%	0.0184

Figure 30 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years



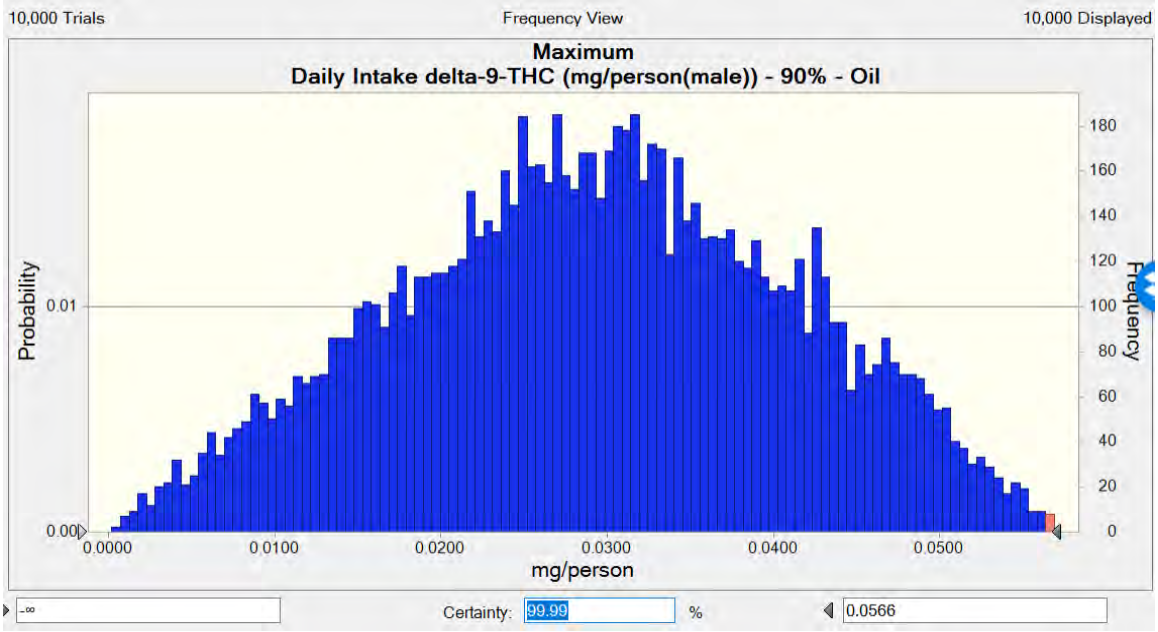
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0145 mg/person/day.

Figure 31 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0038
Mean	0.0061
Median	0.0057
Mode	---
Standard Deviation	0.0031
Variance	0.0000
Skewness	0.4176
Kurtosis	2.42
Coeff. of Variation	0.5008
Minimum	0.0000
Maximum	0.0145
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0000
10%	0.0024
20%	0.0033
30%	0.0041
40%	0.0049
50%	0.0057
60%	0.0067
70%	0.0077
80%	0.0089
90%	0.0106
100%	0.0145

Figure 32 Monte Carlo Model – Hemp Oil Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years



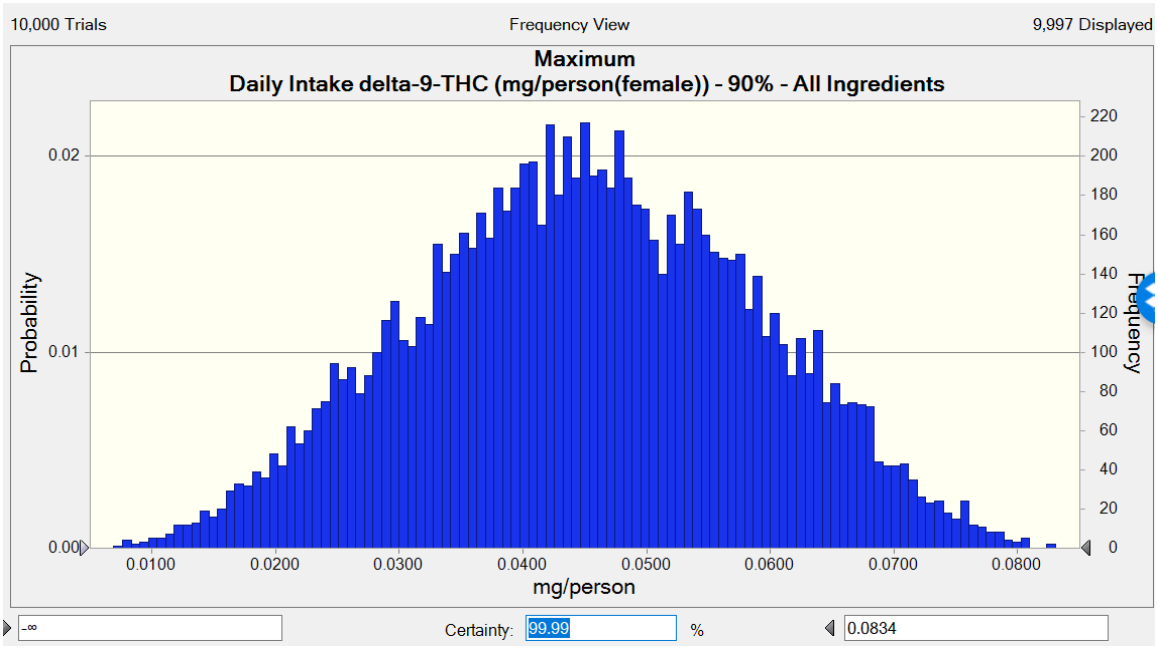
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0566 mg/person/day.

Figure 33 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0300
Mean	0.0293
Median	0.0294
Mode	---
Standard Deviation	0.0118
Variance	0.0001
Skewness	-0.0449
Kurtosis	2.38
Coeff. of Variation	0.4024
Minimum	0.0002
Maximum	0.0569
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0002
10%	0.0134
20%	0.0187
30%	0.0229
40%	0.0262
50%	0.0294
60%	0.0324
70%	0.0359
80%	0.0400
90%	0.0452
100%	0.0569

Figure 34 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – Females Age 6 to 11 Years

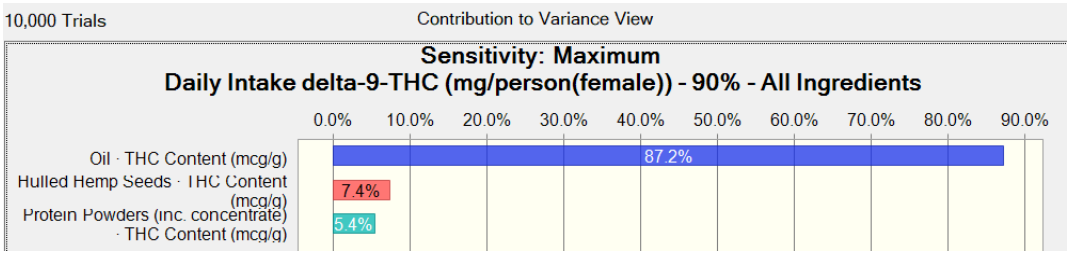


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.0834 mg/person/day.

Figure 35 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile – Females Age 6 to 11 Years

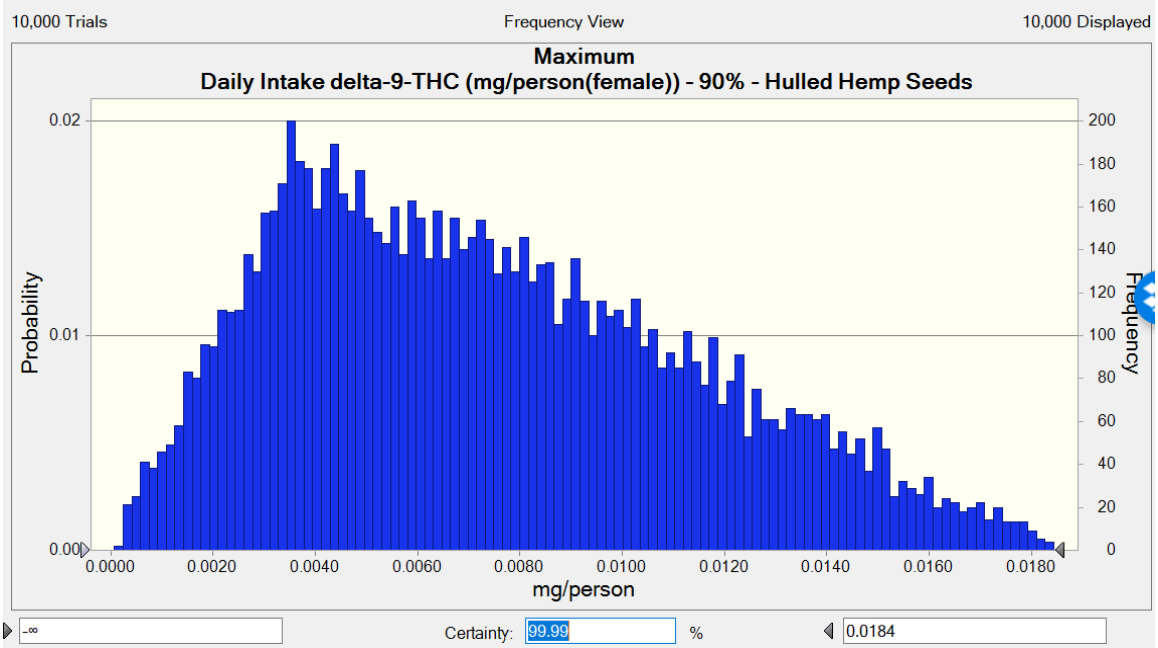
Statistic	Forecast values
Trials	10,000
Base Case	0.0395
Mean	0.0450
Median	0.0449
Mode	---
Standard Deviation	0.0136
Variance	0.0002
Skewness	-0.0203
Kurtosis	2.52
Coeff. of Variation	0.3023
Minimum	0.0050
Maximum	0.0843
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0050
10%	0.0267
20%	0.0331
30%	0.0376
40%	0.0414
50%	0.0449
60%	0.0485
70%	0.0527
80%	0.0571
90%	0.0631
100%	0.0843



Variability in THC within Hemp Oil makes up 87.2% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 7.4% and Protein Powders make up 5.4%

Figure 36 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – Females Age 6 to 11 Years



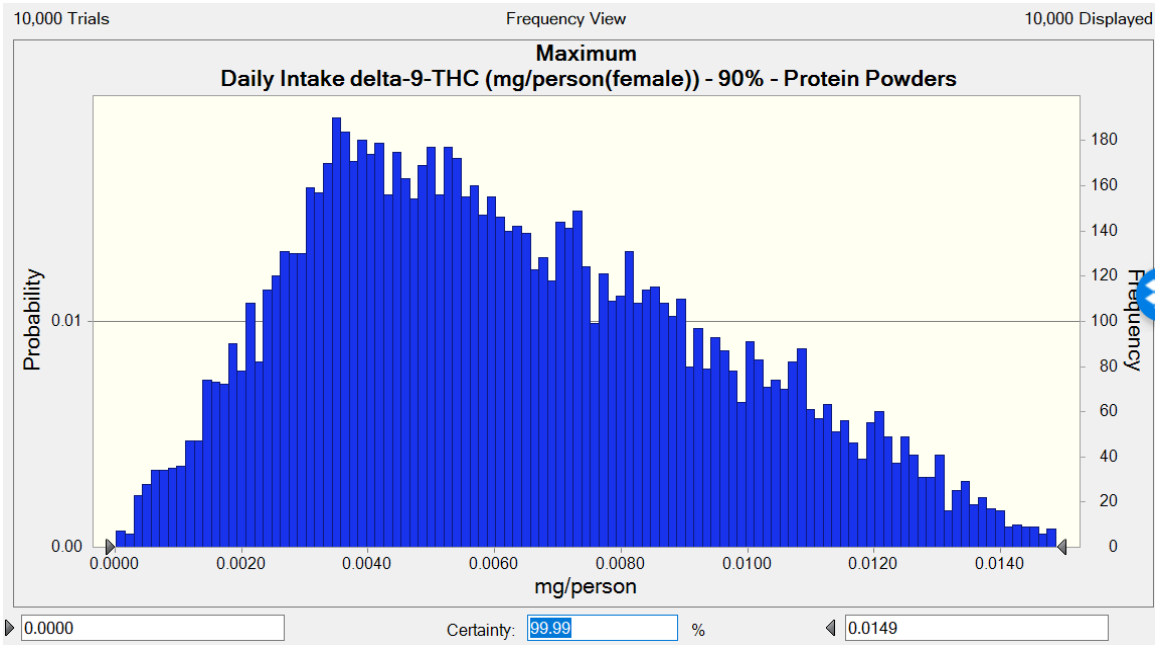
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0184 mg/person/day.

Figure 37 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0035
Mean	0.0074
Median	0.0069
Mode	---
Standard Deviation	0.0040
Variance	0.0000
Skewness	0.4788
Kurtosis	2.44
Coeff. of Variation	0.5382
Minimum	0.0001
Maximum	0.0184
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0027
20%	0.0037
30%	0.0046
40%	0.0057
50%	0.0069
60%	0.0081
70%	0.0094
80%	0.0110
90%	0.0133
100%	0.0184

Figure 38 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – Females Age 6 to 11 Years



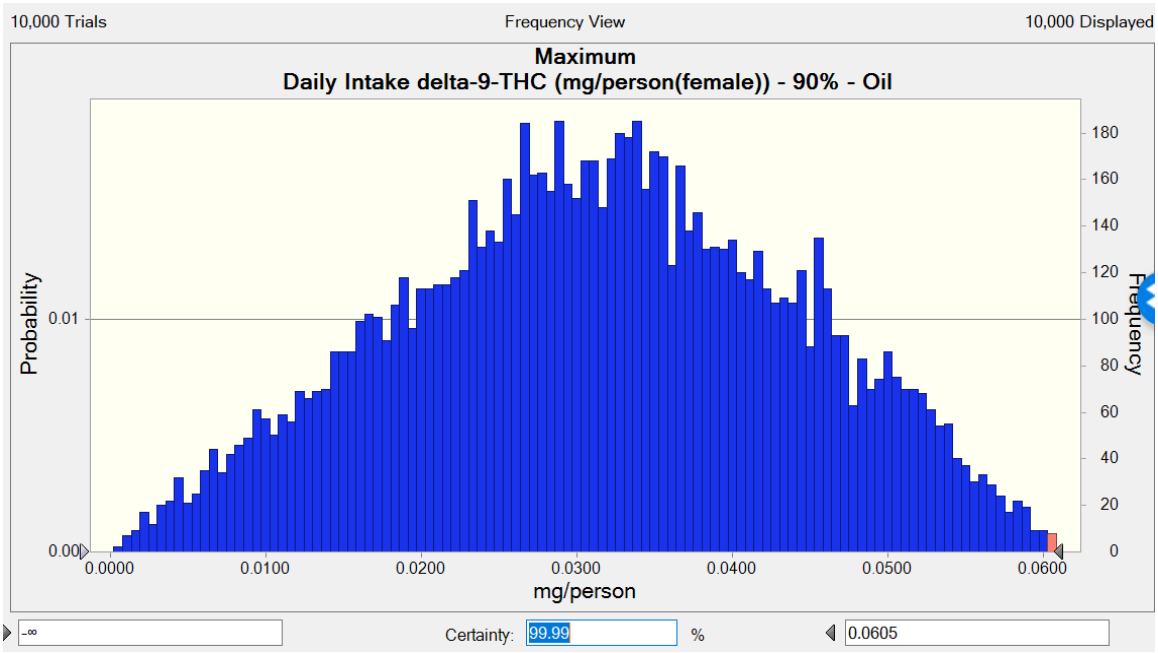
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0149 mg/person/day.

Figure 39 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0039
Mean	0.0063
Median	0.0059
Mode	---
Standard Deviation	0.0032
Variance	0.0000
Skewness	0.4176
Kurtosis	2.42
Coeff. of Variation	0.5008
Minimum	0.0000
Maximum	0.0149
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0000
10%	0.0025
20%	0.0034
30%	0.0042
40%	0.0050
50%	0.0059
60%	0.0068
70%	0.0079
80%	0.0092
90%	0.0109
100%	0.0149

Figure 40 Monte Carlo Model – Hemp Oil Consumption - THC Exposure at 90th Percentile – Females Age 6 to 11 Years



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0605 mg/person/day.

Figure 41 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0321
Mean	0.0313
Median	0.0314
Mode	---
Standard Deviation	0.0126
Variance	0.0002
Skewness	-0.0449
Kurtosis	2.38
Coeff. of Variation	0.4024
Minimum	0.0002
Maximum	0.0608
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0002
10%	0.0143
20%	0.0200
30%	0.0244
40%	0.0280
50%	0.0314
60%	0.0346
70%	0.0383
80%	0.0428
90%	0.0483
100%	0.0608

List of References

List of References

Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci 1995, 56 (23–24):2097–2102.

Abrams RM, Cook CE, Davis KH, Niederreither K, Jaeger MJ, Szeto HH. Plasma delta-9-tetrahydrocannabinol in pregnant sheep and fetus after inhalation of smoke from a marijuana cigarette. Alcohol Drug Res 1985–1986, 6:361–369.

Ahmad GR, Ahmad N. Passive consumption of marijuana through milk: a low level chronic exposure to delta-9-tetrahydrocannabinol(THC). J Toxicol Clin Toxicol 1990;28(2):255–260.

Alaniz VI, Liss J, Metz TD, Stickrath E. Cannabinoid hyperemesis syndrome: a cause of refractory nausea and vomiting in pregnancy. Obstet Gynecol. 2015;125(6):1484-6.

Alt A, Reinhardt G. Positive cannabis results in urine and blood samples after consumption of hemp food products. J Anal Toxicol 1998;22:80–1.

Aluko, R.E. Chapter 7. Hemp Seed (*Cannabis sativa* L.) Proteins: Composition, Structure, Enzymatic Modification, and Functional or Bioactive Properties. In: Sustainable Protein Sources. New York: Elsevier, 2017. Pg 125. Print.

American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk Pediatrics 2001;108(3):776-789.

Angelova V., Ivanova R., Delibaltova V. Ivanov K. Bio-Accumulation and Distribution of Heavy Metals in Fibre Crops (Flax, Cottone, Hemp). Industrial Crops and Products. 2004;19:197-205.

Armentia A, Herrero M, Martin-Armentia B et al. Molecular diagnosis in cannabis allergy. J Allergy Clin Immunol Pract 2014;2:351–352.

Asero R, Mistrello G, Roncarolo D et al. A case of allergy to beer showing cross-reactivity between lipid transfer proteins. Ann Allergy Asthma Immunol 2001;87:65–67.

Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. Neurotoxicol Teratol 1990;12(2):161–168.

Astwood JD, Leach JN, Fuchs RL. Stability of food allergens to digestion in vitro. Nat Biotechnol. 1996;14(10):1269–73.

Bailey JR, Cunny HC, Paule MG, Slikker W Jr. Fetal disposition of delta 9-tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey. Toxicol Appl Pharmacol 1987, 90:315–321.

Baňas B, Beitzke, Carus B, Kerstin Iffland, Kruse D, Sarmento L, Sfrija D. Position paper of the European Industrial Hemp Association (EIHA) on: Reasonable guidance values for THC (Tetrahydrocannabinol) in food products. Nova-Institute, Hürth
(available online at www.eiha.org). 2017.

Bannon GA. What makes a food protein an allergen? Curr Allergy Asthma Rep. 2004;4(1):43–6.

Battista N, Sergi M, Montesano C, Napoletano S, Compagnone D, Maccarrone M. Analytical approaches for the determination of phytocannabinoids and endocannabinoids in human matrices. Drug Testing Analysis 2014;6:7–16.

Beal, J. E. et al. (1997): Efficacy and Safety of Dronabinol for Acquired Immunodeficiency Syndrome-Associated Anorexia, J. of Pain and Symptom Management Vol.14, No. 1, July 1997: 7-14.

Bergeria CL, Heil SH, Surveying Lactation Professionals Regarding Marijuana Use and Breastfeeding. Breastfeeding Medicine 2015;10(7):377-380.

Berlin CM, Briggs GG. Drugs and chemicals in human milk. Seminars in Fetal & Neonatal Medicine. 2005;10:149e159.

Beezhold DH, Hickey VL, Kostyal DA et al. Lipid transfer protein from Hevea brasiliensis (Hev b 12), a cross-reactive latex protein. Ann Allergy Asthma Immunol 2013;90:439–445.

Bortolin, Kristen & Ben-Shoshan, Moshe & Kalicinsky, Chrystyna & Lavine, Elana & Lejtenyi, Christine & Warrington, Richard & Pitt, Tracy. Case Series of 5 Patients with Anaphylaxis to Hemp Seed Ingestion. Journal of Allergy and Clinical Immunology. 137. AB239. 10.1016/j.jaci.2015.12.969.

Bosy TZ, Cole KA. Consumption and quantitation of delta-9-tetrahydrocannabinol in commercially available hemp seed oil products. J Anal Toxicol 2000;24:562–6.

Brenneisen R, Egli A, Elsohly MA, et al. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int J Clin Pharmacol Ther 1996; 34 (10): 446-52.

Brooks E, Gundersen DC, Flynn E, Brooks-Russell A, Bull S. The clinical implications of legalizing marijuana: Are physician and non-physician providers prepared? Addictive Behaviors 72 (2017) 1–7.

Burns L, Mattick RP, Cooke M. The use of record linkage to examine illicit drug use in pregnancy. Addiction 2006;101(6):873–882.

Callaway JC, Weeks RA, Raymon LP, Walls HC, Hearn WL. A positive THC urinalysis from hemp (Cannabis) seed oil. J Anal Toxicol 1997;21:319–20.

Carnes J, De Larramendi CH, Ferrer A et al. Recently introduced foods as new allergenic sources: sensitisation to Goji berries (Lycium barbarum). Food Chem 2013;137:130–135

Chesher, G.B. et al. (1990): The effects of orally administered delta-9-trahydrocannabinol in man on mood and performance measures: a dose-response study, Pharmacol. Biochem. Behav. 1990 Apr; 35(4):861-4.

Cone EJ, Johnson RF, Paul BD, Mell LD, Mitchell J. Marijuana-laced brownies: Behavioral effects, physiologic effects, and urinalysis in humans following ingestion. J Anal Toxicol 1988;12:169-175.

Costantino A, Schwartz RH, Kaplan P. Hemp oil ingestion causes positive urine tests for 9-tetrahydrocanabinol carboxylic acid. J Anal Toxicol 1997;21:482–5.

Crew S. Hemp Oil Canada Inc., Ste. Agathe, MB, Canada. Development of hemp food products and processes. Report prepared for the Agricultural Research and Development Initiative (ARDI), Winnipeg, MB, Canada, 2000).

Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. Neurotoxicol Teratol 2011;33(1):129–136.

Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy.
Arch Dis Child 1986, 61 (5):502–505.

De Larramendi CH, Carnes J, Garcia-Abujeta JL et al Sensitization and allergy to Cannabis sativa leaves in a population of tomato (Lycopersicon esculentum)-sensitized patients. Int Arch Allergy Immunol 2008:146:195–202

DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P et al. Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. Biol Psychiatry 2011;70(8):763–769.

Dotters-Katz SK, Smid MC, Manuck TA, Metz TD. Risk of neonatal and childhood morbidity among preterm infants exposed to marijuana. J Matern Fetal Neonatal Med. 2017;30(24):2933-2939.

Ebo D, Swerts S, Sabato V et al. New food allergies in a european non-mediterranean region: is Cannabis sativa to blame? Int Arch Allergy Immunol 2013;161:220–228.

Ebo DG, Stevens WJ. IgE-mediated food allergy—extensive review of the literature. Acta Clin Belg 2001;56:234–247

Egger M, Hauser M, Mari A et al. The role of lipid transfer proteins in allergic diseases. Curr Allergy Asthma Rep 2010;10:326–335

El Marroun H, Hudziak JJ, Tiemeier H, Creemers H, Steegers EA, Jaddoe VW et al. Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. Drug Alcohol Depend 2011;118(2-3):470–474.

El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatry 2009;48(12):1173–1181.

ElSohly MA, deWit H, Wachtel SR, Feng S, Murphy TP. Delta-9- tetrahydrocannabivarin as a marker for the ingestion of marijuana versus Marinol: results of a clinical study. J Anal Toxicol 2001; 25:565–71.

Escuder-Vieco D, Garcia-Algar Ó, Joya X, Marchei E, Pichini S, Pacifici R, Pallás-Alonso CR. Breast Milk and Hair Testing to Detect Illegal Drugs, Nicotine, and Caffeine in Donors to a Human Milk Bank. Journal of Human Lactation 2016;32(3):542-5.

Escuder-Vieco D, Garcia-Algar Ó, Pichini S, Pacifici R, García-Lara NR, Pallás-Alonso CR. Validation of a screening questionnaire for a human milk bank to determine the presence of illegal drugs, nicotine, and caffeine. J Pediatr. 2014;164(4):811-4.

Faber, Margriet & Van Gasse, Athina & Sabato, Vito & Hagendorens, Margo & Bridts, Chris & Clerck, Luc & Ebo, Didier. Marihuana Allergy: Beyond the Joint. Journal of investigational allergology & clinical immunology. 2015a;25. 70-2.

Faber MA, Sabato V, Bridts CH et al. Clinical relevance of the lipid transfer protein Hev b 12 of Hevea brasiliensis. J Allergy Clin Immunol 2015b;pii: S0091-6749(14)03747-6.

Foeller ME, Lyell DJ. Marijuana Use in Pregnancy: Concerns in an Evolving Era. J Midwifery Womens Health 2017;62:363–367.

Food Standards Australia New Zealand Supporting Document 1 Updated Estimates of Dietary Exposure to 9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) from Foods Containing Low THC Hemp Seed (at Approval) – Proposal P1042 Low THC Hemp Seeds as Food Executive Summary

Fortner N, Fogerson R, Lindman D, Iversen T, Armbruster D. Marijuana-positive urine test results from consumption of hemp seeds in food products. J Anal Toxicol 1997;21:476–81.

Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 1999;21(5):513–525.

Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2003;25(4):427–436.

Frytak S, Moertel CG, Rubin J. Metabolic studies of delta-9-tetrahydrocannabinol in cancer patients. Cancer Treat Rep 1984; 68 (12): 1427-31.

Fu T, Abbott UR, Hatzos C. Digestibility of food allergens and nonallergenic proteins in simulated gastric fluid and simulated intestinal fluid-a comparative study. J Agric Food Chem. 2002;50(24):7154–60.

Garry A, Rigourd V, Amirouche A, Fauroux V, Aubry S, Serreau R. Cannabis and Breastfeeding. J Toxicol. 2009:596149.

Gaylor DW. The use of Haber's law in standard setting and risk assessment. Toxicology 2000, 149 (1):17–19.

Gamboa P, Sanchez-Monge R, Sanz ML et al. Sensitization to Cannabis sativa caused by a novel allergenic lipid transfer protein, Can s 3. J Allergy Clin Immunol 2007;120:1459–1460

Gleason KA, Birnbaum SG, Shukla A, Ghose S. Susceptibility of the adolescent brain to cannabinoids: long-term hippocampal effects and relevance to schizophrenia. Transl Psychiatry 2012;2:e199.

Godding V, Bonnier C, Fiasse L, Michel M, Longueville E, Lebecque P et al. Does in utero exposure to heavy maternal smoking induce nicotine withdrawal symptoms in neonates? Pediatr Res 2004;55(4):645–651.

Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. Neurotoxicol Teratol 2000;22(3):325–336.

Goldschmidt L, Richardson GA, Willford JA, Severtson SG, Day NL. School achievement in 14-year-old youths prenatally exposed to marijuana. Neurotoxicol Teratol 2012; 34(1):161–167.

Goodwin RS, Gustafson RA, Barnes A, Nebro W, Moolchan ET, Huestis MA. Delta-9-tetrahydrocannabinol, 11-hydroxy-delta-9-tetrahydrocannabinol and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol in human plasma following controlled oral administration of cannabinoids. *Therapeutic Drug Monitoring,* 2006 Aug; 28(4): 545-551.

Gustafson RA, Levine B, Stout PR, Klette KL, George MP, Moolchan ET and Huestis MA. Urinary cannabinoid detection times following controlled oral administration of delta-9-tetrahydrocannabinol to humans. *Clinical Chemistry*, 2003 Jul; 49(7):1114-1124.

Gustafson RA, Kim I, Stout PR, Klette KL, George MP, Moolchan ET, Levine B and Huestis MA. Urinary pharmacokinetics of 11-nor-9-carboxy-delta-9-tetrahydrocannabinol after controlled oral delta-9-tetrahydrocannabinol administration. Journal Analytical Toxicology, 2004 Apr; 28(3):160-167.

Hale TW. Medications and Mother's Milk, 15th ed. Plano, TX: Hale Publishing, 2012.

Health Canada Industrial Hemp Regulations (http://laws-lois.justice.gc.ca/PDF/SOR-98-156.pdf); Health Canada Industrial Hemp Technical Manual (https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/hc-ps/alt_formats/hecs-sesc/pdf/pubs/precurs/hemp-indus-chanvre/tech-man/hemp-tech-manual-eng.pdf).

Herman RA, Woolhiser MM, Ladics GS, et al. Stability of a set of allergens and non-allergens in simulated gastric fluid. Int J Food Sci Nutr. 2007;58(2):125–41.

Hollister LE, Gillespie HK, Ohlsson A, et al. Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? J Clin Pharmacol 1981; 21 (8-9 Suppl.):171S-7S.

Hotham N, Hotham E. Drugs in breastfeeding. Australian Prescriber. 2015;38;5:156-160.

House JD, Neufeld J, Leson G. Evaluating the quality of protein from hemp seed (Cannabis sativa L.) products through the use of the protein digestibility-corrected amino acid score method. Journal of Agriculture and Food Chemistry. 2010;58(22):11801-11807.

Howlett AC. Pharmacology of cannabinoid receptors. Annu Rev Pharmacol Toxicol 1995, 35:607–
634.

Huestis MA, Abulseoud O, Sempio C, Andersson M, Newmeyer MN, (unpublished urine data following smoked, vaporized and oral administration of 50.6 mg THC).

Huestis MA, Mazzoni I, Rabin O. Cannabis in Sport: Anti-Doping Perspective. Sports Med. 2011 Nov; 1; 41(11): 949-966.

Hutchings DE, Martin BR, Gamagaris Z, Miller N, Fico T. Plasma concentrations of delta-9-tetrahydrocannabinol in dams and fetuses following acute or multiple prenatal dosing in rats. Life Sci 1989, 44 (11):697–701.

Indorato F, Liberto A, Ledda C, Romano G, Barbera N. The therapeutic use of cannabinoids: Forensic aspects. Forensic Science International 2016;265:200–203.

Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC: National Academy Press; 2005.

Interpretation of listing of "tetrahydrocannabinol" in Schedule I [Interpretive Rule]. Federal Register 2001;195:51530–44.

Jansson LM, Bunik M, Bogen DL. Lactation and the Marijuana-Using Mother Breastfeeding Medicine 2015;10(6):1.

Jarlenski M, Zank J, Tarr J, Chang JC. Public health messages about perinatal marijuana use in an evolving policy context. Substance Abuse. 2017;38(1):48-54.

Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, Abdel-Latif ME, Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology 2014;34:417–424.

Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, Abdel-Latif ME, Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology 2014;34(6):417-24.

Jegou S, Douliez JP, Molle D et al. Purification and structural characterization of LTP1 polypeptides from beer. J Agric Food Chem 2000;48:5023–5029.

Jenkins JA, Breiteneder H, Mills EN. Evolutionary distance from human homologs reflects allergenicity of animal food proteins. J Allergy Clin Immunol. 2007;120(6):1399–405.

Jones PJH, Papamandjaris AA. Lipids: cellular metabolism. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition. 10th ed. Washington, DC: Wiley-Blackwell; 2012:132-48.

Kacew S Adverse effects of drugs and chemicals in breast milk on the nursing infant. J Clin Pharmacol. 1993;33(3):213-21.

Khare M, Taylor AH, Konje JC, Bell SC. Delta9-tetrahydrocannabinol inhibits cytotrophoblast cell proliferation & modulates gene transcription. Mol Hum Reprod 2006;12(5):321–333.

Klonoff-Cohen H, Lam-Kruglick P. Maternal and paternal recreational drug use and sudden infant death syndrome. Arch Pediatr Adolesc Med 2001;155(7):765–770.

Larramendi CH, Lopez-Matas MA, Ferrer A et al. Prevalence of sensitization to Cannabis sativa. Lipid-transfer and thaumatin-like proteins are relevant allergens. Int Arch Allergy Immunol 2013;162:115–122

Law B, Mason PA, Moffat AC, et al. Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin. J Pharm Pharmacol 1984; 36 (5):289-94.

Lehmann T, Sager F, Brenneisen R. Excretion of cannabinoids in urine after ingestion of cannabis seed oil. J Anal Toxicol 1997;21:373–5.

Leson G, Pless P, Grotenhermen F, Kalant H, ElSohly MA. Evaluating the impact of hemp food consumption on workplace drug tests. J Anal Toxicol 2001;25:691–8.

Liston J. Breastfeeding and the use of recreational drugs – alcohol, caffeine, nicotine and marijuana. Breastfeeding Review 1998;6(2):27-30.

Manitoba Agriculture, Province of Manitoba. Agriculture Mycotoxins. https://www.gov.mb.ca/agriculture/food-safety/at-the-food-processor/print,mycotoxins.html. Accessed 12/18/2017.

Marchei E, Escuder D, Pallas CR, Garcia-Algar O, Gómez A, Friguls B, Pellegrini M, Pichini S. Simultaneous analysis of frequently used licit and illicit psychoactive drugs in breast milk by liquid chromatography tandem mass spectrometry. J Pharm Biomed Anal. 2011;55(2):309-16.

Martin BR, Dewey WL, Harris LS, Beckner JS. 3H-delta 9-tetrahydrocannabinol distribution in pregnant dogs and their fetuses. Res Commun Chem Pathol Pharmacol 1977, 17:457–470.

Masilamani, M, Commins, S, ShrefflerW. Determinants of Food Allergy. Immunol. Allergy Clin. North Am.2012;32(1)11-33.

Matsuda LA. Molecular aspects of cannabinoid receptors. Crit Rev Neurobiol 1997, 11:143–166.

Metz TD, Allshouse AA, Hogue CJ, Goldenberg RL, Dudley DJ, Varner MW, Conway DL, Saade GR, Silver RM. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. Am J Obstet Gynecol. 2017;217(4):478.e1-478.

Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. Am J Obstet Gynecol. 2015;213(6):761-78.

Mills E, Madsen C, Shewry P. Food allergens of plant origin–their molecular and evolutionary relationships. Trends in Food Science and Technology. 2003;(14):145–56.

Mölleken and H. Husmann. Cannabinoids in seed extracts of Cannabis sativa cultivars. J. Int. Hemp Assoc. 4: 1, 76–79 (1997).

Mourh J, Rowe H. Marijuana and Breastfeeding: Applicability of the Current Literature to Clinical Practice. Breastfeed Med. Epub 2017 Sep 5.

Murphy LL, Munoz RM, Adrian BA, Villanu´ a MA. Function of cannabinoid receptors in the neuroendocrine regulation of hormone secretion. Neurobiol Dis 1998;5(6PtB):432–446.

Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M et al. Metabolic effects of chronic cannabis smoking. Diabetes Care 2013;36(8):2415–2422.

Nayak AP, Green BJ, Sussman G et al. Characterization of Cannabis sativa allergens. Ann Allergy Asthma Immunol 2013;111:32–37

Neugebauer R, Kline J, Stein Z, Shrout P, Warburton D, Susser M. Association of stressful life events with chromosomally normal spontaneous abortion. Am J Epidemiol 1996;143:588–596.

Newton ER & Hale TW. Drugs in Breast Milk. Clinical Obstetrics and Gynecology. 2015;58(4):868–884.

Odani S and Odani SIolation and Primary Structure of a Methionine and Cysteoine Richseed protein of *Cannabis sativa*. Bioscience, Biotechnology and Biochemistry. 1998. 62:650-654.

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther. 1980 Sep;28(3):409-16.

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma levels of delta 9-tetrahydrocannabinol after intravenous, oral, and smoke administration. NIDA Res Monogr. 1981 Feb;34:250-6.

Ohlsson A, Agurell S, Lindgren JE, Gillespie HK, Hollister LE. Pharmacokinetic studies of delta-1-tetrahydrocannabinol in man. In Pharmacokinetics and pharmacodynamics of psychoactive drugs. Barnett G and Chiang CN (Eds). 1985 Mosby Yearbook, Inc. Volume 4 Pages 75-92.

Perez-Reyes M, Lipton MA, Timmons MC, Wall ME, Brine DR, Davis KH. Pharmacology of orally administered delta-9-tetrahydrocannabinol. Clinical Pharmacology Therapeutics 1973;14:48-55.

Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. N Engl J Med 1982; 307(13): 819–820.

Pertwee R. Cannabinoid Receptors. Academic Press, London, United Kingdom, 1995.

Petro, D. J., Ellenberger, C. Jr. (1981): Treatment of human spasticity with delta 9-tetrahydrocannabinol, J Clin Pharmacol. 1981 Aug-Sep;21(8-9 Suppl): 413S-416S.

Quadri MI, Nasserullah . Hb Bart's levels in cord blood in Hb H disease: follow-up of cases with "probable" Hb H disease. Ann Saudi Med 2001;21:357–358

Reece-Stremtan S, Marinelli KA. The Academy of Breastfeeding Medicine. ABM Clinical Protocol #21: Guidelines for Breastfeeding and Substance Use or Substance Use Disorder, Revised 2015. Breastfeeding Medicine 2015:10(3);135-141.

Reisner SH, Eisenberg NH, Stahl B, Hauser GJ. Maternal medications and breast-feeding. Dev Pharmacol Ther. 1983;6(5):285-304.

Research, Health Protection Branch, Health Canada. Industrial hemp technical manual: TPP-BDS-004 – Basic method for determination of THC in hempseed oil, 1992.

Rihs HP, Rueff F, Lundberg M et al. Relevance of the recombinant lipid transfer protein of Hevea brasiliensis: IgE-binding reactivity in fruit-allergic adults. Ann Allergy Asthma Immunol 2006;97:643–649.

Sadler BM, Wall ME, Perez-Reyes M. The pharmacokinetics of delta-9 -tetrahydrocannabinol after simultaneous intravenous and oral administration. In: Agurell S, Dewey WL, Willette RE, eds. The cannabinoids: chemical, pharmacologic, and therapeutic aspects. New York: Academic Press, 1984:227–38.

Sharma P, Murthy P, Bharath MMS. Chemistry, Metabolism, and Toxicology of Cannabis: Clinical Implications. Iran J Psychiatry 2012;7(4):149-156.

Sipsma A, Divney AA, Magriples U, Hansen N, Gordon D, Kershaw T. Breastfeeding Intentions Among Pregnant Adolescents and Young Adults and Their Partners. Breastfeeding Medicine 2013;8(4):374-380.
adolescents: Initiation, duration, and exclusivity. J Adolesc Health. 2013;53(3):394–400.

Sipsma A, Magriples U, Divney AA, Gordon D, Gabzdyl,E, Kershaw T. Breastfeeding behavior among
Warner TD, Roussos-Ross D, Behnke M. It's Not Your Mother's Marijuana: Effects on Maternal-Fetal Health and the Developing Child. Clin Perinatol. 2014;41(4):877–894.

Smithers LG, Lynch JW, Yang S, Dahhou M, Kramer MS. Impact of neonatal growth on IQ and behavior at early school age. Pediatrics 2013;132(1):e53–e60.

Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. Neurotoxicol Teratol 2006;28(2):286–295.

Sporkert F, Pragst F, Ploner CJ, Tschirch A, Stadelmann AM. Pharmacokinetic investigations and delta-9-tetrahydrocannabinol and its metabolites after single administration of 10 mg Marinol in attendance of a psychiatric study. The Annual Meeting of The International Association of Forensic Toxicologists, Prague, Czech Republic. 2001.

Stadtmauer G, Beyer K, Bardina L et al. Anaphylaxis to ingestion of hempseed (Cannabis sativa). J Allergy Clin Immunol 2003;112:216–217

Strasser, F. et al. (2006): Comparison of Orally Administered Cannabis Extract and Delta-9-Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome: A Multicenter, Phase III, Randomized, Double-Blind,
Placebo-Controlled Clinical Trial From the Cannabis-In-Cachexia-Study-Group, J. Clin. Oncology, 24 (21), July 20 (2006): 3394-3400.

Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray.
Eur J Clin Pharmacol. 2013 May;69(5):1135-47. doi: 10.1007/s00228-012-1441-0. Epub 2012 Nov 22.

Struempler RE, Nelson G, Urry FM. A positive cannabinoids workplace drug test following the ingestion of commercially available hemp seed oil. J Anal Toxicol 1997;21:283–5.

The American College of Obstetricians and Gynecologists. Committee on Obstetric Practice. Marijuana Use During Pregnancy and Lactation. 2015;126(1):234-8.

Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. AIDS Res Hum Retroviruses 1997; 13 (4):305-15.

Van Gasse AL et al. L'allergie au cannabis: bien plus qu'un voyage stupéfiant. Rev Fr Allergol. doi:10.1016/j.reval.2014.01.022

Van Loon LC (1999) Occurrence and properties of plant pathogenesis-related proteins. In: Datta SK, Muthukrishnan S (eds) Pathogenesis-related proteins in plants. CRC Press LLC, Boca Raton, pp 1–19

Wall ME, Perez-Reyes M. The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man. J Clin Pharmacol 1981; 21 (8-9 Suppl.): 178S-89S.

Wall ME, Sadler BM, Brine D, et al. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol, in men and women. Clin Pharmacol Ther 1983; 34 (3): 352-63.

Wang GS Pediatric Concerns Due to Expanded Cannabis Use: Unintended Consequences of Legalization. J. Med. Toxicol. 2017 Mar;13(1):99-105.

Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. In utero marijuana exposure associated with abnormal amygdala dopamine D2 gene expression in the human fetus. Biol Psychiatry 2004;56(12):909–915.

Warner TD, Roussos-Ross D, Behnke. It's not your mother's marijuana: effects on maternal-fetal health and the developing child. Clin Perinatol. 2014;41(4):877-94.

Zajicek, J. P.et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial, Lancet 2003 Nov. 8; 362(9395): 1517-26.

Zajicek; J. P. et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow-up, J. Neurol. Neurosurg. Psychiatry 2005; 76: 1664-69.

Appendix
Expert Review and Resume

Appendix: Expert Review and Commentary on Literature and Expert Resume

Huestis & Smith Toxicology, LLC
683 Shore Road
Severna Park, MD 21146
Phone (410) 544-2456
huestis.smithtoxicologyllc@gmail.com

Professor Dr. Dr. (h.c.) Marilyn A. Huestis
President

Michael L. Smith, PhD, F-ABFT
Vice President

December 30, 2017

Virginia Savoie
Ryan Bracken
Fresh Hemp Foods
Manitoba, Canada

Huestis report on the general safety, potential for a positive urine cannabinoid test, and transfer of ∆9-tetrahydrocannabinol (THC) into human breast milk and infants during breastfeeding after oral THC ingestion

Dear Ms. Savoie and Mr. Bracken,
I conducted a thorough literature search for data related to ingestion of THC-containing foods and liquids, and also on the transfer of THC from the mother to the infant during breastfeeding. I addressed general safety data, possible positive urine cannabinoid test data, and infant THC-exposure from breastfeeding based on oral THC-exposure data from estimated combined daily ingestion of 4 Fresh Hemp Foods products, hulled hemp seed, hemp protein powder, hemp protein concentrate and hemp oil. The mean combined THC dose from all 4 Fresh Hemp Foods Products is estimated at 0.0968 mg/day, and the 90th percentile THC dose is estimated at 0.1938 mg/day.

Executive Summary

Ingestion of a mean daily amount of 0.0968 mg THC from intake of all 4 Fresh Hemp Foods products is too low to produce THC's psychoactive, cognitive and physiological effects. Even at the highly conservative 90th percentile THC dose of 0.1938 mg/day, no effects should be produced based on numerous controlled THC oral administration studies.

Based on 11-nor-9-carboxy-THC (THCCOOH) urine concentrations following controlled oral THC administration, it is highly unlikely that a positive urine cannabinoid test (≥15 µg/L) would be produced following ingestion of a mean total of 0.0968 mg THC from consumption of all four Fresh Hemp Foods hemp products. Based on the studies of Bosy and Cole 2000, Leson et al 2001, and Gustafson et al 2004. In the Bosy and Cole 2000 study, there were no positive urine specimens ≥15 µg/L following the 0.10, 0.17, 0.32, and 0.55 mg THC/d for 7 daily doses. The 0.54 mg and 1.8 mg THC/d doses produced a small number of positive urine specimens ≥15 µg/L. Leson et al 2001 administered four daily THC doses, 0.09, 0.19, 0.29, and 0.45 mg THC in hemp oil for 10 consecutive days each. No positive urine samples were obtained. An individual who ingested a daily THC dose of

0.6 mg produced the highest urine THCCOOH concentration of 5.2 µg/L, well below the 15 µg/L confirmation cutoff of federal drug testing programs. Gustafson et al 2003 determined urinary THCCOOH excretion by GC/MS analysis in 4381 urine specimens collected before, during, and after 5 oral daily 0.39, 0.47, 7.5, and 14.8 mg THC/day to 7 participants. All urine voids were collected over the 10-week study. At the two lowest doses that were 2-5 times higher than the mean or 90th percentile total THC dose if all 4 Fresh Hemp Foods hemp products were ingested, a mean of 2.7 urine samples per subject over 10 days were positive; maximum THC concentrations ranged from 5.4-38.2 µg/L by GC-MS. Therefore, it is highly unlikely that ingestion of all 4 hemp food products would produce a positive urine cannabinoid test.

Based on studies administering known quantities of oral THC and blood/plasma/serum concentrations, we can estimate the blood concentrations that would result from intake of 0.0968 (mean daily mg THC from 4 Fresh Hemp Foods, Ltd products) to 0.1938 (90th percentile daily mg THC from 4 Fresh Hemp Foods, Ltd. Products) mg oral THC. Stott et al 2013 administered two Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses (total 5.4 mg THC) to adults. There are no infant THC administration data. The mean plasma Cmax was <1.2 µg/L THC and <2 µg/L 11-OH-THC. The mean daily amount (0.0968 mg) and 90th percentile (0.1938) of THC exposure from ingesting all 4 Fresh Hemp Foods, Ltd. Products is 55- and 27-fold lower than this exposure, respectively. These data would estimate the plasma Cmax in the breastfeeding mother assuming a 0.0968 mg daily dose as <0.02 µg/L THC and <0.04 µg/L 11-OH-THC, and if the highly conservative 0.1938 mg THC dose is assumed, plasma Cmax in the mother of <0.04 µg/L THC and <0.07 µg/L 11-OH-THC.

In a single maternal plasma and breast milk pair, the THC plasma to breast milk ratio was 8.4. Based on this ratio and the mean-90th percentile maternal plasma THC concentrations, the maximum THC concentration in the breast milk would be between 0.17-0.34 µg/L. There are no data on 11-OH-THC breast milk/plasma ratios, but if one assumed a similar distribution for 11-OH-THC into breast milk, maximum 11-OH-THC concentrations in breast milk would be 0.34-0.59 µg/L.

The estimate of daily breast milk intake is 150 mL/kg/day. Our estimates of maximum THC concentration in breast milk and daily intake would suggest THC intake of 0.05 – 0.09 µg/kg/day THC. As 11-OH-THC is equipotent to THC, assuming the breast milk to plasma ratio is also 8.4, the total active cannabinoids exposure for the infant is estimated to be <0.08-0.14 µg/kg/day. Gustafson et al 2014 administered 0.39 and 0.47 mg THC per day for 5 days, resulting in non-detectable THC concentrations in human plasma. These doses are 2-4 times the dose a breastfeeding mother would consume with all 4 hemp products. This low-level exposure is not expected to produce adverse developmental outcomes in the infant whose mother consumes the maximum amount of all 4 Fresh Hemp Foods, Ltd. per day.

Furthermore, Stott et al 2013 also administered the 5.4 mg THC/day dose for 9 consecutive days and showed that THC and 11-OH-THC concentrations did not accumulate over time. This also demonstrates that daily use of the 4 Fresh Hemp Foods,

Ltd doses that are much lower than the 5.4 mg Stott dose should not accumulate. At birth, a 10 lb. (4.55 kg) infant would receive about 0.14-0.23 µg/day THC and 0.23-0.41 µg/day 11-OH-THC. The total active cannabinoid dose would be approximately 0.37-0.64 µg/day. The oral bioavailability of THC and 11-OH-THC is low, estimated to be 6-12% in adults; bioavailability could be different in the infant although first pass metabolism would still reduce active cannabinoid exposure. This low concentration of active cannabinoids should not produce adverse developmental effects.

General Safety Data following oral THC doses (blood/serum/plasma data)

Early reports on blood/plasma/serum THC concentrations after oral THC administration were primarily related to the abuse potential and detection of use after this route of administration. There are many more reports of blood/plasma/serum concentrations than urine concentrations. These data are useful for determining the bioavailability of the oral route of administration (especially when evaluating transfer of drugs to breast milk in breastfeeding women) and for comparison of oral doses to the Fresh Hemp Foods Ltd. daily oral doses. Later pharmacokinetic studies of oral THC administrations were focused more on the therapeutic uses of THC, for instance in AIDS wasting disease or other indication. There also are data from Sativex oromucosal studies of THC and cannabidiol (CBD) that are relevant but could have slightly higher bioavailability due to bypass of first metabolism for some portion of the administered dose. There were a number of studies evaluating whether or not hemp oil or hemp food products produce positive urine cannabinoid tests. Although many studies administered known quantities of THC in hemp products and quantified 11-nor-9-carboxy-THC (THCCOOH) in urine by GC-MS or LC-MS/MS, some did not quantify the administered THC dose, and therefore, are less informative.

Factors determining individual response to oral cannabis administration include the dose of total THC and THC precursor acid, the degree of conversion of THC precursor acid to THC prior to ingestion, the rate of absorption of THC from the gastrointestinal system that is influenced by the vehicle used, and degree of first-pass THC metabolism. Perez-Reyes et al. 1973 reported that the speed and degree of THC absorption is greatly influenced by the administration vehicle, and based on cumulative urinary excretion data over 72 h, THC absorption rate was affected by the nature of the vehicle, but not the total amount of absorption.

Perez Reyes et al, 1973 administered 35 mg oral THC (containing 50 µc tritium THC) in five different vehicles (ethanol, sesame oil, 5.5% sodium glycholate, 5.5% sodium glycholate and ethanol, and Tween-80) to 40 individuals after fasting, showing that absorption speed and bioavailability was highly dependent upon the vehicle utilized. Plasma, urine and feces were analyzed over 72 h. Total radioactivity of thin layer chromatography bands were used to quantify results. The vehicles providing the highest concentrations in plasma were from highest to lowest bioavailability 5.5% sodium glycholate, sesame oil, Tween-80, ethanol and combined glycholate and ethanol, with peak concentrations between 1-2 h. In addition, with the same vehicle and dose, a large 4.8 inter-individual variability in peak plasma THC concentrations was observed. The

radioactivity represented total THC and metabolite concentrations. The percentage of total radioactivity excreted in the urine in 24 h ranged from 14.1 to 17%, in 48 h from 3.1-4.7%, and in 72 h 1.2 to 2.2%. Total percent of the 35-mg dose excreted in the urine in the sodium glycholate vehicle was 21.9% or 7.7 mg in 72 h. A greater percentage (53.0±5.0% or 18.6 mg) of the 35-mg dose was excreted in the feces over 72 h in 3 subjects receiving the drug in sodium glycholate. For these same 3 subjects, urinary excretion with this vehicle was 22.4±4.3%. The urinary percentage was for all THC and metabolites in the urine, rather than only the THCCOOH metabolite, the current urine target. Separation of the different cannabinoid analytes in urine was not possible with thin layer chromatography. This was one of the only studies that determined THC percentages excreted in urine and feces, and established that about 22% of the dose is excreted in urine and more than 50% in feces.

Ohlsson et al 1980, 1981, Wall and Perez 1981, Hollister et al, 1981 and Ohlsson et al 1985 administered 20 mg oral THC in a chocolate cookie, 10 mg smoked THC, and 5 mg intravenous (IV) THC in 95% ethanol over 2 min to 11 males. Plasma was analyzed from 3 to 240 min (4 h) for smoked and IV doses and from 30 to 360 min (6 h) after oral dosing. THC was analyzed by GC-MS. Maximum plasma THC concentrations (Cmax) after the 20-mg oral dose were 4.4-11 µg/L with time of peak concentration (Tmax) between 60 and 300 min. Compared to the IV dose, bioavailability of the oral dose was 6±3% (4-12%), with slow and irregular absorption. This is one of the only studies administering THC by both the oral and IV routes enabling determination of oral THC bioavailability estimated to be 6-12% in most studies.

THC and Metabolites in Human Plasma Following Oral Administration of 20 mg THC by GC-MS (Wall and Perez-Reyes 1981)

Time minutes	THC µg/L	11-OH-THC µg/L	THCCOOH µg/L
45	0.8±0.4	1.0±0.5	6±4
60	3.8±2.9	3.4±1.6	14±9
75	4.7±3.4	3.7±1.7	22±11
90	5.7±3.5	4.7±1.5	30±10
105	4.9±2.6	5.8±1.7	41±14
120	4.3±0.6	7.2±1.8	54±18
135	7.9±3.6	8.3±1.3	49±6
150	6.6±3.5	8.4±2.1	64±13
165	6.4±3.8	8.3±2.0	65±16
180	7.1±4.9	8.5±2.0	62±17
360	9.3±3.5	8.8±1.7	46±11
1440	1.3±0.4	1.1±0.5	21±8

Wall et al 1983 intravenously administered THC laced with tritium-labeled THC over 15 to 25 min with a mean of 2.2 mg THC to six women and 4.0 mg to 6 men.

Time h	Plasma concentrations		
Women n=6	THC µg/L	11-OH-THC	THCCOOH
0.5	4.8 ± 4.6	1.4±1.3	4.1 ± 3.9
0.75	9.0 ± 8.4	3.8 ± 4.2	15 ± 10
1	7.7 ± 5.9	3.7 ± 2.8	27 ± 18
1.25	8.4 ± 5.3	4.2 ± 2.6	41 ± 21
1.5	9.1 ± 4.7	5.5 ± 2.6	48 ± 28
1.75	9.4 ± 4.5	5.9 ± 2.8	62 ± 28
2	7.4 ± 2.2	5.3 ± 1.6	68 ± 20
2.5	7.2 ± 3.8	4.5 ± 2.-S	64 ± 10
3	6.8 ± 3.1	4.4 ± 2.9	51 ± 14
4	6.2 ± 3.2	2.5 ± 1.7	48 ± 8.0
6	5·.4 ± 4.2	1.6 ± 0.9	38 ± 8.6
8	3.8 ± 2.3	1.2 ± 0.5	39 ± 13
12	3.2 ± l.9	0.9 ± 0.5	28 ± 6.4
24	l.9 ± 0.6	0.7 ± 0.5	21 ± 6.4
30	l.5 ± 1.0	-	15 ± 2.6
48	0.9 ± 0.5	-	12 ± 7.4
72	0.8 ± 0.9	-	8.4 ± 5.3
Men n=6			
0.75	9.1±4.0	2.7 ±0.8	2.7±0.8
1	8.0 ± 7.3	3.4 ± 3.1	23 ± 12
1.25	11 ± 9.3	3.8 ± l.9	47 ± 22
1.5	11 ± 6.6	5.2 ± 1.7	66 ± 32
1.75	13 ± 7.5	5.1 ± 2.1	82 ± 39
2	13 ± 9.1	6.6 ± 3.4	89 ± 40
2.5	14 ± 9.7	5.9 ± 3.0	80 ± 39
3	11 ± 8.2	5.6 ± 3.2	82 ± 37
4	11 ± 6.6	5.6 ± 3.6	82 ± 36
6	10 ± 6.0	4.0 ± 1.8	62 ± 31
8	8.4 ± 4.8	3.4 ± 2.3	51 ± 21
11-12	6.4 ± 3.9	1.9 ± 1.3	37 ± 18
24	3.3 ± 2.4	1.3 ± 1.2	29 ± 14
30	3.2 ± 2.1	0.8 ± 0.6	23 ± 8
48	2.2 ± 1.7	0.6 ± 0.5	14 ± 6
72	1.0 ± 0.6	-	8 ± 5

Four subjects received 20 mg THC in a meat sandwich with plasma collected for up to 5 days and analyzed by high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA) (Law et al 1984).

Mean (n=4) plasma cannabinoid concentrations after 20 mg oral THC (Law et al 1984).

Time h	THC µg/L	THCCOOH µg/L	THCCOOH-glucuronide µg/L
1	1.5±0.2	6.6±2.1	3.4±1.1
2	3.9±1.1	23±6.3	26±3.4
4	6.9±1.4	38±10	107±16
6	3.0±0.9	29±4.7	99±8.3
8	1.8±0.4	24±5.6	80±10
24	0.5±0.1	14±2.5	31±1.3
48	0.2±0.1	6±2.0	17±3.9
72	0.1±0.1	3.3±0.9	9.1±2.7

In a controlled cannabinoid administration study of THC-containing hemp oils and dronabinol, the pharmacokinetics and pharmacodynamics of oral THC were evaluated (Goodwin et al 2005). Up to 14.8 mg THC was ingested by six volunteers each day in three divided doses with meals for five consecutive days. There was a 10-day washout phase between each of the five dosing sessions. THC was quantified in plasma by GC/MS. THC and 11-OH-THC were not detected in plasma following the two lowest doses of 0.39 and 0.47 mg/day THC, while peak plasma concentrations of <6.5 µg/L THC, <5.6 µg/L 11-OH-THC, and <43.0 µg/L THCCOOH were achieved after the two highest THC doses of 7.5 and 14.8 mg/day. This is important because the mean daily THC dose for all four Fresh Hemp Foods products combined is 0.0968 mg. Interestingly, THCCOOH concentrations after the 7.5 mg/day dronabinol dose were greater than or equal to those of the high potency 14.8 mg/day hemp oil dose. Two possible reasons for the higher THC bioavailability in dronabinol are greater protection from degradation in the acidic environment of the stomach due to encapsulation and improved absorption of THC from the sesame oil formulation. Analytes were detectable in plasma 1.5 h after initiating dosing with the 7.5 mg THC/day regimen and 4.5 h after starting the 14.8 mg THC/day sessions. THCCOOH was detected 1.5 h after the first dose, except for the 0.47mg THC/d session, which required 4.5 h for concentrations to reach the LOQ 0.5 µg/L. Plasma THCCOOH concentrations peaked at 3.1 µg/mL during dosing with the low-dose hemp oils. Plasma THC and 11-OH-THC concentrations were negative for all participants at all doses within 15.5 h after the last THC dose. Plasma THCCOOH persisted (LOQ 1 µg/L) for at least 39.5 hours after the end of dosing and at much higher concentrations (up to 43.0 ng/mL). After oral and sublingual administration of THC, THC-containing food products, or cannabis-based extracts, THC and 11-OH-THC concentrations were much lower than after smoked administration.

Since 2013, Nabiximols, an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD in each 100 µL spray was approved in Italy for the treatment of Multiple Sclerosis.
Low blood concentrations were produced by Nabiximols administration, more than 10 times lower than the blood concentrations known to produce psychotropic effects (Indorato et al 2016). Whole venous blood for THC analysis was collected immediately before and at fixed intervals after Nabiximols administration (15, 30 and 60 min). THC and CBD were detected in the blood a few minutes after administration. Fifteen min after administration of 2.7 mg THC (a single puff), THC blood concentrations ranged from 0.2

to 1.2 µg/L. THC Cmax was 1.3 µg/L 30 min after Nabiximol intake. Blood Cmax ranges between 2.5 and 2.9 µg/L after administration of 10.8 mg of THC (four puffs of Nabiximol). Blood samples from 20 patients treated with Nabiximols for short (28 days) or long-term treatment (60 or 90 days) were analyzed. Treatment consisted of one puff 6 times/day of 100 µL containing 2.7 mg of THC and 2.5 mg CBD. 20 patients provided informed consent to participate in short (less than 28 days) or long-term 90 days treatment. The THC blood concentrations of all samples ranged from not detected to 1.3 µg/L with a lower limit of quantification (LOQ) of 0.20 µg/L. Oromucosal administration has a better bioavailability than oral administration due to a lower first pass effect.

THC blood concentrations at 0, 15, 30 and 60 min after the administration of one puff of Nabiximols. 2.7 mg THC, 2.5 mg CBD (Indorato et al 2016)

	THC µg/L 0	THC µg/L 15 min	THC µg/L 30 min	THC µg/L 60 min
N	20	20	20	20
Pos Samples	0	20	18	14
Mean ± SD	<LOQ 0.2	0.47 ± 0.27	0.52 ± 0.30	0.22 ± 0.11

THC blood concentrations at 0, 15, 30 and 60 min after the administration of 1 puff of 2.7 mg THC 6 times a day (Nabiximols) for short term (<28 days) or long term (>28 days) therapy.

	THC µg/L 0	THC µg/L 15 min	THC µg/L 30 min	THC µg/L 60 min
N	20	20	20	20
Short therapy	<LOQ	0.34 ± 0.16	0.26 ± 0.12	0.14 ± 0.07
Long therapy	<LOQ	0.55 ± 0.30	0.69 ± 0.26	0.27 ± 0.10

The following studies contain only blood/plasma/serum data without simultaneous urine results. These data are valuable because they provide information on THC bioavailability after oral THC in food products, including data needed to estimate THC exposure in breastfeeding infants.

Frytak et al 1984 dosed 6 cancer patients with 15 mg oral THC during 5-Fluoruracil and semustine chemotherapy for gastrointestinal malignancy. Median peak plasma concentrations were 3.7 for THC, 6.7 for 11-OH-THC and 62.5 µg/L THCCOOH at 2, 2 and 3 h, respectively. Three additional patients received multiple 15 mg THC doses 2 h prior to chemotherapy and 2 and 8 h after chemotherapy. Peak plasma concentrations (µg/L) ranged from 3.6 - 6.3 for THC, 8.6-15.6 for 11-OH-THC and 98.2-203 for THCCOOH at median times of 1, 2 and 8 h after the first dose. THC and 11-OH-THC concentrations did not appear to accumulate, but THCCOOH plasma concentrations were higher after multiple doses than after the single dose 24 h after dosing. There was erratic gastrointestinal absorption in these patients who had variable gastrointestinal function.

Timpone et al 1997 conducted a randomized, open-label, multicenter study to assess the safety and pharmacokinetics of dronabinol (Marinol) tables for treatment of HIV wasting

syndrome. Twenty patients received dronabinol 2.5 mg twice/day and had a mean peak THC plasma concentration of 2.0 µg/L (0.6 – 12.5) at a mean of 2.1 h (0.7 -8.3). 11-OH-THC mean peak plasma concentration was 4.6 µg/L (0.5 - 37.5) at 2.1 h (0.5 - 8). The LOQ for THC and 11-OH-THC were 0.1 µg/L. Serious adverse events assessed as related to dronabinol included CNS events including confusion, anxiety, emotional lability, euphoria, and hallucinations.

Sporkert et al 2001 investigated the pharmacokinetics of a single 10 mg THC dose in 10 females and 7 males before and up to 24 h after dosing. Plasma THC Cmax µg/L was 4.7 ± 3.0 and Tmax was 60 - 120 min. Mean bioavailability was 7.0±3.0% (2-14%). There was no correlation of THC concentrations and age, sex, body weight and body height.

Maximum plasma concentrations (µg/L) of THC, 11-OH-THC and THCCOOH after 10 mg THC (Sporkert et al 2001).

Subject	THC µg/L Cmax	THC h Tmax	11-OH-THC µg L Cmax	11-OH-THC Tmax h	THCCOOH µg/L Cmax	THCCOOH µg/L Tmax
1	7.3	2	12.8	2	33.2	2
2	3.1	1	4.0	2	45.8	2
3	4.2	1	3.5	1	38.9	2
4	2.5	1	2.1	2	24.7	3
5	2.2	1	1.7	1	29.6	2
6	6.6	2	3.5	3	23.0	3
7	4.6	1	5.6	1	43.5	1
8	4.4	1	1.6	2	24.2	2
9	4.3	1	1.9	1	25.6	1
10	3.1	1	1.7	1	19.2	1
11	12.7	1	4.6	1	14.5	2
12	1.3	1	1.3	1	21.7	2
13	9.8	1	9.4	1	66.8	2
14	3.2	2	5.2	2	45.5	2
15	1.5	1	1.5	2	23.5	3
16	2.6	1	2.8	2	24.6	2
17	5.5	3	5.3	2	38.8	2

Stott et al 2013 administered single Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses as 2 (5.4 mg THC), 4 (10.8 mg THC), 8 (21.6 mg THC) sprays, or multiple sprays (2, 4 or 8 sprays) for 9 consecutive days. With increasing single and multiple doses of THC/CBD spray, the mean plasma Cmax increased for all analytes. There was evidence of dose-proportionality in the single but not the multiple dosing data. The bioavailability of THC was greater than CBD at single and multiple doses, and there was no evidence of accumulation for any analyte with multiple dosing. Inter-subject variability ranged from moderate to high for all pharmacokinetic parameters in this study. Plasma Tmax was longest for all analytes in the 8-spray group, but was similar in the 2 and 4 spray groups. The mean Cmax values (<12 µg/L) recorded in this study were well below those reported

in patients who smoked/inhaled cannabis, which is associated with significant psychoactivity. There was also no evidence of accumulation on repeated dosing.

Since 2013, Nabiximols, an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD in each 100 µL spray was approved in Italy for the treatment of Multiple Sclerosis. Low blood concentrations were produced by Nabiximols administration, more than 10 times lower than the blood concentrations known to produce psychotropic effects (Indorato et al 2016). Blood THC Cmax concentrations after a single 2.7 mg THC oromucosal spray were 0.52 ± 0.30 µg/L. Blood samples from 20 patients treated with Nabiximols for short (28 days) or long-term treatment (60 or 90 days) were analyzed. Treatment consisted of one puff 6 times/day of 100 µL containing 2.7 mg of THC and 2.5 mg CBD. THC blood concentrations of all samples ranged from not detected to 1.3 µg/L with a lower limit of quantification (LOQ) of 0.20 µg/L. These doses of THC are higher than the daily 0.1938 mg THC limit (90^{th} percentile) for Fresh Hemp Foods, Ltd, indicating that consumers would not have psychotropic effects following the mean combined daily THC dose for the 4 hemp products.

In Timpone et al 1997, 20 HIV patients received 2.5 mg Marinol (synthetic THC) twice/day for treatment of HIV wasting syndrome. Mean peak THC plasma concentration was 2.0 µg/L (0.6 – 12.5) at a mean of 2.1 h (0.7 -8.3). 11-OH-THC mean peak plasma concentration was 4.6 µg/L (0.5 - 37.5) at 2.1 h (0.5 - 8). Serious adverse events assessed as related to dronabinol included CNS events of confusion, anxiety, emotional lability, euphoria, and hallucinations.

Stott et al, 2013 administered single Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses as 2 (5.4 mg THC), 4 (10.8 mg THC), 8 (21.6 mg THC) sprays, or multiple sprays (2, 4 or 8 sprays) for 9 consecutive days. With increasing single and multiple doses of THC/CBD spray, the mean plasma Cmax increased for all analytes. There was evidence of dose-proportionality in the single but not the multiple dosing data. There was no evidence of accumulation for any analyte with multiple dosing. The mean Cmax values (<12 µg/L) recorded in this study were well below those reported in patients who smoked/inhaled cannabis, which is associated with significant psychoactivity. In terms of safety, THC/CBD spray was well tolerated in all phases of the study, with no serious AEs or withdrawals due to AEs. All but three AEs were of mild severity, with three of moderate severity. All AEs resolved without sequelae, but most were considered to be related to the study treatment. The most common AEs were dizziness and somnolence. As expected, there was a direct relationship between increasing doses of THC/CBD spray and the frequency of AEs, with all subjects receiving eight sprays of THC/CBD spray experiencing at least one AE.

Treatment-emergent adverse events with a subject incidence of 1 or more (Stott et al 2013)

	2 sprays 5.0 mg THC n = 6		4 sprays 10.0 mg THC n = 12		8 sprays 20.0 mg THC n = 7	
Primary system organ class	# Events	# (%) patients	# Events	# (%) patients	# Events	# (%) patients
Single dose						
Nervous system disorders						
Dizziness	0	0	0	0	3	3 (43)
Headache	2	2 (33)	0	0	1	1 (14)
Somnolence	1	1 (17)	1	1 (8)	1	1 (14)
Disturbance in attention	0	0	0	0	2	2 (29)
Psychiatric disorders						
Disorientation	0	0	0	0	2	2 (29)
Euphoric mood	0	0	1	1 (8)	1	1 (14)
General disorders & administration site conditions						
Feeling abnormal	0	0	1	1 (8)	1	1 (14)
Multiple doses						
Nervous system disorders						
Dizziness	0	0	1	1 (8)	4	3 (50)
Headache	2	2 (33)	1	1 (8)	1	1 (17)
Somnolence	0	0	4	3 (25)	3	3 (50)
General disorders and administration site conditions						
Feeling abnormal	0	0	1	1 (8)	2	1 (17)
Gastrointestinal disorders						
Dry mouth	1	1 (17)	1	1 (8)	2	2 (33)
Psychiatric disorders						
Abnormal dreams	2	1 (17)	1	1 (8)	0	0
Euphoric mood	0	0	4	2 (17)	1	1 (17)

There are few data on THC effects following low oral doses. The Stott data above, are most relevant to the Fresh Hemp Foods comparison for the single 2 spray 5.0 mg THC dose, although this dose is more than 52 times the size of the mean daily THC dose for 4 Fresh Hemp Foods products. In addition, low daily THC doses did not appear to accumulate in blood. These data illustrate that the number of adverse events are low and of minor or moderate severity at much higher THC doses.

Law et al 1984 administered 5.0-5.2 mg THC in a meat sandwich to 5 subjects. None of the subjects reported any psychological effects or any reaction associated with cannabis administration. One of 5 subjects had poor pallor and felt faint.

Brenneisen et al 1996 administered 10 mg Marinol (synthetic THC) to Patient A and 15 mg THC to Patient B for four consecutive days. Peak THC concentrations varied from 2.1-6.9 µg/L in patient A and 2.7-16.9 µg/L in patient B. There were improvements in mobility, walking ability and rigidity in both patients, one patient showed no change in concentration and mood, while the other patient showed mixed changes at the higher 15 mg oral dose.

Bosy & Cole 2000 administered 7 daily doses of hemp oils containing 0.10 and 1.8 mg THC/day. No psychoactive effects were experienced by any of the subjects during the course of the experiment.

Can consumption of mean and 90% percentile THC amounts of all Fresh Hemp Foods products in a single day produce a positive urine cannabinoid test ≥15 µg THCCOOH/L?

The goal was to determine if oral ingestion of combined daily mean or 90% percentile THC amounts of all Fresh Hemp Foods products (hulled hemp seed, hemp protein powder, hemp protein concentrate and hemp oil) could produce positive urine cannabinoid tests. We determined the mean daily THC amounts in each product and daily amounts of THC in all products combined. Fresh Hemp Foods Ltd provided the data on mean and 90th percentile total daily amounts of the 4 products. The THC calculations are based on the new Fresh Hemp Foods, Ltd standards for ≤4 µg THC/g as verified by the Quality Department for hulled hemp seed, hemp protein powder and hemp protein concentrate. The Fresh Hemp Foods, Ltd standard for hemp oil will be the same as the Canadian Industrial Hemp Regulations requirement of ≤10 µg THC/g product. These values were used in determining daily THC intake if the recommended dose of all products were consumed each day. We determined the mean total daily THC amount as 0.0968 mg THC and the total amount based on the 90th percentile of ingestion of all 4 hemp food products as 0.1938 mg.

We reviewed all clinical studies that administered THC by the oral route and measured urine cannabinoids, preferably by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS), although many reports include immunoassay screening data, generally at a 50 µg/L cutoff concentration. The number of studies that included both the dose of THC administered and urine concentrations were limited; therefore, I also surveyed most of the studies administering known quantities of THC and blood/plasma/serum concentrations to help estimate the blood concentrations that would result from intake of 0.0968 (mean daily mg THC from 4 Fresh Hemp Foods, Ltd products) to 0.1938 (90th percentile daily mg THC from 4 Fresh Hemp Foods, Ltd. Products) mg oral THC.

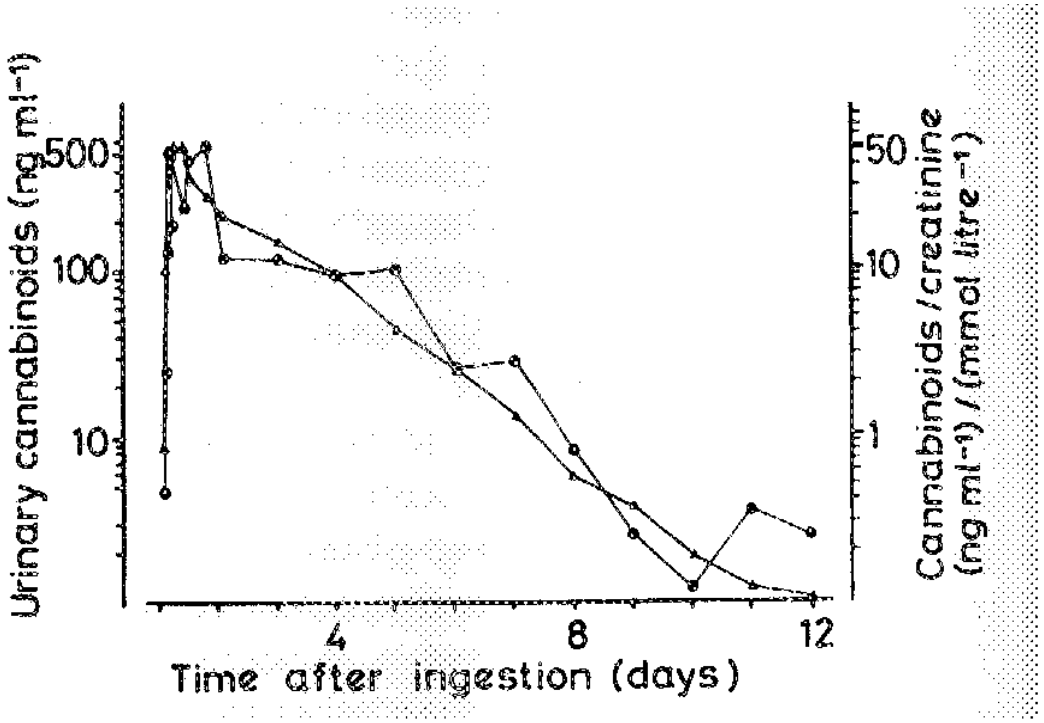
Following oral dosing with 5 mg THC, urinary cannabinoids peaked at 112-210 µg/L at 8-10 h after ingestion by RIA, with positive urine tests for 7 days (Law et al 1984). After the

20-mg dose, urine concentrations increased to 185-1063 µg/L cross reacting cannabinoids 6 h after ingestion, with positive results for 12 days. This was the first report of the importance of the THCCOOH-glucuronide metabolite in plasma and urine and of its instability in urine at higher pH's and after 12 and 90-day room temperature storage. Urine concentrations determined by RIA as compared to GC-MS or LC-MS/MS will be elevated because the radioactivity is for multiple analytes rather than just THCCOOH.

Sadler et al 1984 simultaneously administered 0.141 mg/123 µCi ^{3}H THC intravenous tracer and 20 mg oral THC in sesame oil to 6 males to determine oral THC bioavailability. After 72 h, 21±1% of the tracer was in the urine and 40±2% was in the feces. A low bioavailability of 13% was found due to an extensive first pass effect in the liver.

Five males ingested cannabis-laced brownies in a double-blind crossover study to evaluate urinary cannabinoid excretion (Cone et al. 1988). On three occasions, each subject consumed two brownies containing 1.6 g of cannabis plant material. Placebo cannabis (0% THC) was mixed with 2.8% THC cannabis plant material to produce doses of 0, 22.4 mg THC, and 44.8 mg THC. All urine specimens were collected throughout the study. Urinalyses by EMIT® daub. assay (20 µg/L cutoff) and Abuscreen® RIA for cannabinoids (5 µg/L cutoff) and GC/MS (LOQ 2 µg/L) for THCCOOH indicated that cannabinoid-related metabolites were excreted over a period of 3 to 14 days.

GC/MS Urine THCCOOH results µg/L for one subject following ingestion of 22.2 and 44.4 mg THC in a brownie (left y axis) and µg/mmol THCCOOH creatinine (Cone et al 1988).



GC-MS produced overall results similar to the assay profiles of cannabinoid excretion by EMIT 20 Assay and Abu screen® RIA. With a 5 µg/L THCCOOH cutoff, mean times ± SE to the first negative urine sample were 94.5 ± 26.8 h and 114 ± 33.8 h and mean times ± SE to last positive urine sample were 149 ± 36.2 h and 156 ± 49 h after administration of the 22.4 mg and 44.8 doses, respectively. Individual peak concentrations of total THCCOOH varied from 108 to 325 µg/L (mean± SE= 180 ± 39) and 177 to 436 µg/L (mean± SE= 312 ± 48) after the low and high doses, respectively. An estimation of the cumulative dose of total THCCOOH excreted in urine after both cannabis doses was 1.3% of the administered dose. Excretion of detectable amounts of cannabinoid metabolites occurred for approximately 6 days (range 3-11 days) after 22.4 mg THC, and for slightly longer periods of time (range 3-14.5 days) after the 44.8 mg dose.

Brenneisen et al 1996 dosed 2 participants with organic spasticity with multiple oral THC doses every 24 h and determined plasma concentrations by GC-MS. After four daily 10 mg THC oral doses, THC plasma concentrations of Subject A were detectable from 1 to 8 h with a mean peak concentration of 3.5 ± 2.3 µg/L (2.1 - 6.9 µg/L) at 2.0 ± 1.3 h (range

Table IV. GC/MS and Abuscreen RIA Assay of Specimens from Subjects Who Ingested Marijuana-Laced Brownies

Subject	Dose equivalent (cigarettes)	GC/MS* Time to first negative (h)	GC/MS* Time to last positive (h)	GC/MS* Peak concn (ng/ml)	GC/MS* Time to peak concn (h)	GC/MS* THCCOOH Cumulative dose (0/a)	RIA** Time to first negative (h)	RIA** Time to last positive (h)
H	1	73.1	131.8	156	9.4	1.21	93.3	159.5
	2	85.7	110.8	436	14.0	1.43	113.3	127.5
K	1	53.5	74.3	121	7.4	1.16	53.5	74.3
	2	56.2	100.2	234	5.5	1.07	117.1	132.0
L	1	84.4	243.0	191	21.3	1.83	86.1	144.3
	2	106.0	147.2	392	21.2	1.70	130.2	217.5
M	1	199.5	223.5	325	12.6	1.74	199.5	247.4
	2	245.6	346.8	323	25.4	1.52	245.6	346.8
N	1	61.8	72.2	108	6.5	0.63	61.8	76.1
	2	77.7	76.6	177	7.5	0.80	77.7	127.5
Mean±SE	1	94.5±26.8	149.0±36.2	180±39	11.4±2.7	1.31 ±0.22	98.8±26.2	140.3±31.9
	2	114.2±33.8	156.3±49	312±48	14.7 ±3.8	1.30±0.16	136.8±28.6	190.3±42.7

"Cutoff = 5 ng/ml THCCOOH.
•• Cutoff = 10 ng/ml THCCOOH equivalents.

1 to 4 h). Mean peak THCCOOH concentration for Subject A was 79.6 µg/L at 5.5 ± 3.0 h (2 - 8 h). Subject B received four daily oral doses of 15 mg THC with a mean peak THC concentration of 7.2 µg/L (2.7 to 16.9 µg/L) THC at 5.0 ± 3.5 h (range 2 - 8 h). Mean peak THCCOOH concentration for Subject B was 185 ± 42.0 µg/L (146 – 244 µg/L) at 6.5 h (2 - 8 h). There was little THC accumulation with multiple doses of the 10 and 15 mg THC. This is important for our understanding of the excretion of daily Fresh Hemp Foods Ltd h products that entail a much lower mean daily dose of 0.0938 mg THC. Concentrations were less than the THC LOQ (0.5 µg/L) between 4 and 24 h.

Several studies reported that ingestion of hemp oil causes positive urine tests for cannabinoids. Lehmann et al. 1997 reported THC concentrations of 3–1500 µg/g in 25 hemp oil samples. Six individuals ingested one or two tablespoons of hemp oil containing 1500 µg/g THC (11 and 22 g of hemp oil, or 16.5 – 33 mg THC). Positive urine specimens were observed with a 50 µg/L cannabinoid immunoassay cutoff and a 15 µg/L THCCOOH GC/MS cutoff for up to 6 days. Morning urine samples were collected for 6 days and screened by immunoassay, and THCCOOH determined by GC-MS. Urine samples were positive for cannabinoids up to 6 days with the Abuscreen OnLine immunoassay with a 50 µg/L cutoff and THCCOOH concentrations were 5 to 431 µg/L. All subjects reported THC-specific psychotropic effects. All urine samples were positive at a 15µg/L GC-MS cutoff from 12 to 60 h and at 84 h except for 1 participant. Two participants' urine samples were greater than 15 µg/L for 132 h after the single dose.

Table II. Urine THCCOOH Concentrations (ng/ml) after Ingestion of 11 g and 22 g of Cannabis Seed Oil as Analyzed by GC-MS*

Time after in2estion (h)	Subjects					
	1	2	3	4	5	6
0	0	0	0	0	0	0
12	298	378	280	81	431	281
36	154	186	121	104	242	263
60	65	71	77	54	57	213
84	35	30	78	10	49	69
108	12	13	31	13	12	46
132	11	9	24	6	5	30

•subjects 1-3 ingested 22 g cannabis seed oil, and subjects 4-6 ingested 11g cannabis seed oil.

A commercially available health food product of cold-pressed hemp seed oil was ingested by one volunteer twice a day for 4 1/2 days (135 mL total) (Struempler et al 1997). Urine specimens collected from the volunteer were subjected to standard workplace urine drug testing procedures, and the following concentrations of THCCOOH were detected: 41 µg/L THCCOOH at 45 h, 49 µg/L at 69 h, and 55 µg/L at 93 h. Ingestion was discontinued after 93 h, and the following concentrations were detected: 68 µg/L at 108 h, 57 µg/L at 117 h, 31 µg/L at 126 h, and 20 µg/L at 142 h. The first specimen that tested negative (50 µg/L initial immunoassay test, 15 µg/L confirmatory GC-MS was at 146 h, which was 53 h after the last hemp seed oil ingestion. Four subsequent specimens taken to 177 h were also negative. This study indicates that a workplace urine drug test positive for cannabinoids may arise from the consumption of commercially available cold-pressed hemp seed oil.

In a 1997 survey of hemp oils in the US, THC concentrations between 11-117µg/g were noted (Mölleken and Husmann 1997). These oils were produced from imported Chinese seeds. Presence of THC in hemp seed products is predominantly caused by external contact of the seed hull with cannabinoid-containing resins in bracts and leaves during maturation, harvesting, and processing. The seed kernel is not entirely THC-free but contains, depending on the hemp variety, less than 0.5 µg/g of THC. These studies also showed that the use of low-THC cultivars and thorough seed cleaning is effective in reducing THC levels in the main products currently made from the seed kernel for human

consumption, that is, oil and hulled seeds (Leson et al, 2001). Since 1998, more thorough seed drying and cleaning appears to have considerably reduced THC levels in seeds and oil available in the U.S. Results from the mandatory THC analysis of seeds and oil produced in Canada and a study evaluating the effectiveness of various dry and wet cleaning methods show typical THC concentrations of 5 and 2 µg/g, respectively, in oil and hulled seeds from Canada (Crew 2000).

ElSohly et al. 2001 administered a single 15-mg dronabinol dose to four individuals over 3 sessions in a within-subject, crossover design, with a 1 week washout period between sessions. Each subject received, in separate sessions and in randomized order, an oral dose of Marinol (15 mg), a smoked dose of THC (16.9 mg) or a smoked dose of 17 mg THC and 1 mg THCV. Every urine sample was collected for 24 h, and then samples were collected once a day for 6 days. The limits of detection for THC and THCV were 1 µg/L. THCCOOH concentrations for the 4 subjects after the 15-mg oral THC dose ranged from 2.4 - 362 µg/L, with 43.1% of urine samples (22 of 51) ≥15µg/L up to one week after ingesting the drug.

Grauwiler et al 2008 evaluated the sensitivity and specificity of the CEDIA and FPIA immunoassays to detect cannabinoids with a 50 µg/L cutoff and a 15 µg/L LC-MS/MS cutoff (LOQ for THCCOOH 1 µg/L) in urine samples from volunteers receiving 20 mg oral synthetic THC (Marinol) or five different Cannabis sativa extracts. Urine samples were collected in an open, randomized, single-center, three-period crossover study in 18 healthy male volunteers. Urine samples were collected from all volunteers at 0, 4, 12, 24, 48, and 72 h after cannabinoid administration. Urine samples were analyzed with and without hydrolysis.

Sensitivity and specificity using 50 µg/L CEDIA/FPIA and 15 µg/L LC-MS/MS cutoffs for urine samples collected after 20 mg Marinol and 5 different cannabis extracts, each containing 20 mg THC (Grauwiler et al 2008).

		LC-MS/MS Hydrolyzed THCCOOH			LC-MS/MS Nonhydrolyzed THCCOOH & THCCOOH-gluc		
		Neg	Pos	% Pos	Neg	Pos	% Pos
CEDIA	Neg	105	34		105	34	
	Pos	22	164	61%	27	160	60%
CEDIA hydrolyzed	Neg	104	57		114	56	
	Pos	17	146	63%	21	141	59%
FPIA	Neg	100	18		102	16	
	Pos	16	171	62%	22	165	59%
FPIA hydrolyzed	Neg	102	19		102	18	
	Pos	14	179	63%	19	172	61%

The data above document that almost 60% of urine samples were positive following ingestion of 20 mg THC in 6 different formulations. Also, the immunoassays showed similar positive results between hydrolyzed and non-hydrolyzed urine samples.

Nabiximols deliver 2.7 mg THC and 2.5 mg CBD in each 100 µL oromucosal spray (Indorato et al 2016). Urine samples from 20 patients treated with Nabiximols for short (28 days) or long-term treatment (60 or 90 days) were analyzed. Positive urine test results (cut-off 25 µg/L) by the Drug-Screen-THC immunoassay occurred in all patients during the three months of follow-up, despite low concentrations in blood samples. Treatment consisted of one puff 6 times/day of 100 µL containing 2.7 mg of THC and 2.5 mg CBD. Urine samples were analyzed before and after starting the treatment and once a month for the 3 months of treatment. THCCOOH (cut-off: 25 µg/L) confirmation in urine was performed by GC–MS. Oromucosal administration has a better bioavailability than oral administration due to a lower first pass effect.

THCCOOH urine concentrations before starting therapy (T0) and after 1, 2, 3 months of Nabiximols therapy. Daily THC intake was 2.7 mg X 6 per day = 16.2 mg THC per day

Duration	THCCOOH µg/L Before drug	THCCOOH µg/L 1 month	THCCOOH µg/L 2 months	THCCOOH µg/L 3 months
Short therapy	<LOQ	61.3±27.5	-	-
Long therapy	<LOQ	59.8±23.6	62.6±25.2	63.2±24.8

In our last cannabinoid administration study at the National Institute on Drug Abuse, we administered 50.6 mg THC by the smoked, vaporized and oral routes to 11 chronic frequent and 9 occasional cannabis users (Huestis, unpublished data). The chronic frequent cannabis users had high residual cannabinoid concentrations and will not be included here. However, occasional cannabis users' urine THC-glucuronide, THCCOOH, THCCOOH-glucuronide concentrations were quantified by LC-MS/MS. The maximum analyte urine concentration (Cmax), time of maximum concentration (Tmax), concentration of the last positive sample (Clast) and time of the last positive sample (Tlast) are presented after oral administration of 50.6 mg THC.

	Median	Range
THC-glucuronide		
Cmax (ug/L)	3.3	2.4 – 23
Tmax (h)	5.5	3.2 – 14.2
Clast (≥1ug/L)	1.4	1.0 - 20.6
Tlast (h)	10	5 – 37
THCCOOH		
Cmax (ug/L)	10.6	1.6 - 28
Tmax (h)	9.4	5.5 - 21
Clast (≥0.5ug/L)	0.8	0.6 - 1.7
Tlast (h)	51	44 - 55.3
THCCOOH-gluc		
Cmax (ug/L)	354	116 - 667

Tmax (h)	6.7	5.5 - 24.9
Clast (ug/L)	20.7	12.2-34.1
Tlast (h)	52.9	48.9-59.9

%Pos (THCCOOH + THCCOOH-gluc) ≥ 15 ug/L up to 54 h

Sessions 1-4	84.6	27.3-100% up to 54 h

The most relevant oral THC administration studies for predicting the possibility of a positive urine cannabinoid test following oral THC ingestion were published by Bosy & Cole 2000, Leson et al 2001, and Gustafson et al 2004.

The purpose of the Bosy and Cole 2000 study was to quantify THC concentrations by GC-MS in commercially available hemp oils and to determine THCCOOH urine concentrations following 7 daily 15-g doses of hemp oil products containing from 11.5 to 117.5 µg/g THC. This represents daily THC doses of 0.17 to 1.8 mg. These doses exceeded the mean and were close to the 90% percentile of the combined 4 Fresh Hemp Foods products daily THC amounts and are highly relevant. Urine samples were tested by the Abbott AxSYM® FPIA and Roche On-line® KIMS immunoassays and by GC-MS to determine THCCOOH concentrations before and 6 h after each dose. After the last dose of oil, urine samples were collected for one week to determine the length of time an individual remains positive after this dosing regimen. Volunteers selected to participate in this study were required to submit three pre-study urine samples to verify no recent THC use. The 15-g quantity was selected because it approximates one tablespoon, a dose that was frequently recommended by manufacturers. One volunteer consumed two 1000-mg Health from the Sun Hemp 1000 gel caps which is the recommended dose indicated on the product. Urine samples were collected for one week after the last dose of oil to determine an excretion profile and the time when the subjects' urine drops below the screening positive cutoff. Peak THCCOOH concentrations in the participants' urine ranged from 1.8 to 48.7 µg/L. There were no positive urine specimens ≥15 µg/L following the 0.10, 0.17, 0.32, and 0.55 mg THC/d for 7 daily doses. The 0.54 mg and 1.8 mg THC/d doses produced positive urine specimens ≥15 µg/L.

Subjects ingesting low doses of THC (0.10, 0.17 & 0.32 mg THC/d) had immunoassay results well below the 50-µg/L immunoassay positive cutoff. Subjects ingesting medium doses of THC in hemp oil (0.54 & 0.55 mg THC/d) produced positive immunoassay screen results in the third and fourth days of ingestion. These two subjects had negative immunoassays within 24 h after ingestion ceased. The subject ingesting a high dose (1.8 mg THC/d) screened positive on the first day and was immunoassay negative within 72 h after last ingestion.

The impact of extended daily ingestion of THC via hemp oil on urine concentrations of THCCOOH for four daily THC doses (0.09, 0.19, 0.29, and 0.45 mg THC) was determined (Leson et al 2001). Fifteen THC-naïve adults ingested, over 4 successive 10-day periods, single daily THC doses. Websar Laboratories, Inc. (Ste. Anne, MB, Canada) quantified total THC concentration in the oil in triplicate by the method used to meet regulatory requirements in Canada (Research, Health Protection Branch, Health Canada 1992).

Hemp oil results were 6.2 ± 0.5, 13.3 ± 0.8, 20.7 ± 1.2, and 31.7 ± 1.4 µg THC/g; the corresponding actual doses per 15-mL aliquots, using a specific density of 0.95 for all four oil blends, were 0.09, 0.19, 0.29, and 0.45 mg THC. The Subjects self-administered THC in 15-mL aliquots (20 mL for the 0.6-mg dose) of four different blends of hemp and canola oils. Urine specimens were collected prior to the first ingestion of oil, on days 9 and 10 of each of the four study periods, and 1 and 3 days after the last ingestion. All specimens were confirmed for THCCOOH by GC–MS, and analyzed for creatinine to identify dilute specimens. None of the subjects who ingested daily doses of 0.45 mg THC screened positive and only one specimen screened positive at the 50 µg/L cutoff at a daily THC dose of 0.6 mg. The highest THCCOOH concentration was 5.2 µg/L, well below the 15 µg/L confirmation cutoff of federal drug testing programs. A THC intake of 0.6 mg/day is equivalent to the consumption of approximately 125 mL of hemp oil containing 5 µg/g of THC or 300 g of hulled seeds at 2 µg/g. These THC concentrations are now typical in Canadian hemp seed products. Concentrations were sufficiently low to prevent confirmed positives from the extended and extensive consumption of hemp foods with low THC content. A summation of these results found no positive urine specimens ≥15 µg/L, in fact all below 5.5 µg/L after 4 daily doses of up to 0.6 mg/day, and only a single specimen positive by RIA at 50 µg/L.

Tables below include the calculated THC doses and the immunoassay and GC-MS urine results after hemp oil administration.

Table II. Summary of Urine Analyses by Radioimmunoassay and GC–MS

THC dose (mg/day)	#ofSpecimens *n*	GC–MS		RIA				
		″2.5ng/mL	>2.5ng/mL*	< 10 ng/mL	< 20 ng/mL	< 50 ng/mL	< 100 ng/mL	% Specimens ≥ 20 ng/mL
Baseline	15	15	0	15	0	0	0	0
0.09	29	29	0	28	1	0	0	0
0.19	30	30	0	21	8	1	0	3
0.29	30	28	2	17	9	4	0	13
0.45 (0.6)†	22 (6)	16 (6)	6 (0)	8 (3)	4 (1)	10 (2)	0 (0)	43
Washout day 1†	11 (3)	10 (2)	1 (1)	6 (2)	2 (0)	3 (0)	0 (1)	29
Washout day 3†	10 (3)	10 (3)	0 (0)	10 (3)	0 (0)	0 (0)	0 (0)	0
Total number of specimens including baseline	159	149	10	113	25	20	1	13
Total number of specimens excluding baseline	144	134	10	98	25	20	1	15

* Maximum GC–MS value measured 5.2 ng/mL.
† Values in parentheses refer to 0.6 mg/day dose in Period 4.

Gustafson et al 2003 determined urinary THCCOOH excretion by GC/MS analysis in 4381 urine specimens collected before, during, and after 5 oral daily 0.39, 0.47, 7.5, and 14.8 mg THC/day to 7 participants. All urine voids were collected over the 10-week study. At the federally mandated immunoassay cutoff (50 µg/L), mean detection rates were <0.2% during ingestion of the two low doses typical of current hemp oil THC concentrations. These low oral THC data are 2-4 times higher than the mean and 90th percentile combined daily THC doses present in the 4 Fresh Hemp Food products and suggest that positive urine THCCOOH tests are possible but likely <0.05% of the mean and <0.1% of the 90% of the combined intake. Only four of 7 participants produced a mean of 3.1 positive urine

THCCOOH specimens after the 0.39 mg/day and 2 of 7 had a mean of 2.4 positive samples during and for the 10 days following 5 daily doses, range 0-13 total specimens). Positive cannabinoid urine tests ≥15 µg/L occurred as early as 14.6 h and as late as 110.5 h after the start of 5 daily doses. Mean detection rate for the 0.39 mg THC/d was 2.6% positive tests with a range of 0 to 10.3% positive tests at ≥15 µg/L. Mean detection rate for the 0.47 mg THC/d was 2.3% positive tests with a range of 0 to 8.7% positive tests at ≥15 µg/L. Maximum metabolite concentrations were 5.4 – 38.2 µg/L for the low THC/day doses. The two high doses produced mean detection rates of 23 – 46% with intermittent positive tests up to 118 h with an LOQ of 2.5 µg/L. Maximum metabolite concentrations were 19.0 – 436 µg/L for the high THC/day doses. Urine tests have a high likelihood of being positive after Marinol therapy. The high 14.8 mg dose was prepared from a high THC content hemp oil of 347 µg/g, and the 0.47 mg dose was from a 92 µg/g hemp oil. Individuals absorbed enough drug from hemp oils containing high THC concentrations to produce a positive sample by the first urine void.

% Positive urine samples at 15 µg/L GC-MS THCCOOH cutoff (Gustafson 2003.

THC dose mg/day	0	0.39	0.47	7.5	14.8
Specimens ≥15 µg/L					
Mean # (SD)	0	3.1 (4.6)	2.4 (0.7)	33.7 (14.0)	31.7 (14.4)
Range		0–13	0–9	10–48	7–47
Detection rate % over 15 d					
Mean	0	2.6 (3.7) %	2.3 (4.0)%	37.8 (19)%	31.9 (16.8)%
Range		0-10.3%	0-8.7%	10.4-62%	5.7-58.8%
1st Positive h					
Mean (SD)	0	55.9 (28.3)	19.9 (3.1)	21.1 (18.7)	23.1 (25.5)
Range		14.6-75.7	17.7-22.1	5.8-59.8	6.8-79.3
Last Positive h					
Mean (SD)	0	34.1 (28.0)	16.0	63.0 (32.4)	63.8 (18.3)
Range		13.4-66.0		23.8–111	29.5-84.2
1st Negative h					
Mean (SD)	0	2.6 (2.0)	1.7	36.1 (27.3)	22.7 (28.4)
Range		1.2-4.8		5.6-91.6	0.3-75.0
Cmax µg/L					
Mean (SD)	2.0	19.8 (13.1)	12.2 (9.6)	146 (143)	116 (93.2)
Range	0-3.5	7.3-38.2	5.4-31.0	26.0–436	19.0–264
Tmax					
Mean (SD)	0	99.9 (40)	85.9 (23.9)	97.8 (24.2)	104 (42.2)
Range		35.7-151	40.8-112	52.1-119	46.0-157

Urinary THCCOOH terminal elimination half-lives after oral THC ingestion

Table I. Urinary 11-Nor-9-Carboxy-$^{\Delta 9}$-Tetrahydrocannabinol Terminal Elimination Half-Lives (h) after Oral ^{9}-Tetrahydrocannabinol

Subject	N*	Elimination Half-lives (h) 7.5 mg/day† (Capsule)	N	14.8 mg/day (Liquid)	N	0.47 mg/day (Capsule)	N	0.39 mg/day (Liquid)
A	12	61.5	6	64.8	12	51.7	7	44.2
C	9	79.4	6	79.3	8	59.0	9	84.1
G	12	88.8	6	25.6	6	34.7	7	31.4
H	6	23.6	8	23.9	6	11.6	6	59.8
L	9	49.4	7	81.0	7	65.0	10	45.8
N	10	82.1	8	45.0	6	58.0	10	37.6
P	7	63.2	7	45.3	6	29.5	6	48.7
Mean (± SD)	–	64.0 (22.5)	–	52.1 (21.8)	–	44.2 (19.4)	–	50.3 (17.4)

* Number of points on excretion curve used to determine terminal elimination half-life.

† Dronabinol, synthetic ^{9}-tetrahydrocannabinol, 2.5 mg THC capsules.

Table 2. Cannabinoid immunoassay data for 50 µg/L cutoff.

THC dose, mg/day	Assay	Detection rate,[a] % Mean (SD)	Range	First positive,[b] h Mean (SD)	Range	Last positive,[c] h Mean (SD)	Range	First negative,[d] h Mean (SD)	Range
0	Emit II	0.0		0.0		0.0		0.0	
	DRI	0.0		0.0		0.0		0.0	
	CEDIA	0.0		0.0		0.0		0.0	
0.39	Emit II	0.2 (0.6)	0–1.6	104[e]		6.2[e]		1.2[e]	
	DRI	0.1 (0.3)	0–0.8	112.2[f]		6.2[f]		1.2[f]	
	CEDIA	0.0		0.0		0.0		0.0	
0.47	Emit II	0.7 (1.0)	0–1.9	28.5[g] (32.1)	29.5–87.1	0.0		3.1[g] (1.3)	1.8–4.3
	DRI	0.0		0.0		0.0		0.0	
	CEDIA	0.0		0.0		0.0		0.0	
7.5	Emit II	45.7 (14.1)	34.4–73.1	7.7 (5.6)	1.9–10.6	58.4 (24.3)	15.9–91.1	44.1 (25.4)	16.6–83.9
	DRI	39.4 (14.8)	21.9–66.7	13.0 (12.0)	1.9–36.8	53.6 (27.3)	15.9–87.9	30.3 (19.4)	16.3–71.0
	CEDIA	30.7 (14.4)	12.5–50.0	22.7 (17.8)	1.9–52.8	41.4 (23.5)	15.9–67.0	24.2 (11.7)	15.1–45.0
14.8	Emit II	41.2 (7.4)	32.6–54.4	7.4 (3.1)	4.0–13.0	65.6 (28.8)	19.3–117.5	32.1 (15.5)	5.7–53.9
	DRI	34.3 (9.6)	20.3–46.6	9.9 (4.4)	4.3–16.1	48.6 (20.3)	12.6–67.3	15.9 (16.0)	2.6–45.9
	CEDIA	23.5 (11.5)	5.7–37.5	17.3 (9.2)	4.3–32.5	46.6 (20.2)	12.6–67.3	13.5 (11.3)	2.6–29.0

[a] Detection rate: number of positive samples divided by total number of samples from first dose to last sample of the session × 100.

[b] First positive: time from first dose to first positive sample.

[c] Last positive: time from last dose to last positive sample.

[d] First negative: time from last dose to first negative sample.

[e] One of seven participants had two positive samples.

[f] One of seven participants had a single positive sample.

[g] Three participants had positive samples.

The results of these three studies are not consistent. Bosy and Cole 2000 found no positive urine tests after 7 daily doses of 0.10, 0.17, and 0.32 mg THC/d and testing urine samples up to 6 h after dosing and daily for 7 days. However, dosing 0.54 and 0.55 mg THC/d produced different results, with some urine samples positive after the 0.54 mg regimen and no samples positive after the 0.55 mg regimen. Only a single individual was administered each dose. Leson et al found no positive GC/MS results ≥15 µg/L following 4 daily up to 0.6 mg THC/day doses, but all urine specimens were not collected and analyzed. Gustafson et al 2003 administered 5 daily doses of 0.39 and 0.47 mg THC/d to 7 individuals and all urine specimens were collected and analyzed. Less than 0.2% of urine specimens screened positive at a 50 µg/L cutoff; however, in one subject receiving the 0.39 mg regimen, up to 10.3% of urine specimens were positive for THCCOOH ≥15 µg/L. Therefore, it is possible that individuals consuming 0.1938 mg THC/d in Fresh Hemp Foods, Ltd products (90^{th} percentile) over 5 days could screen positive for THCCOOH in urine at mandated cutoff concentrations. It is apparent that the vehicle is important for absorption, as a 0.47 mg THC/d hemp oil produced fewer positive urine specimens than the 0.39 mg THC/d dose in Gustafson et al. 2003.

The following manuscripts describe urine THCCOOH results after unknown oral THC doses.

Thirteen volunteers consumed 40 to 90 mL of hemp seed oils containing 7 to 150 µg/mL THC and others ate hemp food products (Alt et al, 1998). Some urine samples were positive for up to 80 h, and the highest serum concentrations were 6 µg/L. The total amounts ingested were not described.

Callaway et al, 1997 reported positive urine cannabinoid tests following ingestion of hemp seed oil, but the dose was unknown.

Costantino et al. 1997 reported that seven individuals ingesting 15 mL of hemp oil of an unknown THC concentration had positive urine drug tests by immunoassay at a cutoff of 20 µg/L for up to 48 h after ingestion. GC/MS analysis of urine specimens for THCCOOH, the primary urinary metabolite of THC, identified concentrations up to 78.6 µg/L. This is substantially above the federally mandated urine THCCOOH confirmation cutoff concentration of 15 µg/L. It is of concern that legitimate consumption of hemp oil may be interpreted as illicit drug exposure and that hemp oil ingestion may be used to conceal illicit cannabis use.

Commercially available snack bars and other foodstuffs prepared from pressed hemp seeds were ingested by volunteers (Fortner et al, 1997). Urine specimens were collected for 24 h after ingestion of the foodstuffs containing hemp seeds and tested for marijuana using an EMIT immunoassay and GC-MS. Specimens from individuals who ate one hemp seed bar demonstrated little marijuana immunoreactivity, and only one specimen screened positive at a 20-ng/mL cutoff. Specimens from individuals who ate two hemp seed bars showed increased immunoreactivity, and five specimens screened positive at a 20-ng/mL cutoff. A single specimen yielded a quantitative GC-MS value (0.6 µg/L), but it failed to meet reporting criteria. Several specimens from individuals who ate three

cookies made from hemp seed flour and butter screened positive at both 50- and 20-ng/mL cutoffs. Two specimens produced quantitative GC-MS values (0.7 and 3.1 ng/mL), but they failed to meet reporting criteria. Several specimens also tested positive with an FDA-approved on-site marijuana-screening device. Hemp seeds similar to those used in the foodstuffs did not demonstrate the presence of marijuana when tested by GC-MS. In this study, ingestion of hemp seed food products resulted in urine specimens that screened positive for marijuana. No specimens gave a GC-MS quantitative value above the limit of detection for marijuana.

Infant THC-exposure from breastfeeding based on estimated oral THC ingestion of 4 Fresh Hemp Foods products, hulled hemp seed, hemp protein powder, hemp protein concentrate and hemp oil by breastfeeding women.

There was a surprising lack of information related to this question in the published literature, with most articles focused on THC transfer during the perinatal period that included transfer during gestation and breastfeeding. Additional sources of data included websites and books on the topic.

The lack of controlled THC administration studies is obvious due to ethical and medical concerns with unnecessarily exposing the fetus and neonate to an exogenous compound. After extensive searching, I found no data relating ingestion of a known amount of THC by the mother and resultant breast milk THC concentrations. Neither are there controlled studies of THC administration to the infant and resultant infant plasma or urine THC concentrations. There are data estimating the volume of daily breast milk ingested by neonates and infants, effects on the fetus following in utero THC exposure and on the neonate following THC breast milk exposure. In addition, there are many reports advising for or against breastfeeding if the mother uses cannabis. The list of references reviewed for this report is included below.

A summary of the available literature on this topic is included. Data were available to estimate THC and 11-OH-THC daily exposure in breast milk. This calculation required data on plasma THC concentrations after oral THC intake. These data were available from the general safety data provided above for oral THC ingestion.

I evaluated the safety of THC exposure from Fresh Hemp Foods, Ltd hemp products including hulled hemp seed, hemp protein powder, hemp protein concentrate and hemp oil in the breastfeeding population. Fresh Hemp Foods Ltd provided the data on total amounts of each product consumed each day. Maximum cumulative THC exposure estimates for individuals over the age of two were based on the individual using the mean and 90th percentile amounts of all products in a single day. These data were used as mean and 90th percentile amounts of all products in a single day exposures for the lactating woman.

The THC calculations are based on the new Fresh Hemp Foods, Ltd standards for ≤4 µg THC/g as verified by the Quality Department for hulled hemp seed, hemp protein powder and hemp protein concentrate. The Fresh Hemp Foods, Ltd standard for hemp oil will be

the same as the Canadian Industrial Hemp Regulations requirement of ≤10 µg THC/g product. These values were used in determining daily THC intake if the recommended dose of all products were consumed each day.

Preclinical data

Reisner et al 1983 reported that only 0.2% of a labeled THC dose to squirrel monkeys appeared in their breast milk as hydrophilic & lipophilic metabolites within 24 hours; 0.01% of the dose appeared in the squirrel monkeys' offspring's urine. In lactating ewes, milk contained less radiolabel than their feces or urine, with radiolabel being detected 4 and 96 hours after THC injection (Mourh and Rowe 2017). Endocrine and behavioral changes were noted in suckling rodents after THC exposure in breast milk. THC acted as an in vivo weak competitor of the estrogen receptor, producing a primary estrogen effect in male & female rats (Warner et al 2014). In addition, THC was shown to reduce trophoblast cell proliferation and inhibit placenta development. In some studies, THC also produced hormonal changes reducing fertility. In animal models, THC crossed the placenta resulting in fetal plasma concentrations approximately 10% of maternal plasma concentrations after acute exposure; however, significantly higher fetal concentrations were observed after repetitive exposures (American College of Obstetricians & Gynecologists' Committee on Obstetric Practice 2015). Furthermore, these clinicians noted that although animal models may be poor surrogates for the human condition, endocannabinoids played key roles in normal fetal brain development, including neurotransmitter systems, and neuronal proliferation, migration, differentiation, and survival.

Battista et al 2014 noted that the endocannabinoid-CB1 receptor system is important for milk suckling, and in growth and development early in life. It was suggested that increased endocannabinoids and/or cannabinoids in milk might have relevant effects on breastfed newborns.

Murphy et al 1998 showed that THC inhibited gonadotropin, prolactin, growth hormone and thyroid-stimulating hormone release and stimulated release of corticotropin, inhibiting the quantity and reducing the quality of breast milk. In a recent review, Mourh and Rowe 2017 demonstrated that animals exposed to THC in milk had decreased prolactin concentrations and motor, neurobehavioral, & developmental effects. Lactating rats and non-pregnant rhesus monkeys displayed lower prolactin concentrations following THC injections, with maximum reductions of 74% (in male monkeys) and 85% (in female monkeys) over the first 30-90 minutes. There was a >70% reduction in prolactin from baseline after 1.25 mg/kg THC and >90% reduction following a 4 mg/kg dose over 30-60-min. In addition, lactating rats displayed lower blood oxytocin concentrations following THC dosing. THC prevented suckling-induced oxytocin secretion by the posterior pituitary, leading to a longer delay in initial ejection of milk and between successive ejections. Additional effects seen in monkeys & rats included lethargic behavior, reduced maternal care, and anxiety.

In milk samples from buffaloes eating cannabis plants, 50% contained cannabinoids (Ahmad and Ahmad 1990). Consumers of the contaminated milk were passively exposed to THC and metabolites were detectable in at least 30% of children up to the age of 3 years. Mouse pups whose mothers consumed food containing hashish during lactation weighed significantly less (by 10– 14%) than control pups from day 11 onward. The endocannabinoids play key roles in normal fetal brain development, including neuronal proliferation, migration, differentiation, & survival (The American College of Obstetricians & Gynecologists' Committee on Obstetric Practice 2015). Suggested that this occurred due to malnutrition (which could be the result of poorer milk production in the mothers or the direct influence of THC on the pups). The degree to which we can correlate effects of THC exposure in breast milk in animals and humans, especially neurobehavioral changes, is unclear. Also, the animal doses were frequently greater than those in human studies and were usually administered intravenously, making comparison of pharmacokinetics difficult. Exposure to cannabis includes exposure to numerous other cannabinoids, terpenes and polyaromatic hydrocarbons and might have different effects than synthetic IV THC.

Clinical data & recommendations

All drugs may pass into breast milk depending upon the drug's molecular weight and size, protein binding, amount of free drug in the blood, the lipophilicity of the drug, and the drug's pKa. Berlin and Briggs describe the transport of compounds across the mammary alveolar cells as primarily due to transcellular diffusion, in which small molecules (molecular weight 100-200) pass through with the flow of water due to hydrostatic or osmotic pressure differences. Larger molecular weight compounds may enter milk through intercellular diffusion, explaining the presence in breast milk of maternal proteins such as cow milk antigen and antibodies. The 3-dimensional shape of the molecule also may be a determinant in transfer to breast milk. Ionophore diffusion facilitates charged ions transfer and carrier proteins transfer other substances. THC is a highly lipophilic compound and transfers readily into breast milk.

Perez-Reyes and Wall reported that cannabis & metabolites pass into breast milk in concentrations dependent upon the amount of drug ingested by the mother. These authors published the one and only breast milk/plasma THC ratio data (one single paired sample) as the primary source for THC concentrating in breast milk, and many recommendations to not breastfeed if the mother continues to use marijuana. Breast milk from two chronic frequent cannabis users were studied. There were no data on the amount of THC ingested by the women, thus, there are no data on maternal THC intake per event or per day. Woman #1 reported smoking cannabis once per day and woman #2 reported smoking approximately seven times per day. A single matched plasma and breast milk sample was collected from woman #2, as described as under steady state conditions. THC concentrations in the plasma were 7.2 µg/L THC, 2.5 µg/L 11-OH-THC, and 19 µg/L THCCOOH, and 60.3, 1.1, and 1.6 µg/L THC, 11-OH-THC and THCCOOH concentrations in the breast milk, respectively. These are the sole data supporting a human THC breast milk/plasma ratio of 8.4, indicating that THC is concentrated up to 8-fold in breast milk compared to maternal plasma. At these concentrations, it was

estimated that the infant's daily THC exposure was 0.01 to 0.1 mg THC/day. There were no observable side effects in the infant receiving this amount of THC (Hale 2012). Concentrations in woman #1's breast milk were 105 µg/L THC, with no detectable 11-OH-THC and THCCOOH. Marcei et al 2011 reported cannabinoid concentrations in breast milk from one lactating woman of 86 µg/L THC and 5 µg/L 11-OH-THC, but maternal plasma was not tested. Also, the duration of THC in the breast milk after cessation of use is unknown (Wang 2016). The evidence is unclear if breastfeeding benefits (nutrition, immune protective factors, sudden infant death syndrome (SIDS), bonding, etc.) outweigh potential THC breast milk exposure risks.

Most experts refer to the effects of in utero cannabis exposure as a means of evaluating potential adverse developmental outcomes; however, this is inappropriate to determine the risk of ingesting THC in breast milk. Blood THC concentrations in pregnant women who smoke or vaporize cannabis are much higher (can be as high as 200-400 µg/L immediately after inhalation, and typical abused oral THC doses range from 10-100 mg or more. Furthermore, most women who use cannabis during pregnancy continue use during breastfeeding, making it difficult to assign causation to one source of exposure.

Reported cannabis use prevalence rates in pregnancy vary from 3-34% (Metz & Stickrath 2015), with cannabis the most common illicit drug taken during gestation. Sixty percent of women who used cannabis in the year prior to pregnancy continued to use more than 10 joints per week, indicating that many women continue use throughout pregnancy. Identification of cannabis use in the mother at birth does not differentiate the amount of use and designation of occasional or chronic frequent use. The American College of Obstetricians & Gynecologists' Committee on Obstetric Practice (2015) estimate that 48–60% of cannabis users continue use during pregnancy, with many women believing that it is relatively safe to use during pregnancy and less expensive than tobacco. Colorado's largest local Tri-County health department serves >26 % of the population (Wang 2016). Their Women's Infants & Children (WIC) Program survey revealed 7.4% of mothers aged <30 years & 4% of mothers >30 years are current cannabis users. Of all cannabis users (past, ever, current), 35.8% said they used at some point during pregnancy, 41% since the baby was born & 18% while breastfeeding.

Breast milk samples (N=109) from lactating women were analyzed for cannabinoids and questionnaires were completed about their drug use during pregnancy and while breastfeeding (Mourh & Rowe 2017). Of 19 women reporting drug use, 1 had 20 µg/L THC in her breast milk, with no detectable cannabinol or cannabidiol, and her urine was positive for cannabinoids. Another woman not reporting drug use had 31 µg/L THC in her breast milk with no detectable cannabidiol. Infant THC exposure was estimated as 2 and 3.1 µg THC/100 mL breast milk. Oral THC bioavailability is estimated to be 6-12%; using the higher 12% oral THC bioavailability, infant exposure was estimated at 0.24 & 0.37 µg THC. Maternal THC dose and dosing time in relation to breast milk collection were unknown.

Astley & Little 1990 suggested that cannabis use by the breastfeeding mother during the first month of life could impair neurodevelopment. Glial and myelin formation in the infant

brain continues after birth during breastfeeding and might lead to sedation and weakness. Other disadvantages include the possibility that THC in breast milk may decrease the production, volume, composition & ejection of breastmilk, resulting in poor feeding patterns (Liston 1998).

The American Academy Pediatrics Committee on Drugs 2001 noted that there were no reported adverse effects of cannabis ingestion from breast milk in published studies.

In the WHO Breastfeeding 1997 Report, it was estimated that in one feeding the infant will ingest 0.8% of the weight-adjusted maternal intake of 1 joint (Garry et al 1990). The authors suggest that mothers who use cannabis must stop breastfeeding, or ask for medical assistance to stop cannabis use, to provide their babies with all the benefits of human milk. THC in breast milk could sedate the infant and result in growth delays.

Liston 1998 suggested that infants exposed to marijuana via breast milk show signs of sedation, reduced muscular tonus, & poor sucking. Two studies evaluated the effects of cannabis use by the lactating mother on their child's development. In the first, no significant differences were found in terms of weaning, growth, and mental or motor development with regard to age. The second study found that cannabis exposure via the mother's milk during the first month postpartum appeared to be associated with a decrease in infant motor development at one year of age. Infants exposed to cannabis for more than half of the days during the 1st trimester of gestation or 1st month of lactation had significantly lower mean Psychomotor Development. Other factors come into play like cannabis exposure during pregnancy, passive exposure to cannabis smoke in ambient air, or the quality of the mother-child relationship. There are no studies relating to the long-term effects of marijuana exposure through breast milk. There are almost no studies of lactation exposure only; the infant was usually prenatally exposed and almost all of their mothers continued use after birth (Reece-Stremtan et. al 2015).

Despite preclinical studies suggesting that THC exposure during breastfeeding can reduce the quality and quantity of breast milk, these effects have not been confirmed in humans (Sharma et al 2012). According to Warner et al 2014, the identification of side effects in the lactation-exposed infant are inconsistent and there are no long-term outcome studies. Hotham and Hotham 2015 stated that the most commonly used drugs are relatively safe for breastfed babies. Drugs contraindicated during breastfeeding include anticancer drugs, lithium, oral retinoids, iodine, amiodarone & gold salts. Estimated intake by an exclusively breastfed baby is 150 mL/kg/d.

Hale 2012 placed cannabis in highest risk category, L5 or Hazardous, stating that using cannabis during breastfeeding clearly outweighs the benefits of breastfeeding; however, many lactation experts disagree with this conclusion. Jansson et al 2015 noted the importance of active, passive (from maternal sidestream smoke) and cumulative exposures to breastfed infants must be considered. THC delivered via lactation to the infant may affect the ontogeny of various neurotransmitter systems, leading to changes in neurobiological functioning. The authors describe the recent new recommendation by the Academy of Breastfeeding Medicine as erroneous & disappointing, and question why

a recommendation would err on the side of breastfeeding with potentially toxic exposures and other risk factors that could portend short- & long-term infant harm.

Most adverse effects of drugs in breast milk occurred in newborns under 2 months and rarely in those older than 6 months (Jansson et al 2015). A follow-up study of 1-year-old breastfed infants of mothers who used cannabis found some impairment in motor development, although researchers found it difficult to determine whether in utero exposure or breastfeeding was the greater influence. Women should be encouraged to stop using cannabis & avoid exposure of the baby to second-hand smoke.

In a survey of mothers by lactation experts, 15% of women reported using cannabis during breastfeeding (Bergeria and Heil 2015). Forty-four percent of the lactation experts reported that their recommendations were based on marijuana use factors like the severity of maternal use. Another 41% reported recommending continued breastfeeding because benefits outweigh harms, and the remaining 15% recommended that a woman should stop breastfeeding if she cannot stop using marijuana. Infants whose mothers used marijuana during lactation (n = 27) had similar growth outcomes, mental & motor development, & weaning ages compared with infants of non-using mothers (n=35). In contrast in a larger study, significant deficits in motor development was found at 1 year of age among exposed infants (n = 68) versus matched controls (n = 68); however, marijuana exposure occurred during the first trimester of pregnancy & the first month of lactation, making it difficult to determine which period of exposure had a stronger influence on infant motor development.

The American College of Obstetricians & Gynecologists Committee on Obstetric Practice released new recommendations on breastfeeding and marijuana use in 2015. Obstetricians and gynecologists should be discouraged from prescribing or suggesting marijuana use for medicinal purposes during preconception, pregnancy, & lactation. There are insufficient data to evaluate effects of marijuana use on infants during lactation & breastfeeding; thus, marijuana use is discouraged. In animal models, THC crossed the placenta, producing fetal plasma levels that were approximately 10% of maternal levels after acute exposure. Significantly higher fetal concentrations were observed after repetitive exposures. Animal models demonstrate that endocannabinoids play key roles in normal fetal brain development, including in neurotransmitter systems, & neuronal proliferation, migration, differentiation, & survival. Breastfeeding women should be informed that the potential risks of exposure to marijuana metabolites are unknown & should be encouraged to discontinue marijuana use.

The strongest determinant of breast milk medication concentration is the non-protein bound maternal plasma drug concentration (Newton & Hale 2015). THC is a highly bound drug that should result in lower breast milk concentration; however, THC has a large volume of distribution (Vd) in maternal compartments, with especially rapid tissue sequestration that will reduce maternal free drug concentrations. However, THC is a highly lipid soluble drug that passes through the alveolar cells more easily and is sequestered in milk. Marijuana is an example of a highly lipid soluble drug with higher concentrations in breastmilk based on a single paired maternal plasma and breast milk

sample. THC's pKa is 10.2, leading to ion trapping in milk due to the higher ionization at lower pH. The relative infant dose (RID) is amount of the drug dose to the breastfeeding infant. The infant dose (mg/kg/d) is divided by the mother's dose (mg/kg/d). An RID <10% is considered acceptable in healthy postnatal infants. The bioavailability of the drug in the infant must be known. THC's oral bioavailability is low- estimated to be about 6-12% in adults. Premature, term or ill neonates could have higher absorption rate than adults. The ultimate measure of drug in breast milk is the infant's plasma blood concentrations but none have been published. Mothers are advised to choose drugs with a low M/P ratio and to avoid drugs with a long half-life (12-24 h).

The Academy of Breastfeeding Medicine stated that "A recommendation of abstaining from any marijuana use is warranted. At this time, although the data are not strong enough to recommend not breastfeeding with any marijuana use, we urge caution (Foeller & Lyell 2017).

We included the data for marijuana use during breastfeeding because no data are available for oral THC dosing and breastfeeding; however, maternal blood THC concentrations following maternal cannabis smoking or vaporization can be as high as 200-300 µg/L, while blood THC concentrations after oral THC from ingestion of Fresh Hemp foods is expected to be low.

Based on the studies administering known quantities of THC and blood/plasma/serum concentrations, we can estimate the blood concentrations that would result from intake of 0.0968 (mean daily mg THC from 4 Fresh Hemp Foods, Ltd products) to 0.1938 (90^{th} percentile daily mg THC from 4 Fresh Hemp Foods, Ltd. Products) mg oral THC. Stott et al 2013 administered two Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses (total 5.4 mg THC) to adults. There are no infant THC administration data. The mean plasma Cmax was <1.2 µg/L THC and <2 µg/L 11-OH-THC. The mean daily amount (0.0968 mg) and 90^{th} percentile (0.1938) of THC exposure from ingesting all 4 Fresh Hemp Foods, Ltd. Products is 55- and 27-fold lower than this exposure, respectively. These data would estimate the plasma Cmax in the breastfeeding mother assuming a 0.0968 mg daily dose as <0.02 µg/L THC and <0.04 µg/L 11-OH-THC, and if the highly conservative 0.1938 mg THC dose is assumed, plasma Cmax in the mother of <0.04 µg/L THC and <0.07 µg/L 11-OH-THC.

Furthermore, based on the Monte Carlo simulation, the maximum THC exposure was estimated at 0.1025 mg 99.9% of the time based on ingestion of all 4 hemp food products. This amount is 53 times lower than the 5.4 mg THC Stott et al dose, estimating a maximum THC concentration of <0.02 µg/L and <0.04 µg/L.

In a single maternal plasma and breast milk pair, the THC plasma to breast milk ratio was 8.4. Based on this ratio and the mean-90% maternal plasma THC concentrations the maximum THC concentration in the breast milk would be between 0.17-0.34 µg/L. There are no data on breast milk/plasma ratios, but if one assumed a similar distribution for 11-OH-THC into breast milk, maximum 11-OH-THC concentrations in breast milk would be 0.34-0.59 µg/L.

The estimate of daily breast milk intake is 150 mL/kg/day. Our estimates of maximum THC concentration in breast milk and daily intake would suggest THC intake of 0.05 – 0.09 µg/kg/day THC. As 11-OH-THC is equipotent to THC, assuming the breast milk to plasma ratio is also 8.4, the total active cannabinoids exposure for the infant is estimated to be <0.08-0.14 µg/kg/day. Gustafson et al 2014 administered 0.39 and 0.47 mg THC per day for 5 days, resulting in non-detectable THC concentrations in human plasma. These doses are 2-4 times the dose a breastfeeding mother would consume with all 4 hemp products. This low-level exposure is not expected to produce adverse developmental outcomes in the infant whose mother consumes the maximum amount of all 4 Fresh Hemp Foods, Ltd. per day.

Estimated THC food daily intake mg	Maternal THC plasma Cmax µg/L	Maternal 11-OH-THC plasma Cmax µg/L	Breast Milk THC Cmax µg/L B/P 8.4	Breast Milk 11-OH-THC Cmax µg/L B/P 8.4	Infant THC Exposure µg/kg/day*	Infant 11-OH-THC Exposure µg/kg/day
0.0968	<0.02	<0.04	<0.17	<0.34	<0.03	<0.05
0.1938	<0.04	<0.07	<0.34	<0.59	<0.05	<0.09
0.1025	<0.02	<0.04	<0.17	<0.34	<0.03	<0.05
5.4@	<1.2	<2	<10.1	<16.8	<1.5	<2.5
0.39#	ND	ND				
0.47#	ND	ND				

@Stott et al 2013 oral mucosa THC dose; #Gustafson et al 2014 oral THC dose
*150 mL/kg/day infant breast milk dose

Furthermore, Stott et al 2013 also administered the 5.4 mg THC/day dose for 9 consecutive days and showed that THC and 11-OH-THC concentrations did not accumulate over time. This also demonstrates that daily use of the 4 Fresh Hemp Foods, Ltd doses that are much lower than the 5.4 mg Stott dose should not accumulate. At birth, a 10 lb. (4.55 kg) infant would receive about 0.14-0.23 µg/day THC and 0.23-0.41 µg/day 11-OH-THC. The total active cannabinoid dose would be approximately 0.37-0.64 µg/day. The oral bioavailability of THC and 11-OH-THC is low, estimated to be 6-12% in adults; bioavailability could be different in the infant although first pass metabolism would still reduce active cannabinoid exposure. This low concentration of active cannabinoids should not produce adverse developmental effects.

References for general safety, blood/plasma/serum THC concentrations and urine cannabinoid tests

Alt A, Reinhardt G. Positive cannabis results in urine and blood samples after consumption of hemp food products. J Anal Toxicol 1998;22:80–1.

Bosy TZ, Cole KA. Consumption and quantitation of delta-9-tetrahydrocannabinol in commercially available hemp seed oil products. J Anal Toxicol 2000;24:562–6.

Brenneisen R, Egli A, Elsohly MA, et al. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int J Clin Pharmacol Ther 1996; 34 (10): 446-52.

Callaway JC, Weeks RA, Raymon LP, Walls HC, Hearn WL. A positive THC urinalysis from hemp (Cannabis) seed oil. J Anal Toxicol 1997;21:319–20.

Cone EJ, Johnson RF, Paul BD, Mell LD, Mitchell J. Marijuana-laced brownies: Behavioral effects, physiologic effects, and urinalysis in humans following ingestion. J Anal Toxicol 1988;12:169-175.

Costantino A, Schwartz RH, Kaplan P. Hemp oil ingestion causes positive urine tests for 9-tetrahydrocanabinol carboxylic acid. J Anal Toxicol 1997;21:482–5.

Crew S. Hemp Oil Canada Inc., Ste. Agathe, MB, Canada. Development of hemp food products and processes. Report prepared for the Agricultural Research and Development Initiative (ARDI), Winnipeg, MB, Canada, 2000).

ElSohly MA, deWit H, Wachtel SR, Feng S, Murphy TP. Delta-9- tetrahydrocannabivarin as a marker for the ingestion of marijuana versus Marinol: results of a clinical study. J Anal Toxicol 2001; 25:565–71.

Fortner N, Fogerson R, Lindman D, Iversen T, Armbruster D. Marijuana-positive urine test results from consumption of hemp seeds in food products. J Anal Toxicol 1997;21:476–81.

Frytak S, Moertel CG, Rubin J. Metabolic studies of delta-9-tetrahydrocannabinol in cancer patients. Cancer Treat Rep 1984; 68 (12): 1427-31.

Goodwin RS, Gustafson RA, Barnes A, Nebro W, Moolchan ET, Huestis MA. Delta-9-tetrahydrocannabinol, 11-hydroxy-delta-9-tetrahydrocannabinol and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol in human plasma following controlled oral administration of cannabinoids. *Therapeutic Drug Monitoring,* 2006 Aug; 28(4): 545-551.

Gustafson RA, Levine B, Stout PR, Klette KL, George MP, Moolchan ET and Huestis MA. Urinary cannabinoid detection times following controlled oral administration of delta-9-tetrahydrocannabinol to humans. *Clinical Chemistry*, 2003 Jul; 49(7):1114-1124.

Gustafson RA, Kim I, Stout PR, Klette KL, George MP, Moolchan ET, Levine B and Huestis MA. Urinary pharmacokinetics of 11-nor-9-carboxy-delta-9-tetrahydrocannabinol after controlled oral delta-9-tetrahydrocannabinol administration. *Journal Analytical Toxicology,* 2004 Apr; 28(3):160-167.

Hollister LE, Gillespie HK, Ohlsson A, et al. Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? J Clin Pharmacol 1981; 21 (8-9 Suppl.):171S-7S.

Huestis MA, Abulseoud O, Sempio C, Andersson M, Newmeyer MN, (unpublished urine data following smoked, vaporized and oral administration of 50.6 mg THC).

Indorato F, Liberto A, Ledda C, Romano G, Barbera N. The therapeutic use of cannabinoids: Forensic aspects. Forensic Science International 2016;265:200–203.

Interpretation of listing of “tetrahydrocannabinol” in Schedule I [Interpretive Rule]. Federal Register 2001;195:51530–44.

Law B, Mason PA, Moffat AC, et al. Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin. J Pharm Pharmacol 1984; 36 (5):289-94.

Lehmann T, Sager F, Brenneisen R. Excretion of cannabinoids in urine after ingestion of cannabis seed oil. J Anal Toxicol 1997;21:373–5.

Leson G, Pless P, Grotenhermen F, Kalant H, ElSohly MA. Evaluating the impact of hemp food consumption on workplace drug tests. J Anal Toxicol 2001;25:691–8.

Mölleken and H. Husmann. Cannabinoids in seed extracts of Cannabis sativa cultivars. J. Int. Hemp Assoc. 4: 1, 76–79 (1997).

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther. 1980 Sep;28(3):409-16.

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma levels of delta 9-tetrahydrocannabinol after intravenous, oral, and smoke administration. NIDA Res Monogr. 1981 Feb;34:250-6.

Ohlsson A, Agurell S, Lindgren JE, Gillespie HK, Hollister LE. Pharmacokinetic studies of delta-1-tetrahydrocannabinol in man. In Pharmacokinetics and pharmacodynamics of psychoactive drugs. Barnett G and Chiang CN (Eds). 1985 Mosby Yearbook, Inc. Volume 4 Pages 75-92.

Perez-Reyes M, Lipton MA, Timmons MC, Wall ME, Brine DR, Davis KH. Pharmacology of orally administered delta-9-tetrahydrocannabinol. Clinical Pharmacology Therapeutics 1973;14:48-55.

Research, Health Protection Branch, Health Canada. Industrial hemp technical manual: TPP-BDS-004 – Basic method for determination of THC in hempseed oil, 1992.

Sadler BM, Wall ME, Perez-Reyes M. The pharmacokinetics of delta-9 - tetrahydrocannabinol after simultaneous intravenous and oral administration. In: Agurell S, Dewey WL, Willette RE, eds. The cannabinoids: chemical, pharmacologic, and therapeutic aspects. New York: Academic Press, 1984:227–38.

Sporkert F, Pragst F, Ploner CJ, Tschirch A, Stadelmann AM. Pharmacokinetic investigations and delta-9-tetrahydrocannabinol and its metabolites after single administration of 10 mg Marinol in attendance of a psychiatric study. The Annual Meeting of The International Association of Forensic Toxicologists, Prague, Czech Republic. 2001.

Struempler RE, Nelson G, Urry FM. A positive cannabinoids workplace drug test following the ingestion of commercially available hemp seed oil. J Anal Toxicol 1997;21:283–5.

Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray.
Eur J Clin Pharmacol. 2013 May;69(5):1135-47. doi: 10.1007/s00228-012-1441-0. Epub 2012 Nov 22.

Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. AIDS Res Hum Retroviruses 1997; 13 (4):305-15.

Wall ME, Perez-Reyes M. The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man. J Clin Pharmacol 1981; 21 (8-9 Suppl.): 178S-89S.

Wall ME, Sadler BM, Brine D, et al. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol, in men and women. Clin Pharmacol Ther 1983; 34 (3): 352-63.

References for determining infant THC exposure from breastfeeding

Ahmad GR, Ahmad N. Passive consumption of marijuana through milk: a low level chronic exposure to delta-9-tetrahydrocannabinol(THC). J Toxicol Clin Toxicol 1990;28(2):255–260.

Alaniz VI, Liss J, Metz TD, Stickrath E. Cannabinoid hyperemesis syndrome: a cause of refractory nausea and vomiting in pregnancy. Obstet Gynecol. 2015;125(6):1484-6.

American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk Pediatrics 2001;108(3):776-789.

Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. Neurotoxicol Teratol 1990;12(2):161–168.

Battista N, Sergi M, Montesano C, Napoletano S, Compagnone D, Maccarrone M. Analytical approaches for the determination of phytocannabinoids and endocannabinoids in human matrices. Drug Testing Analysis 2014;6:7–16.

Bergeria CL, Heil SH, Surveying Lactation Professionals Regarding Marijuana Use and Breastfeeding. Breastfeeding Medicine 2015;10(7):377-380.

Berlin CM, Briggs GG. Drugs and chemicals in human milk. Seminars in Fetal & Neonatal Medicine. 2005;10:149e159.

Brooks E, Gundersen DC, Flynn E, Brooks-Russell A, Bull S. The clinical implications of legalizing marijuana: Are physician and non-physician providers prepared? Addictive Behaviors 72 (2017) 1–7.

Burns L, Mattick RP, Cooke M. The use of record linkage to examine illicit drug use in pregnancy. Addiction 2006;101(6):873–882.

Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. Neurotoxicol Teratol 2011;33(1):129–136.

DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P et al. Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. Biol Psychiatry 2011;70(8):763–769.

Dotters-Katz SK, Smid MC, Manuck TA, Metz TD. Risk of neonatal and childhood morbidity among preterm infants exposed to marijuana. J Matern Fetal Neonatal Med. 2017;30(24):2933-2939.

El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatry 2009;48(12):1173–1181.

El Marroun H, Hudziak JJ, Tiemeier H, Creemers H, Steegers EA, Jaddoe VW et al. Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. Drug Alcohol Depend 2011;118(2-3):470–474.

Escuder-Vieco D, Garcia-Algar Ó, Pichini S, Pacifici R, García-Lara NR, Pallás-Alonso CR. Validation of a screening questionnaire for a human milk bank to determine the presence of illegal drugs, nicotine, and caffeine. J Pediatr. 2014;164(4):811-4.

Escuder-Vieco D, Garcia-Algar Ó, Joya X, Marchei E, Pichini S, Pacifici R, Pallás-Alonso CR. Breast Milk and Hair Testing to Detect Illegal Drugs, Nicotine, and Caffeine in Donors to a Human Milk Bank. Journal of Human Lactation 2016;32(3):542-5.

Foeller ME, Lyell DJ. Marijuana Use in Pregnancy: Concerns in an Evolving Era. J Midwifery Womens Health 2017;62:363–367.

Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 1999;21(5):513–525.

Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2003;25(4):427–436.

Garry A, Rigourd V, Amirouche A, Fauroux V, Aubry S, Serreau R. Cannabis and Breastfeeding. J Toxicol. 2009:596149.

Gleason KA, Birnbaum SG, Shukla A, Ghose S. Susceptibility of the adolescent brain to cannabinoids: long-term hippocampal effects and relevance to schizophrenia. Transl Psychiatry 2012;2:e199.

Godding V, Bonnier C, Fiasse L, Michel M, Longueville E, Lebecque P et al. Does in utero exposure to heavy maternal smoking induce nicotine withdrawal symptoms in neonates? Pediatr Res 2004;55(4):645–651.

Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. Neurotoxicol Teratol 2000;22(3):325–336.

Goldschmidt L, Richardson GA, Willford JA, Severtson SG, Day NL. School achievement in 14-year-old youths prenatally exposed to marijuana. Neurotoxicol Teratol 2012; 34(1):161–167.

Hale TW. Medications and Mother's Milk, 15th ed. Plano, TX: Hale Publishing, 2012.

Hotham N, Hotham E. Drugs in breastfeeding. Australian Prescriber. 2015;38;5:156-160.

Jansson LM, Bunik M, Bogen DL. Lactation and the Marijuana-Using Mother Breastfeeding Medicine 2015;10(6):1.

Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, Abdel-Latif ME, Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology 2014;34:417–424.

Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, Abdel-Latif ME, Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology 2014;34(6):417-24.

Jarlenski M, Zank J, Tarr J, Chang JC. Public health messages about perinatal marijuana use in an evolving policy context. Substance Abuse. 2017;38(1):48-54.

Kacew S Adverse effects of drugs and chemicals in breast milk on the nursing infant. J Clin Pharmacol. 1993;33(3):213-21.

Khare M, Taylor AH, Konje JC, Bell SC. Delta9-tetrahydrocannabinol inhibits cytotrophoblast cell proliferation & modulates gene transcription. Mol Hum Reprod 2006;12(5):321–333.

Klonoff-Cohen H, Lam-Kruglick P. Maternal and paternal recreational drug use and sudden infant death syndrome. Arch Pediatr Adolesc Med 2001;155(7):765–770.

Liston J. Breastfeeding and the use of recreational drugs – alcohol, caffeine, nicotine and marijuana. Breastfeeding Review 1998;6(2):27-30.

Marchei E, Escuder D, Pallas CR, Garcia-Algar O, Gómez A, Friguls B, Pellegrini M, Pichini S. Simultaneous analysis of frequently used licit and illicit psychoactive drugs in breast milk by liquid chromatography tandem mass spectrometry. J Pharm Biomed Anal. 2011;55(2):309-16.

Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. Am J Obstet Gynecol. 2015;213(6):761-78.

Metz TD, Allshouse AA, Hogue CJ, Goldenberg RL, Dudley DJ, Varner MW, Conway DL, Saade GR, Silver RM. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. Am J Obstet Gynecol. 2017;217(4):478.e1-478.

Mourh J, Rowe H. Marijuana and Breastfeeding: Applicability of the Current Literature to Clinical Practice. Breastfeed Med. Epub 2017 Sep 5.

Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M et al. Metabolic effects of chronic cannabis smoking. Diabetes Care 2013;36(8):2415–2422.

Murphy LL, Munoz RM, Adrian BA, Villanu´ a MA. Function of cannabinoid receptors in the neuroendocrine regulation of hormone secretion. Neurobiol Dis 1998;5(6PtB):432–446.

Neugebauer R, Kline J, Stein Z, Shrout P, Warburton D, Susser M. Association of stressful life events with chromosomally normal spontaneous abortion. Am J Epidemiol 1996;143:588–596.

Newton ER & Hale TW. Drugs in Breast Milk. Clinical Obstetrics and Gynecology. 2015;58(4):868–884.

Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. N Engl J Med 1982; 307(13): 819–820.

Reece-Stremtan S, Marinelli KA. The Academy of Breastfeeding Medicine. ABM Clinical Protocol #21: Guidelines for Breastfeeding and Substance Use or Substance Use Disorder, Revised 2015. Breastfeeding Medicine 2015:10(3);135-141.

Reisner SH, Eisenberg NH, Stahl B, Hauser GJ. Maternal medications and breast-feeding. Dev Pharmacol Ther. 1983;6(5):285-304.

Sharma P, Murthy P, Bharath MMS. Chemistry, Metabolism, and Toxicology of Cannabis: Clinical Implications. *Iran J Psychiatry* 2012;7(4):149-156.

Sipsma A, Divney AA, Magriples U, Hansen N, Gordon D, Kershaw T. Breastfeeding Intentions Among Pregnant Adolescents and Young Adults and Their Partners. Breastfeeding Medicine 2013;8(4):374-380.

Sipsma A, Magriples U, Divney AA, Gordon D, Gabzdyl, E, Kershaw T. Breastfeeding behavior among adolescents: Initiation, duration, and exclusivity. J Adolesc Health. 2013;53(3):394–400.

Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. Neurotoxicol Teratol 2006;28(2):286–295.

Smithers LG, Lynch JW, Yang S, Dahhou M, Kramer MS. Impact of neonatal growth on IQ and behavior at early school age. Pediatrics 2013;132(1):e53–e60.

The American College of Obstetricians and Gynecologists. Committee on Obstetric Practice. Marijuana Use During Pregnancy and Lactation. 2015;126(1):234-8.

Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. In utero marijuana exposure associated with abnormal amygdala dopamine D2 gene expression in the human fetus. Biol Psychiatry 2004;56(12):909–915.

Warner TD, Roussos-Ross D, Behnke M. It’s Not Your Mother’s Marijuana: Effects on Maternal-Fetal Health and the Developing Child. *Clin Perinatol*. 2014;41(4):877–894.

Warner TD, Roussos-Ross D, Behnke. It's not your mother's marijuana: effects on maternal-fetal health and the developing child. Clin Perinatol. 2014;41(4):877-94.
Wang GS Pediatric Concerns Due to Expanded Cannabis Use: Unintended Consequences of Legalization. J. Med. Toxicol. 2017 Mar;13(1):99-105.

10 pages of Curriculum Vitae removed in accordance with the Privacy Act of 1974.

FDA ATTY

CONTRACT IN-HOUSE COUNSEL & CONSULTANTS, LLC

September 14, 2018

Via E-Mail
Patrick Cournoyer, Ph.D.
Consumer Safety Officer
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration

Re: FDA Additional Questions Regarding GRN 765, 771, and 778

Dr. Cournoyer,

Thank you again for your time by telephone on August 16, 2018, and subsequent e-mail on August 31, 2018. In the pages that follow are the detailed replies to your questions.

This response adds nearly 100-pages and dozens of new references to Fresh Hemp Foods GRAS notices. As described below, there is an abundance of good evidence for the consumption of hemp as described in GRN 765, 771, and 778, including the historical record, the animal studies where no lethal dose could be obtained in large mammals and where high dose testing typically produced small, transitory, toxicological effects, and in the human clinical studies.

We feel strongly that GRNs 765, 771, and 778 fully satisfies the "reasonable certainty of no harm standard" (21 C.F.R. 170.30).

Kind Regards,

Digitally signed by Marc C. Sanchez, Esq.
Date: 2018.09.14 16:29:31 -04'00'
Adobe Acrobat Reader version: 2018.011.20058

(b) (6)

Marc C. Sanchez, Esq.
Regulatory Counsel
Fresh Hemp Foods Ltd.

Food
Medical Device
Dietary Supplements

Research Triangle, NC | Washington D.C.
Ph. 202.765.4491 | Fax 202.464.2529
www.fdaatty.com

Responses to Additional Information Request

Table of Contents

1. Animal toxicology data

Traditional animal toxicological studies typically form the foundation of scientific food safety assessments. NOAEL or LOAEL values from animal studies are often used to calculate a margin of exposure, which facilitates risk management. Animal studies can also be useful for addressing specific endpoints such as developmental and reproductive toxicity. Amending your safety narrative to include a robust discussion of animal toxicology data would serve as an appropriate context for the human data discussed in the original submission. You may wish to consult EFSA's scientific opinion (2015), which includes a detailed discussion of animal studies and could serve as a useful reference for a revised safety narrative.

Response:

All preclinical studies referenced in the "EFSA Scientific Opinion on the risks for human health related to the presence of Δ9-tetrahydrocannabinol (THC) in milk and other food of animal origin", and in the ANZFA Final Assessment Report Application A360 Use of Industrial Hemp as a Novel Food were reviewed. In addition, a brief literature search was performed in PubMed for any recently published articles that could be informative.

Review of Experimental Animal Studies on THC Effects

THC Toxicity LD50

The median lethal doses of oral THC in rats and mice were 666 mg Δ9-THC/kg bw and 482 mg Δ9-THC/kg bw, respectively (Phillips et al., 1971). No deaths occurred when dogs were administered 3000 mg/kg bw oral THC and rhesus monkeys received 9000 mg/kg bw oral THC (Thompson et al., 1973a). To date, there are no human deaths attributed to oral THC self-administration; therefore, there is no established human lethal dose (Huestis review of published literature).

Effects of THC on the Endocrine Hormone System

According to the ANZFA Final Assessment Report endocrine hormone changes were the most sensitive indicator of oral THC administration in experimental animals; however, the changes were transitory and not strongly dose-related. Following intramuscular injection of 0.625 mg/kg bw or greater THC to female rats, luteinizing (LH) and follicle stimulating (FSH) hormones were reduced (Smith et al. 1978). THC also inhibited the surges of LH and FSH that are essential for ovulation by suppressing normal circulating levels of LH in female rats and monkeys (Smith et al., 1979). In addition, the normal rhythm of menstrual cycles in monkeys were disrupted. THC altered pituitary secretion of LH, FSH and prolactin when administered acutely or repeatedly to intact and ovariectomized female rats, (Steger et al., 1980, 1981). Oral THC administration of 0.5 mg/kg to rats reduced LH concentrations 60 min after dosing but not at 30 or 120 min (Murphy et. al.1990). Similarly, single oral 0.1, 1 or 10 mg/kg bw THC doses reduced plasma LH and testosterone at 60 min, but there was no dose-response effect (Steger et. al. 1990).

THC and other cannabinoids may affect the hypothalamic-pituitary-gonadal axis mainly via the interaction with CB1 receptors expressed in the hypothalamus, resulting in a depression of the reproductive hormones, prolactin, and growth hormone (EFSA Journal 2015;13(6):4141). Lower oral doses and intravenous (IV) and intraperitoneal (IP) routes of administration led to minor changes, suggesting a lack of relevance of these changes. THC increases the secretion of adrenocorticotropin (ACTH) that stimulates the synthesis of glucocorticoids in the adrenal gland. Acute 2-50 mg/kg bw THC administration elevated plasma corticosterone concentrations in both male and female rats (ANZFA Final Assessment Report). THC induced age-degenerative changes in rat brain tissue similar to those resulting from elevated corticosterone (Landfield et. al. 1988). Later, Block et. al. 1991 did not observe changes in cortisol concentrations in male frequent cannabis users, consistent with other human data from earlier studies. Also, through hormonal effects, THC can inhibit milk production and release, with possible adverse implications for postnatal growth. Other preclinical studies documented THC disruption of the hypothalamus and pituitary gland.

Acute and chronic THC administration altered pituitary gonadotropin concentrations in animals; Wenger et. al. (1992) suggested that this might be mediated through direct effects on catecholamines, such as norepinephrine.

Five or 10 mg/kg bw IP THC for 5 days produced a significantly higher incidence of abnormal sperm in mice (Zimmerman et al 1979). Early 1980's studies reported that THC decreased concentrations of male reproductive hormones and sex organ weights, but later studies did not support these findings. The authors suggested that effects observed in animals were not considered significant to human health assessment. Early human and primate studies indicated that cannabis exposure produced no effect or a transient reduction in plasma LH and testosterone concentrations (Cone et al., 1986; Smith and Asch, 1984). Similarly, early studies in male rats did not provide conclusive evidence that THC inhibits growth hormone secretion. Direct infusion of THC into the brain of adult male rats suppressed growth hormone secretion (ANZFA Final Assessment Report). Circulating thyroxine levels also were reduced following acute or chronic THC administration in male rats and rhesus monkeys. THC treatment also affected the release of oxytocin (Tyrey & Murphy, 1988).

A recent review evaluated the current literature on cannabis use and regulation of the female hypothalamic-pituitary-ovarian (HPO) axis, ovarian hormone production, the menstrual cycle, and fertility (Brents 2016). Daily 2.5 mg/kg bw IM THC dosing during the follicular phase of the menstrual cycle induced longer, anovulatory cycles in rhesus monkeys, while luteal phase length was not affected at doses up to 5.0 mg/kg bw. The authors stated that overall findings from human and animal studies suggest that acute THC suppresses the release of gonadotropin-releasing hormone (GnRH) and thyrotropin-releasing hormone (TRH) from the hypothalamus, preventing these hormones from stimulating the release of prolactin and the gonadotropins, FSH and LH, from the anterior pituitary. Thrice-weekly administration of THC (2.5 mg/kg bw) robustly suppressed serum estradiol, progesterone, LH, and prolactin, and inhibited ovulation and menses, but the monkeys developed complete tolerance after about 4 months after this high THC dose. Two studies examined cannabis effects across the menstrual cycle in humans and found no effects.

Different experimental procedures and different cannabis exposure histories can affect experimental results, but the ANZFA report concluded that there is general agreement that cannabinoids do alter reproductive hormones controlling testicular function. Although some disturbances are noted in animals after acute THC exposure, the doses were 2 mg/kg bw THC or higher, and the route of administration had greater bioavailability than oral administration being considered here. In addition, tolerance to THC effects developed with subchronic exposure.

Effects on reproduction

Decreases in testicular, seminal vesicle, prostate and ovarian weights, and increases in pituitary and adrenal weights were documented in preclinical studies following cannabinoid exposure (WHO, 1997). An elevated risk of birth complications, abnormal labor progress and/or premature births have not been confirmed in cannabis users. Fetal hypoxia is suggested to be the mechanism for observed reproductive effects, similar to the effects produced by cigarette smoking (WHO, 1997). THC in milk and other food of animal origin decreases the number of viable pups, an increase in fetal mortality and early resorptions (EFSA Journal 2015).

THC rapidly transfers across the placenta to the developing fetus (Bailey et. al., 1987). Pregnant rhesus monkeys receiving 0.3 mg/kg bw IV THC had peak plasma THC concentrations after 3 mins in maternal blood and after 15 mins in the fetus, within 3 h maternal and fetal plasma THC concentrations were equivalent. THC crosses the placenta to the vascular system of the fetus although in rats, sheep, dogs and monkeys fetal plasma concentrations were lower than maternal concentrations.

Effects on intrauterine and post-natal development

THC produced teratogenic effects in some preclinical studies, although these studies had questionable study designs (Abel, 1985), and were not consistent with other well-conducted oral THC studies (Fleischmann et al., 1975). Dose-related maternal toxicity and embryotoxicity was noted when THC was administered early in gestation, but malformations were only observed following high dose IP administration. A confounding issue in these studies is the significant THC-induced reduction of food and water intake by the pregnant rats during treatment in this and other studies at lower dose levels (15 mg/kg bw, Hutchings et al. 1987). This may partially account for the poor fetal

development. The only consistent finding was a decrease in birthweight (Abel, 1985). Hernandez et al (1997) administered 5 mg/kg bw THC daily to pregnant rats, much lower THC doses than those used previously in fetal toxicity studies, and showed doubling of tyrosine hydroxylase activity in specific fetal brain cells. These data documented that THC could produce physiological effects at lower doses, albeit at doses almost a thousand-fold higher than those from ingesting maximal doses of hemp foods. There were no behavioral alterations in the offspring of dams exposed to 50 mg/kg bw THC (Abel et. al., 1984). Long-term effects of developmental THC exposure were noted in adult animals, suggesting that the brain is more sensitive during development than in adult animals (Downer et al., 2007). In addition, THC doses that did not have detrimental effects alone potentiated effects of additional chemical insults (Hansen et al., 2008).

Effects on the immune system

IP doses of 15 - 50 mg/kg bw THC to mice resulted in resistance to bacterial or viral infections (ANZFA Final Assessment Report). Although multiple studies established that THC is an immunomodulator, this occurred only at relatively high doses. A single 10 mg/kg bw THC dose inhibited functional and/or biochemical immune parameters following THC exposure and in mice, following repeated dosing up to 14 days (EFSA 2015). Apoptosis in bone marrow-derived dendritic cells from mice and in macrophages isolated from the peritoneal cavity in mice were demonstrated following THC. Inflammatory myeloid cells and macrophages/monocytes were the most sensitive to THC. Perinatal exposure of mice to THC caused fetal thymic atrophy and T cell dysfunction postnatally.

THC in high doses of 10 to 50 mg/kg bw caused immune disturbances.

Genotoxicity and carcinogenicity

THC is not mutagenic in the Ames test (Zimmerman et. al., 1978), although cannabis smoke was sometimes mutagenic. THC interfered with the normal cell cycle (Zimmerman & McClean, 1973) and also decreased DNA, RNA and protein synthesis (Blevins & Regan, 1976). THC also disrupted microtubule formation (Tahir & Zimmerman, 1992). There was no increase in sister-chromatid exchanges (SCE) in cannabis users' lymphocytes compared to tobacco smokers (Joergensen et. al., 1991).

The US National Toxicology Program evaluated THC's carcinogenicity at high 125, 250 and 500 mg/kg/day doses in rats and mice (NTP, 1996). Thyroid hyperplasia was observed in male and female mice at all doses. Zebrafish embryos had defects following exposure to 2 ppm THC in solution for greater than 24h (Thomas et al., 1975). No evidence of teratogenicity following exposure to THC in rodent studies was observed (EFSA Journal 2015). Epidemiological studies in human pregnant cannabis users do not support an increase in congenital malformations (Knight et al., 1994; Astley, 1992; Witter & Niebyl, 1990).

Neurotoxicity

Following long term exposure to THC in rats, morphological changes in synapses and hippocampal neuronal loss were observed (Sidney et al. 1997). Mice received up to 100 mg THC/kg bw IP to control seizures (Rosenberg et al., 2017). Activity was reduced in some mice, and no adverse effects were reported. Gerbils were dosed with 50 mg THC/kg bw IP to control seizures without adverse effects (Ten Ham et al., 1975). In addition, chronic administration of cannabis for one year to rhesus monkeys impaired their ability to perform operant tasks, but performance returned to normal three weeks after treatment (Slikker et. al., 1992). THC effects in experimental animal models include alterations in locomotor activity and decreased responsiveness to amphetamine, reduced social interactions and impaired learning (EFSA Journal 2015). Effects occurred only immediately following acute or chronic THC dosing in adult animals exposed to THC during development. While activity effects had a biphasic dose-dependence curve, impairment of learning and memory were consistent across most studies (exception: Silva et al., 2012), and were long lasting even after single administration of low THC doses.

Well-controlled preclinical studies provided data only in response to high THC doses that have important methodological problems related to depression of maternal food and water consumption (Abel, 1985). When pregnant rats received daily oral 15 or 50 mg/kg bw THC, dose-related decreases in birth weight and weight gain in the offspring were reported; however, decrease in birth weight was most likely due to poor maternal nutrition and

dehydration in the THC treated group, rather than from any direct toxic effects (Hutchings, 1985). Such studies are unlikely relevant to low-dose human exposure.

The effect on reproductive hormone concentrations was the most sensitive parameter for cannabinoid toxicity in animals. In rats, LH and FSH changes were observed at 0.1 mg/kg bw oral THC, although there was no apparent dose-response relationship. Exposure at 0.1 mg/kg much higher than cumulative daily exposure to all hemp products described in this application. Furthermore, the significance of much of the preclinical data to humans is unclear since high THC concentrations were employed, dose-response relationships were generally not demonstrated, and frequently the route of administration was IP or IV rather than oral.

Based on the data included in the ANZFN review, it was not possible to establish a level at which no effects were observed; however, the lowest-observed-effect level (LOEL) was 5 mg/person, equivalent to a dose of 60 µg/kg bw. Effects at this dose were minimal and reversible. There were no psychotropic effects observed at this dose. In order to take account of the possible variability in response in the human population, an uncertainty factor of 10 should be applied to the LOEL to derive an overall tolerable daily intake of 6 µg/kg bw.

Total THC exposures in µg/kg bw following ingestion of all three Fresh Hemp Foods Ltd. hemp products (Hulled Hemp Seed, Hemp Protein Powder and Hemp Seed Oil) according to body weight are shown in Table 1. Refer to response to Question 4 and referenced Tables and Figures for values. The data are presented in three different ways. In column B, the data are based on consuming the maximum amount recommended for each product and total THC at the highest permissible concentration- if Hulled Hemp Seed contained 4 µg/g THC (maximal permitted limit by Fresh Hemp Foods Ltd), Hemp Protein Powder (maximal 4 µg/g) and Hemp Seed Oil (maximal 10 µg/g). Body weights for each age level and suggested meal amounts for each age are contained in other attached tables. Average µg/g bw THC exposures are 2.2 and 2.5 for males and females 2 years and older, respectively, which is below the acceptable daily intake established by the German, Swiss, Australian and New Zealand regulatory standards. This concentration is approximately double that recommended by the EFSA and Austrian regulatory standards. Column C addresses total THC exposures from all three hemp products based on the actual total THC concentrations in Fresh Hemp Foods Ltd. products. Based on these more precise total THC concentrations, average µg/g bw THC exposures are 0.7 and 0.8 for males and females 2 years and older, respectively, which is below the acceptable daily intake established by all regulatory standards, including the EFSA standard. Column D addresses total THC exposure based on the Monte Carlo predicted exposure at the 99.9% certainty level. The Monte Carlo predictions were based on the more precise Total THC concentrations (limit of quantification [LOQ] of 0.2 µg/g for analyses of total THC in Hulled Hemp Seed, Hemp Protein Powder and Hemp Seed Oil). Average µg/g bw THC exposures are 1.3 and 1.5 for males and females 2 years and older, respectively, which is below the acceptable daily intake established by all regulatory standards except for the EFSA standard in milk products of 1 µg/kg bw. The Monte Carlo data assume ingestion of the maximal amount of all three hemp food products at the highest certainty level and this yields concentrations only slightly above the EFSA recommendations and below all the other international regulatory bodies.

However, these low total THC exposures are 100 to 1000 fold lower than the total THC exposures described above in the animal toxicology data. Furthermore, many of the animal studies utilized IV or IP routes of administration with higher THC bioavailability than through the oral consumption of hemp food products. THC exposure from hemp foods in infants and toddlers is addressed in the response to Question 9.

2. Assurance of conformity to Health Canada industrial hemp regulations

Yang et al. (2017) report that samples of hempseed purchased from grocery stores in Canada exceeded Health Canada's THC limit of 10 µg/g, sometimes by more than 10-fold. Please discuss this finding in light of your assurance that THC levels in your hempseed are below 4 µg/g.

Yang, Y., Lewis, M.M., Bello, A.M., Wasilewski, E., Clarke, H.A., and Kotra, L.P. (2017). Cannabis sativa (Hemp) Seeds, Δ (9)-Tetrahydrocannabinol, and Potential Overdose. Cannabis Cannabinoid Res 2: 274-281.

Response:

Yang et al (2017) did not report the identity or country of origin for any of the samples included in their article. This lack of information makes it difficult to confirm what controls or testing was applied by the manufacturers to assure their products comply with the Canadian Regulations.

Fresh Hemp Foods Ltd. assures that its products comply with Health Canada's THC limit of ≤10 µg/g. All Fresh Hemp Foods Ltd. hempseed products are produced in accordance with Health Canada's *Industrial Hemp Regulations* and Fresh Hemp Foods Ltd. specifications and quality management systems.

Mandatory requirements per *Industrial Hemp Regulations*

- Only Health Canada approved low THC cultivars may be grown for seed production. Refer to 2018 cultivar list to see current authorized varieties (accessible at https://www.canada.ca/en/health-canada/services/health-concerns/controlled-substances-precursor-chemicals/industrial-hemp/commercial-licence/list-approved-cultivars-cannabis-sativa.html)
- All hemp crops intended for seed production in Canada must be grown by licensed growers using pedigreed seed
- Growers are not allowed to save seed from year to year for planting
- Industrial hemp crops must be tested for conformance with the limit of ≤0.3% THC before their seeds are allowed to be harvested for food production. Testing must be done by accredited laboratories using the gas chromatography (GC) methodology cited in Health Canada's Industrial Hemp Technical Manual (HECS-OCS-001, Basic Analytical Procedure for the Determination Of Delta-9-tetrahydrocannabinol (THC) in Industrial Hemp)
- Hempseed derivatives must be tested to confirm compliance with the limit of ≤10 µg/g THC by accredited laboratories using the GC-MS methodology cited in Health Canada's Industrial Hemp Technical Manual (HECS-OCS-004, Basic Method for Determination of THC in Hempseed Oil)

Fresh Hemp Foods Ltd. Specification and Quality Management Systems

- Only seed produced from Health Canada approved low THC cultivars are processed into food ingredients by Fresh Hemp Foods Ltd.
- All whole hemp seed processed by Fresh Hemp Foods Ltd. must be thoroughly cleaned to stringent Fresh Hemp Foods Ltd. specifications by a licensed seed cleaner to remove plant debris (the source of THC and THCA contamination on the seed surface) and other contaminants
- All hemp seed derivatives must be tested for conformance with the Fresh Hemp Foods Ltd. Total THC specification prior to sale; specifically, ≤10 µg/g for Oil and ≤4 µg/g for Protein Powder and Hulled Hemp Seed. Testing must be done by accredited laboratories using the HECS-OCS-004 GC-MS method. Which is required to have a minimum 4 µg/g LOQ.

Delta-9-tetrahydrocannabinolcarboxylic acid (THCA) is known to rapidly decarboxylate to THC when exposed to heat and slowly convert during ambient temperature storage (Citti et al. 2018, Escrivá et al. 17). EFSA's Scientific Opinion (2015) and Lachenmeier and Walch (2005) report that studies examining analytical techniques for

quantification of THC confirmed that GC quantifies Total THC (free THC and THCA) because of the high temperature to which the sample is exposed during injection Health Canada (2013).

Fresh Hemp Foods Ltd. commissioned tests to verify THC content of its Hulled Hemp Seed, Protein Powder and Hemp Oil. These tests were performed by accredited labs that are quantifying Total THC using method HECS-OCS-004.. Refer to response for Question 4 for a summary of these historical data. The historical data confirm that the Fresh Hemp Foods Ltd. products comply with the maximum THC limits required by the *Industrial Hemp Regulations* and/or the tighter limits self-imposed by Fresh Hemp Foods Ltd.

Consultation with Dr. Art McElroy, a plant breeder with a back ground in genetics and almost 20 years experience working with industrial hemp confirms that any THCA or THC that is detected in a hemp seed derivative resulted from cross contamination of the shell exterior with the essential oil produced by the trichomes. However, the levels of THC in the flower parts (bracts) is very low in industrial hemp, so any resin that could stick to the seed is expected to contain low levels of cannabinoids. Molecular genetic research performed over the last few years elucidated the THC transcriptome and confirmed that there is no evidence that the alleles for THC are expressed in anything other than the trichomes on Cannabis plants. It is the common belief of plant breeders that there is no evidence of production THC within the seed (McElroy 2018). This supports the interpretation that the inhomogeneous THC content identified by Yang et al. (2017) during their analysis of commercial hulled hemp seeds is due to inadequate cleaning of the intact raw seed by the manufacturer prior to dehulling, because no significant THC is found when hempseeds are cleaned properly (Hemphill, Turner and Mahlberg 1980, Ross et al. 2000, Karimi and Hayatghaibi 2006). This is also consistent with the work of Citti et al. 2018 who report that the concentration of cannabinoids in hemp seed oil depends on the cleaning process of the seed and is highly variable amongst different varieties. In support, they reference low THC European cultivars authorized for seed production which are regulated to a maximum limit of 0.2% THC resulting in THC contamination in hemp seed oil which is generally low and only exceptionally exceeds the German limit of 5 mg/kg.

The European approach of controlling THC in the cultivar is in place to reduce exposure of the seed to high levels of THC in the resin. Health Canada utilizes a similar approach and requires authorized low THC cultivars with a maximum 0.3% THC to be used for seed production. Health Canada reinforces this approach by disallowing growers to retain seed from year to year for planting, thereby preventing the possibility of a variety reverting to producing high THCA and Δ-9-THC. Fresh Hemp Foods Ltd. only processes seeds grown from Health Canada authorized low THC cultivars, so it can be expected that the resulting seed derivatives were exposed to less cannabinoids than seeds produced from non-authorized cultivars.

Plant breeders are using molecular markers to eliminate THC production from new hemp varieties. The intent of their work is to produce varieties which have non-detectable amounts of THC even in the bracts, so there will be absolutely none on the seed McElroy (2018). This is highly relevant to the continued safety of industrial hemp since these new varieties will eventually be available to produce seed for human food.

3. Fresh Hemp's specification for THC limits and testing methodology

The analytical methodology cited in your notices as part of the specification limit for THC is Health Canada's Industrial Hemp Technical Manual. The methods described in this manual are intended for the analysis of dried leaf powder or seed oil and the applicability of the methods to analysis of seeds is not discussed. Yang et al. (2017), for example, reported significant variation in the detectable level of cannabinoids among batches of hempseed and notes that this inconsistency might be attributable to variations among the hempseeds themselves as well as to variability in the extraction process. Yang et al. suggest that THC may partition into seed material due to its higher oil content compared to the rest of the plant and the hydrophobicity of THC, and that analysis of seed material may result in an underestimation of THC content. Considering this information, please discuss the analytical method you use to assure your hempseed products conform with specifications, and why you think this method is appropriate for ensuring actual THC levels in seed remain below your specification of 4 µg/g.

Response:

Sample preparation is the most important step to achieve accurate and precise results in almost any analytical protocol. Sample preparation is typically achieved in four or five steps, including matrix homogenization, analyte extraction, clean-up to eliminate interfering materials, and preconcentration of the extract into a small volume.

The Industrial Hemp Technical Manual also outlines sample preparation procedures for the saponification and preconcentration of the extract for analysis GC-MS. While this method does not explicitly outline the extraction methods for plant tissues and foodstuffs, the author of the reference for the method highlighted the importance of the preparation of plant and foodstuff samples. The author's suggested and preferred method is through grinding, suggesting the use of a Retsch mill (of the type used in the generation of the data used in this submission) to reduce particle size prior to solvent extraction (Giroud, C., 2002). Consultation with the accredited laboratories confirms that the hemp samples (hulled hemp seed, hemp protein powder, hemp meal powder, hemp hearts) are milled to a homogeneous fine powder to make the material compositionally uniform and to maximize sample surface area to ensure complete saponification and extraction of the cannabinoid analytes.

One validated method had a sample preparation step of grinding using a mortar and pestle prior to THC analysis (Meng et al.), a method that would arguably provide more variation than grinding using a mechanical mill but still provided adequate particle size reduction.

Liquid-liquid microextraction (LLE) is the most widely used method for extraction of analytes from complex matrices (Ridgeway et al., 2007). Coupled with saponification, this method ensures the full recovery of cannabinoids. Because cannabinoids are strongly lipophilic, cannabinoid–lipid binding is viewed as a potential reason why cannabinoid values may be under-reported in THC quantification (Wei et al, 2016). Saponification is commonly used as a separation method. The saponification of oils from oilseeds will allow for the separation of fats from unsaponifiable hydrophobic compounds such as alkylphenols, a compound class that includes cannabinoids (Fontanel, 2013). Wei et al., 2016 speculated that formation of esters between cannabinoids and fatty acids could result in low recovery and observed "remarkable improvement in preparation efficiency" following saponification. Wei suggested that two major mechanisms underlie the improvement in sensitivity and efficiency. First is the conversion of triacylglycerols (TAG) into water-soluble materials. Conversion of TAG during saponification would reduce any triacylglycerol–cannabinoid binding. The second suggested mechanism is the liberation of cannabinoids from fatty acids during saponification.

After saponification, the THC is extracted using 3 successive portions of 3 mL petroleum ether/diethyl ether (1:1, v/v). The organic solutions are then combined and evaporated under nitrogen. After the sample is preconcentrated, the sample is derivatized and injected into the gas chromatography-mass spectrometry (GC-MS). GC-MS historically has been the favorite choice for cannabinoids analysis in both biological matrices and hemp products due to its versatility and feasibility (Lachenmeier and Walch, 2005, Pelligrini et al, 2004). Georgi et al followed a similar method for quantifying THC in a variety of food products using hexane extraction saponification, and GC-MS analysis, and demonstrated a LOQ of 12.9-17.3 µg/kg foodstuff.

4. THC values for Monte Carlo modeling

In your notices, you provide an exposure assessment model that uses THC concentration data obtained from 'historical third-party analytical testing.' Please discuss the data used in more detail, for example: the number of samples, their source, whether they are representative of the cultivars used, the analytical methodology used, limits of detection (LOD) or quantification, and how results below the LOD were handled.

Response:

Refer to Table 2 for summary detailing the Fresh Hemp Foods Ltd. historical data.

The historical data used in the original GRN765, 771, 778 notices was reassessed. Reports providing Total THC results were included. Analysis was performed using the Health Canada GC-MS method described in question 3. Health Canada approved low THC cultivars were used to produce the seed which was processed into the derivatives that were tested. Results were analysed to determine mean, minimum, maximum and standard deviation (Table 2).

Hulled Hemp Seed was tested 20 times with an LOQ of 0.2 µg/g. The mean is 0.3 µg/g, minimum is 0.1 µg/g (1/2 of LOQ concentration) and the maximum is 1.5 µg/g. Hemp Oil was tested 106 times with a 0.2 µg/g limit. The mean value is 6.0 µg/g, minimum is 0.1 µg/g and the maximum is 9.9 µg/g. Hemp Protein Powder was tested 6 times with an LOQ of 0.2 µg/g. The mean is 0.6 µg/g, minimum is 0.1 µg/g and maximum is 1.2 µg/g. Hundreds of other tests are routinely performed at an LOQ of 4 µg/g which is more cost effective and meets routine quality control criteria than the lower LOQ of 0.2 µg/g. The higher LOQ did not provide the level of sensitivity needed for the determinations made in these GRNs. Based on the intake and exposure levels discussed in the notices, use of the lower LOQ does not provide any additional benefit to justify the cost or adoption into the quality program.

The mean, minimum and maximum values obtained from this recent assessment of the historical data resulted in slightly different values compared to the evaluation performed during the original assessment. Accordingly, Fresh Hemp Foods Ltd. recalculated the THC exposure estimates using the mean historical THC concentrations and also recreated the THC exposure estimates using the crystal ball (Monte Carlo) probability model with a very high level of uncertainty. These updated data are provided to amend the relevant portions of the original notices and to determine µg/kg bw exposure estimates.

As described above in response to Question 1, the mean historical total THC values were used to determine how much Total THC would be consumed from food consumed at the 90% percentile and which contains maximum level of hemp ingredients (Tables 1, 16, 21). The mean, minimum and maximum total THC concentrations from the historical hemp testing were inputted as the key assumptions (refer to Table 2 and Figures 5, 6, 7) and the estimated total THC exposure based on body weight resulting from maximum consumption of each hemp material (Table 21) was inputted into the crystal ball probability model. The model ran the trial 10,000 times, each time selecting a different combination of THC µg/kg bw values from the individual ingredients, and then combining all results to produce the histograms shown in Figures 8 to 75. Refer to Table 1 for a summary of the predicted Total THC exposure based on body weight at a 99.99% certainty level for each of the age groups.

Children age 6 to 11 months were predicted to be exposed to 2.5 and 2.7 µg/kg bw for males and females respectively. Males age 11 to 23 months were predicted to be exposed to 6.4 µg/kg bw and females were predicted to be exposed to 5.9 µg/kg bw. Male and female children age 2 to 5 years and 6 to 11 years were predicted to be exposed to 5.1, 5.0. 3.5 and 3.7 µg/kg/bw respectively. Males age 2 years and older were predicted to be exposed to 1.3 µg/kg bw and females were predicted at 1.5 µg/kg bw.

Table 1 reflects the current information from the notices as well as this response. The exposure in µg/kg bw is estimated using three scenarios; specifically, THC based on maximum Fresh Hemp Foods Ltd. specifications (column A), THC based on mean historical testing levels (column B) and THC based on predicted values from probability modelling (column C). Each scenario uses the same level of cumulative hemp consumption in their calculations. The differences in values relates to how the quantity of Total THC provided by the hemp has been estimated. Multiple upper bound factors were used in the estimates of Total THC consumption for each age group:

1. Maximum level of the hemp seed derivatives defined in GRN765 Hulled Hemp Seed, 771 Hemp Protein Powder and 778 Hemp Oil being included into foods
2. 90th percentile consumption of all foods that may contain hemp
3. Cumulative consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil at maximum inclusion and 90th percentile
4. Lowest body weight for children age 11 to 23 and 6 to 11 months based on anthropometric reference data for children, Fryar et al. (2016)
5. 100% replacement of fluid milk by hemp based beverage in children age 6 to 11 months and use of cumulative hemp consumption levels for 2 to 5 years old to estimate consumption by children age 11 to 23 months

The most conservative estimate of exposure relates to the consumption of hemp which contains maximum levels of Total THC as permitted by the Fresh Hemp Foods specifications.

The least conservative estimate based relates to the consumption of hemp which contains the mean Total THC level using historical data obtained by Fresh Hemp Foods Ltd. between 2011 and 2018 (Table 2).

The most representative estimate of exposure is determined from the forecasted values generated by the Monte Carlo model. Exposure was calculated using the Total THC based on body weight predicted at the 99.99% certainty level instead of the mean to add another conservative upper bound factor to the calculations.

5. Potential conversion of THCA to THC

You state that THC and THCA are present in the plant at ratio of approximately 1 to 9, that THCA is non-psychotropic, and that THCA converts to THC with heat and with time. Citti et al. (2018) report that conversion of THCA to THC can occur at room temperature with a half-life of approximately 49 days, and the reaction is further accelerated by sunlight and heat. Further, Escrivá et al. (2017) note that conversion of THCA to THC begins immediately after harvest.

Throughout processing, cooking, and storage, significant conversion of THCA to THC appears possible. It was not clear whether this was accounted for in your exposure estimate. Please discuss whether the analytical methods for measuring THC also measure THCA and whether your specification of 4 µg/g is a combined limit for both THC and THCA.

Citti C, Pacchetti B, Vandelli MA, Forni F, Cannazza G. J. (2018) Pharm Biomed Anal. 149: 532-540.

Escrivá Ú, Jesús Andrés-Costa M, Andreu V, Picó Y. (2018) Food Chem. 254: 391

Response:

Refer to responses for Question 2 and 4. Fresh Hemp Foods Ltd. uses accredited labs who are quantifying Total THC (THC and THCA).

In fresh, unprocessed hemp plants, THC mostly occurs in the form of its inactive carboxylic acid precursor: i.e. Δ9-tetrahydrocannabinol-carboxylic acid or THCA). THCA is present at a rate of about 90% of the total THC and is devoid of psychotropic effects (Dewey, 1986). However, THCA can be decarboxylated, i.e. converted into its active form, usually with heat, to provide its biologically active product THC. Decarboxylation occurs primarily as a function of time, pressure, temperature and long exposure to light, for instance in food processing or when combusted. Thus, largely unprocessed foods, such as cold-pressed oils, usually contain large fractions of the pharmacologically inactive THCA. THC can naturally accumulate even if THCA-containing material is not heated, with a half-life of between 35 and 91 days (depending on storage conditions and type of material this half-life can even be considerably longer), whereas THC degrades to cannabinol (CBN) at a half-life rate of only 24 to 26 months (Lindholst, 2010).

THC exposure estimates in GRN765, 771, 778 were conservatively estimated based on the cumulative consumption of Hulled Hemp Seed, Hemp Oil and Hemp Protein powder containing the maximum levels of Total THC per Fresh Hemp Foods Ltd. specifications. Results obtained with the GC method outlined in Health Canada's Industrial Hemp Technical Manual (HECS-OCS-004), quantifies the "total THC content" which includes not only THC, but the precursor THCA, since it is decarboxylated by the heat in the inlet of the GC (Health Canada, 2013). While THCA has no psychoactive effect, the useful and logical reason for its co-quantification is the possibility of increased THC content in hemp food products based on the age of the material (Escrivá et al., 2017) through heat applied during processing into value added products, or over shelf-life due to heat or exposure to light (Citti et al., 2018). Consequently, the 'total THC content' is also determined in the 'Community method for the quantitative determination of Δ-9-tetrahydrocannabinol' enforced at the EU level (Regulation (EC) No 796/2004, Annex I)18, and the 'Gas chromatographic determination of tetrahydrocannabinol in cannabis' enforced in Canada (Bureau of Drug Research, Health Protection Branch, 1992). The THC and THCA in hemp plant materials are extracted simultaneously from the plant matrix by a non-polar solvent and the extract is analysed by GC. THCA is decarboxylated quantitatively to THC during the saponification process (heating at 70°C for 2 hours) and in the injector (>200 °C) of the gas chromatograph and detected/quantified as THC. THC can degrade to cannabinol (CBN), with about 10% of THC's psychoactivity. Trofin et al. (2012) demonstrated the degradation kinetics of THC to CBN under ambient temperatures and exposure to light.

6. Other cannabinoids

Huestis (2007) states that "Cannabis sativa contains over 421 chemical compounds, including over 60 cannabinoids ..." Please discuss the typical levels and any associated limits for other cannabinoids, such as THCA (if not already accounted for in limits for THC), CBD, and CBDA. Briefly describe why levels of cannabinoids other than THC or any other chemicals that may be present in hemp seed products are safe.

Huestis, M.A. (2007). Human cannabinoid pharmacokinetics. Chem Biodivers 4, 1770-1804.

Response:

The firm is unaware of any other regulatory body or organization monitoring or regulating all 421 chemical compounds or 60 cannabinoids, all of which are naturally occurring in hemp. Currently only THC, which often includes THCA, and CBD levels are studied or regulated. As Huestis (2007) stated, "Cannabinoid pharmacokinetics research is challenging due to low analyte concentrations, rapid and extensive metabolism, and physico-chemical characteristics hindering the separation of drugs of interest from biological matrices and from each other." The body of scientific research reflects this with very limited research conducted on these compounds and cannabinoids. In particular, for terpenes which are rarely studied. These compounds and cannabinoids occur at low levels and the safety can be inferred from historical consumption, animal studies and human studies. In the historical data, humankind has cooked and pressed hemp plants for thousands of years, which would include exposure to these compounds and cannabinoids. In human studies, for example, 800mg CBD oral administration has produced no adverse effects. Exposure levels of CBD have exploded recently with the popularity of CBD supplementation. The levels proposed in the GRNs is considerably lower than any CBD supplement. Even at worse case intake levels, these compounds and cannabinoids would only be present in extremely low levels that are not only unreasonable to isolate and remove but very likely impossible to do so.

Based on a limited analysis the firm found the following.

Fresh hemp Foods Ltd. tested Hulled Hemp Seed, Hemp Oil and Hemp Protein Powder for 9 cannabinoids including THC, THCA, Δ-8-Tetrahydrocannabinol (Δ-8-THC), Cannabidiol (CBD), Cannabidiolic acid (CBDA), CBN, Δ-9-Tetrahydrocannabivarin (THCV), Cannabigerol (CBG) and Cannabichromene (CBC). The data on the other cannabinoids is largely based on analysis of Hulled Hemp Seed and Hemp Oil that was produced in 2018.

One lot of Hemp Protein Powder was tested for CBD (refer to Table 3). The lot contained 20 µg/g CBDA. The other cannabinoids were not tested.

Twelve lots of Hemp Oil were tested for some or all of the above 9 cannabinoids (refer to Table 3). All lots contained CBDA with the highest amount of 150 µg/g. None of the lots tested for THCV and Δ-8-THC had detectable concentrations. CBC was identified in two lots, CBD in three, CBG in two lots, one lot had THC and one lot had THCA

Eleven lots of Hulled Hemp Seed were tested for some or all of the above 9 cannabinoids (refer to Table 5). Δ-8-THC, THC, THCA and THCV were not identified in any lot. CBC, CBD, CBG were not detected in nine lots and eight lots contained no CBN. Nine lots contained CBDA, with the highest concentration 120 µg/g. One lot had 30 µg/g CBC, 20 µg/g CBD, 20 µg/g CBG and 10 µg/g CBN (lot NADI147FC), Only one other lot contained measurable CBN (lot TEAB15NCJ).

Refer to Tables 6 and 7 for estimate of exposure levels to other cannabinoids at upper bound consumption levels of all hemp ingredients. The historical data available to estimate other cannabinoids are relatively small. The highest tested concentration of each cannabinoid was used to estimate the concentration in the other hemp materials. For instance, the highest CBDA concentration was 150 µg/g in one lot of Hemp Oil so this concentration was used to calculate the upper bound estimates for Hulled Hemp Seed and Hemp Protein Powder. All estimates were calculated at the 90th percentile for consumption of hemp in food based on the NHANES data as detailed in the notices (Table 36 of GRN765)) except for the estimated exposure for children under the age of 24 months. The NHANES data used in the notices did not include data for children under the age of 24 months; therefore, 2 to 5 year

old children's intake was used to conservatively estimate exposure for children 12 to 23 months. Exposure of Infants 11 months and younger was estimated by substituting hemp-based beverage in place of fluid milk into a typical daily meal plan as recommended by the United States Department of Agriculture Infant Meal Pattern, USDA 2016.

Industrial hemp varieties show THC/CBD ratios ranging from 0.06:1 to 0.5:1. Thus, CBD is by far the dominant cannabinoid in industrial hemp varieties (de Meijer et al. 1992). This ratio is an intentional effect of specialized plant breeding intended to lower the psychoactive THC content. CBG, CBC and CBD are also found in industrial hemp. Using the upper bound cumulative estimated cannabinoid exposure, it can be conservatively estimated that males and females age 2 years and older would be exposed to 5420 µg/g CBDA, 723 µg/g CBD and 361 µg/g CBN per day from the cumulative consumption of all hemp materials in the notices. Male and female children age 2 to 5 years would be exposed to 4332 µg/g CBDA, 578 µg/g CBD and 289 µg/g CBN per day and 3800 µg/g CBDA, 507 µg/g CBD and 253 µg/g CBN per day respectively. Male and female children age 6 to 11 years would be exposed to 4548 µg/g CBDA, 606 µg/g CBD and 303 µg/g CBN per day and 4664 µg/g CBDA, 622 µg/g CBD and 311 µg/g CBN per day respectively. Infants from birth to 5 months are not expected to consumer hemp products directly so no estimate on other cannabinoid exposure is provided for this age range. Male and female infants age 6 to 11 months are anticipated to consume some hemp containing foods resulting in an estimated exposure of 2130 µg/g CBDA, 284 µg/g CBD and 142 µg/g CBN. Male and female children age 12 to 23 months would be exposed to 4332 µg/g CBDA, 578 µg/g CBD and 289 µg/g CBN per day and 3800 µg/g CBDA, 507 µg/g CBD and 253 µg/g CBN per day respectively. The levels of CBD estimated for all age groups, even when considering CBDA contribution is significantly lower than the levels that have been evaluated in human clinical studies.

Bergamaschi et al. (2011) assessed CBD's safety and side effects in a comprehensive review of 132 published in-vitro and in-vivo studies. The authors report that several studies suggest that CBD is non-toxic in non-transformed cells and does not induce changes in food intake or catalepsy, does not affect physiological parameters (heart rate, blood pressure and body temperature) or gastrointestinal transit and does not alter psychomotor or psychological functions. They also reported that chronic use and high doses up to 1,500 mg/day CBD are reportedly well tolerated in humans. However, they also report that in vitro and in vivo studies showed potential drug metabolism interactions, cytotoxicity, and decreased receptor activity and these data therefore highlight the need for careful monitoring of CBD use in humans, especially when CBD is used in clinical practice, such as in the treatment of psychiatric disorders or as an option for drug abuse treatment. CBD concentrations for pharmacotherapy are many times higher than the level conservatively estimated from the upper bound exposure detailed in Tables 6 and 7 for all age groups. The European Industrial Hemp Association reviewed clinical data on CBD and determined that doses ranging from 20 to 200 mg CBD per day exert physiological effects, but substantial pharmacological activity is not observed under approx. 200 mg oral CBD per day for an average adult EIHA (2017).

Karniol et al. (1975) evaluated an oral 50 mg/day CBD dose and determined that it did not cause any measurable effect on pain threshold, skin sensitivity, heart rate, electrocardiogram, blood pressure and body temperature but appeared to slightly increase the effect of THC on some physiological and psychological processes. The highest estimated exposure level of CBN at 361 µg/g from the cumulative daily consumption of all hemp ingredients was found in all individuals age 2 years and older. This level is over 100 times lower than the level evaluated by Karniol et al.

Animal studies suggest that CBN is as effective as THC in influencing gonadotropin and testosterone secretion. The LOAEL for this effect was 0.1 mg oral CBN (the same as for THC) in a study by Steger et al. (1990) with male rats. However, much higher THC doses had no effect on testosterone concentrations in humans (Dax et al.1989; Mendelson et al. 1978).

Health Canada published an information document intended for use by health care professionals in medical treatment of patients with cannabis or cannabinoids. Their review is a summary of peer-reviewed literature and international reviews concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. It is intended to complement other reliable sources of information. Health Canada reports that drug type cannabis contains a large number of compounds spanning many chemical classes including cannabinoids, nitrogenous compounds, amino acids, proteins, enzymes, glycoproteins, hydrocarbons, simple alcohols, aldehydes, ketones and

acids, fatty acids, simple esters and lactones, steroids, terpenes, non-cannabinoid phenols, flavonoids, vitamins, and pigments. It can be anticipated that low THC industrial hemp contain the same compounds. Health Canada further elaborates that relatively little is known about the pharmacological actions of the various other compounds found within cannabis (e.g. terpenes, flavonoids), but that it is believed that some of these compounds (e.g. terpenes) may have a broad spectrum of action (e.g. anti-oxidant, anti-anxiety, anti-inflammatory, anti-bacterial, anti-neoplastic, anti-malarial), although this this information comes from a few in vitro and in vivo studies and no clinical trials exist to support these claims. Terpenes vary widely among cannabis varieties, and the theory that they may somehow modify or enhance the physiological effects of the cannabinoids, for the moment, is hypothetical as there is little, if any, pre-clinical evidence to support this hypothesis and there are no clinical trials on this subject (Health Canada, 2013).

Cannabinol (CBN) is a product of Δ-9-THC oxidation and has 10% of the activity of Δ-9-THC. Its effects are not well studied but it appeared to have some possible immunosuppressive properties in a small number of in vitro studies. Cannabigerol (CBG) is a partial CB1/2 receptor agonist and a small number of in vitro studies suggest it may have some anti-inflammatory and analgesic properties and that it may also block 5-HT1A receptors and act as an α2-adrenoceptor agonist (Health Canada, 2013).

Health Canada reviewed clinical data and reported that two types of mechanisms could govern possible interactions between CBD and THC: those of a pharmacokinetic origin, and those of a pharmacodynamic origin. CBD lacks detectable psychoactivity and does not appear to bind to either CB1 or CB2 receptors at physiologically meaningful concentrations, but it affects the activity of a significant number of other targets including ion channels, receptors, and enzymes. Despite the limited and complex nature of the available information, it generally appears that CBD pre-administration may potentiate some THC effects (through a pharmacokinetic mechanism), whereas simultaneous co-administration of CBD and THC may result in attenuation of THC effects (through a pharmacodynamic mechanism). However, Karschner et al found no pharmacokinetic or pharmacodynamic interaction in humans between CBD and THC when they were in a 1:1 ratio in the cannabis plant extract (Sativex). The ratio between the two phytocannabinoids also plays a role in determining whether the overall effect will be potentiating or antagonistic. CBD-mediated attenuation of THC-induced effects may be observed when the ratio of CBD to THC is at least 8 : 1 (±11.1), whereas CBD appears to potentiate some of the effects associated with THC when the CBD to THC ratio is around 2 : 1 (±1.4). Potentiation of THC effects by CBD may be caused by inhibition of THC metabolism in the liver, resulting in higher plasma levels of THC. This contrasts with the review performed by Huestis (2017) which identified Hunt et al. (1981) as reporting that the pharmacokinetics of THC were not affected by CBD, except for a slight slowing of the metabolism of 11-OH-THC to THCCOOH. The Huestis review also identified data indicating that co-administration of CBD did not significantly affect the total clearance, volume of distribution, and terminal elimination half-lives of THC metabolites. Concentration vs. time curves, and ratios of the maximum average concentration and AUC values for 11-OH-THC/THC, THCCOOH/THC, and THCCOOH/11-OH-THC showed that CBD only partially inhibited the hydroxylation of THC to 11-OH-THC catalyzed by CYP 2C, when data were compared after oral administration of THC alone, as compared to a THC and CBD preparation (Nadulski et al., 2005). Like THC, CBD concentrations are high in the liver following oral administration due to a significant first-pass effect; however, unlike THC, a large proportion of the CBD dose is excreted unchanged in the feces (Wall et al., 1976). The effect of CBD on hydroxylation of THC was small in comparison to overall variability. There is virtually no information in the peer-reviewed scientific or medical literature concerning the effects of varying CBD to THC ratios in the treatment of different medical disorders (Health Canada, 2013).

Tetrahydrocannabivarin (THCV) acts as a CB1 receptor antagonist and CB2 receptor partial agonist in vitro and in vivo and pre-clinical studies suggest it may have anti-epileptiform/anti-convulsant properties. Much of what is known about the beneficial properties of the non-psychotropic cannabinoids (e.g. CBD, THCV) is derived from in vitro and animal studies and a few clinical studies. However, the current available data suggest potential therapeutic indications for psychosis, epilepsy, anxiety, sleep disturbances, neurodegeneration, cerebral and myocardial ischemia, inflammation, pain and immune responses, emesis, food intake, type-1 diabetes, liver disease, osteogenesis, and cancer properties (Health Canada, 2013).

THC, CBD, and CBN are known to inhibit CYP isozymes such as CYP1A1, 1A2, and 1B1 (Yamaori et al. (2010). Cannabis may therefore increase the bioavailability of drugs metabolized by these enzymes. Such drugs include amitryptiline, phenacetin, theophylline, granisetron, dacarbazine, and flutamide. THC, THCCOOH, CBD, and CBN all stimulate, and in some cases even inhibit, the activity of the drug transporter P-glycoprotein in vitro (Zhu et al. 2006). This suggests a potential additional role for these cannabinoids in affecting the therapeutic drug efficacy and toxicity of co-administered drugs. Health Canada therefore advises in their review that clinicians should be aware of other medications that the patient is taking and carefully monitor patients using other drugs along with cannabis or cannabinoids.

The cannabis terpenoids are limonene, myrcene, a-pinene, linalool, b-caryophyllene, caryophyllene oxide, nerolidol and phytol. They share a precursor with the phytocannabinoids and are synthesized in the secretory cells inside glandular trichomes. Terpenoids may represent up to 10% of the trichome content (Russo, 2011), and should also be present in the resin that adheres to hemp seed during harvesting. The cannabis terpenoids are all flavour and fragrance components that have been designated Generally Recognized as Safe by the US Food and Drug Administration and other regulatory agencies (Russo, 2011). They are common to the human diet and are present in other foods at varying levels, specifically, lemon (limonene), hops (myrcene), pine (a-pinene), lavender (linalool), pepper (b-caryophyllene), lemon balm (caryophyllene oxide), orange (nerolidol) and green tea (phytol). In-vitro studies demonstrate their pharmacological activity and they appear to be synergistic with the phytocannabinoids (Russo, 2011).

7. Heavy metals and aflatoxins

Although Angelova et al. (2004) state that concentrations of heavy metals are highest in roots and lowest in seeds, we note that the data from the study show that only Pb clearly fits this pattern, whereas Cu, Zn, and Cd do not. Since you state that hemp is known to uptake metals, please explain why you consider the risk of presence of heavy metals to be low. You state that because risk is low, testing is not needed per lot, but instead on an as-needed basis determined by risk. Please describe the risk conditions that would warrant testing for heavy metals. Also, please describe the risk conditions that warrant testing for aflatoxins.

Angelova V, Ivanova R, Delibaltova V, Ivanov K. (2004) Industrial Crops and Products. 19: 197–205.

Response:

Aflatoxin

Mycotoxins are produced by molds and can have a negative impact on human and animal health. Aflatoxins are a mycotoxin that can be found in oilseeds, such as hemp. Aflatoxin production is more likely to occur when the oilseeds moisture content is 20-25% (Manitoba Agriculture, Mycotoxins, accessed August 29, 2018).

Fresh Hemp Foods Ltd. contracts hemp seed growers to immediately dry harvested hemp seed. Contracted specifications require moisture to be $\leq 9.5\%$. Samples are submitted to our laboratory after harvest and regularly throughout storage for laboratory testing with results communicated to the farmer suppliers. As we manage the risk of aflatoxin by maintaining low moisture, aflatoxins are not tested in every seed lot but rather at a lower frequency on final product based on risk.

Refer to Tables 8 to 10 for historical 3rd party laboratory aflatoxin testing results confirming that Hulled Hemp Seed, Hemp Oil and Hemp Protein Powders were tested below the limit of detection (<5 ng/g) at a 3rd party accredited laboratory.

Heavy Metals

Proposition 65, officially known as the Safe Drinking Water and Toxic Enforcement Act of 1986, was enacted in November 1986. The proposition protects the state's drinking water sources from being contaminated with chemicals known to cause cancer, birth defects or other reproductive harm, and requires businesses to inform Californians about exposures to such chemicals.

Certain listed chemicals, such as lead, are naturally distributed through the environment in air, soil, and water. As a result, crops grown in western Canada often contain varying levels of heavy metals. These heavy metals are considered naturally occurring. During manufacture of our products, we do not add heavy metals.

Fresh Hemp Foods Ltd. tests raw hemp seed and the hemp seed derivatives described in GRN765, 771, 778 for the most common heavy metals; arsenic, cadmium, mercury, and lead. We conducted continuous validation studies to verify heavy metals level in our products. Refer to Figures 1 to 4 and Tables 11 to 13 for historical 3rd Party Laboratory Heavy Metal Testing Results and trending data. Historic testing results confirm that while these heavy metals are naturally occurring, our processing does not increase levels of these heavy metals beyond limits as set by Proposition 65. Typical heavy metal levels tested in our products are Arsenic < 0.16 µg/g, Cadmium < 0.14 µg/g, Mercury < 0.10 µg/g and Lead < 0.18 µg/g. Therefore, heavy metals are not tested in every seed lot but rather at a lower frequency on final product or upon customer request.

8. Anti-nutritional factors

You state that, "there are no known anti-nutritional properties," without citing evidence. According to Galasso et al. (2016), high variability of antinutritional compounds, including phytic acid, were found in hempseed from various cultivars. The authors state that, "the high phytate content found ... will greatly limit the use of this protein source in novel food or feed formulations." Please discuss antinutritional factors in hempseed, addressing information in the literature showing their presence.

Galasso, I., Russo, R., Mapelli, S., Ponzoni, E., Brambilla, I.M., Battelli, G., and Reggiani, R. (2016). Variability in Seed Traits in a Collection of Cannabis sativa L. Genotypes. Front Plant Sci 7, 688.

Response:

In hemp, antinutrients including trypsin inhibitors, phytic acid, glucosinolates, and condensed tannins were identified in the cotyledon fractions. Of these, the concentration of phytic acid is generally viewed as being considerable in all varieties, while the content of cyanogenic glycosides, condensed tannins, trypsin inhibitors and saponins are typically at acceptable levels in hemp seed meals, and in fact, may be inversely correlated with phytic acid content (Russo and Reggiani, 2013). Other researchers found the non-nutritive compounds in seeds varied among genotypes, and phytic acid was the most abundant (Galasso et al., 2016).

Phytate, the salt form of phytic acid, is the primary phosphorus storage compound of cereal grains, oil seeds, and tree nuts. Across these types of materials, phytate may account for 1-7% of the kernel dry weight and upwards of 75% of the total kernel phosphorus (Raboy, 2003). Phytate is historically considered an anti-nutrient because it will chelate minerals such as calcium, magnesium, iron, and zinc. More recently, the ability of phytic acid to chelate minerals was reported to have some protective effects. In animal studies, phytic acid was shown to decrease iron-mediated colon cancer risk and lower serum cholesterol and triglycerides (Zhou and Erdman, 1995). Phytic acid is also a contributor to the total antioxidant capacity of foods and may have potential functions of reducing lipid peroxidation in foods (Schlemmer et al. 2009). These beneficial effects were summarized:

"In industrialised countries where various civilisation diseases are prevalent, the beneficial properties of phytic acid, such as its anticancer, antioxidative and anti-calcification activities, are of great importance. Due to the enormous problems of civilisation diseases, any contribution to prevent these diseases is highly significant. If phytate really does show these beneficial properties in humans, then phytate will be no longer considered an antinutrient." "Terms for phytate such as 'antinutrient' or , 'bad food compound'
should belong to the past."

Human intake of phytate is well documented, as is the higher level of phytate associated with vegetarian diets (Schlemmer et al., 2009). The greatest phytate intake ever reported in humans was 5770 mg for a lacto-ovo vegetarian community. A study in American students and university faculty staff members (19–35 years) showed

ranges from 198 to 3098 mg (Held et al., 1988), with a high mean daily phytate intake of 1293 mg. In another study measuring phytate in the western diets of omnivorous females and males, the phytate intake was found to be 631 mg (590–734 mg) and 746 mg (714–762 mg) and in female and male vegetarians (1250 ±450 and 1550 ±550 mg, respectively (Ellis et al., 1987). Comparatively, diets that do not follow "typical" western patterns exhibit higher phytate intake. Adult Asian immigrants to Canada consuming a lacto-ovo vegetarian diet showed a daily phytate intake of 1487 ±791 mg (Bindra et al., 1986). Mexican infants aged 18–30 months showed a daily phytate intake of 1666 ±650 mg and youth (7–9 years) 3380 ±1070 mg (Murphy et al., 1992). Females in Guatemala also demonstrate a high daily phytate consumption of 2254 mg for females (15–37 years) (Fitzgerald et al., 1993).

Refer to Table 14. For Canadian grown seed, 3 consecutive lots of hulled hemp seed averaged 32 mg/g phytic acid. Coarse hemp flour, which is the ground press cake from hemp oil production, averaged 22.4 mg/g phytic acid for 3 consecutive lots. In comparison, hemp protein concentrates of 50% and 70% protein content (three consecutive lots each) averaged 36.3 mg/g, and 13.6 mg/g respectively.

Although the phytic acid levels in hemp are higher than some cereals, some common foods such as Peanuts, Almonds, Walnuts, Cashews, and Pecans have higher reported phytic acid levels above that of hemp (Schlemmer et al., 2009). When comparing the cumulative total exposure of phytate through hemp ingredients (hemp hearts and protein), one observes that the total phytate contributed to the diet from the conservative estimate of hemp material consumed per day falls well within the range of phytate ingested when consuming one reference amount of common foods including wheat bran (RACC of 15g), and many types of nuts (RACC of 30g). Refer to Table 15 for summary of phytate levels in common foods.

9. Exposure in infants/toddlers

Your safety narrative discusses exposure to THC in children 2-11 years old and the breastfed population. However, you do not discuss exposure and safety in infants and toddlers who directly consume foods derived from hempseed. Also, your narrative did not include a published report of a toddler with mild cannabinoid poisoning upon 3-week ingestion of hemp seed oil at what was considered a low dose (Chinello et al., 2017). Please discuss this sub-population in an amended safety narrative.

Chinello, M., Scommegna, S., Shardlow, A., Mazzoli, F., De Giovanni, N., Fucci, N., Borgiani, P., Ciccacci, C., Locasciulli, A., and Calvani, M. (2017). Cannabinoid Poisoning by Hemp Seed Oil in a Child. Pediatr Emerg Care 33, 344-345.

Response:

Huestis Review of Chinello et al., 2017 article

At the time of the review of effects of THC in children, this article was not found, and may not have been available through online searches. This 2017 case report described a 2-yr-7-month-old child prescribed 2 teaspoons of hemp oil per day to improve his immune system (Chinello M, et al., Pediatr Emer Care 2017;33: 344–345). After 21 days of dosing, the child was brought to an emergency department presenting with symptoms of decreased alertness, refusal to walk, and no verbal response in the last 2 hours. Examination reported paleness, stupor, low reactivity to stimulation, fixed gaze with pupils of medium size and normal reaction to light, and conjunctival hyperemia. The child had a positive urine test for cannabinoids (>50 µg/L) that was also positive after 19 h in the emergency department. The hemp oil was later determined by GCMS to contain 0.06% THC. Using standard conversion measures and assuming the oil had a density of 1 g/mL, the child had ingested approximately 6 mg THC per day for 21 days. The average weight of a child 2-5 years old is 14.2 kg, yielding a daily THC intake in this child of 423 µg/kg bw. The hospital conducted basic genetic tests and did not find any indications of unusual metabolism in this child. After discharge the parents reported irritability that disappeared after a few days and at a 6-month follow-up the child was healthy.

This is a case of a child ingesting hemp oil for multiple days for medicinal purposes and presenting with symptoms consistent with ingestion of an effective THC dose. The hemp oil described had a THC content higher than for most currently marketed hemp oils that lowered THC content over time and in 2008 contained less than 0.012% THC (Holler et al., 2008). Our estimates show that daily intake of our product at the 90th percentile level for a child is estimated to be 10.2 µg/kg total THC from the most conservative estimate of maximal ingested Hulled Hemp Seed, Protein Powder and Hemp Oil in one day, only 2.8 µg/kg total THC based on historical data and 5.0 µg/kg bw based on the conservative Monte Carlo data with certainty of 99.99%. Our estimates are 41 to 151 times lower than this child received on a daily basis. The illness of the child in this case report was clearly due to receiving a high daily 6 mg/day dose of THC in hemp oil.

Huestis For the purposes of this response, we divided infants into newborn to 2 months, 2 to 5 months, 6 to 11 months, and toddlers as 12 to 24 months old. Data in the original submission were supplied for children 2 to 5 years and 6 to 11 years old.

Although we provided maximal total THC exposure data for children 2-5 years old following ingestion of all three hemp food products consumed in a single day, and information on infants being breastfed by women consuming the maximum of all three hemp foods in a single day, we did not address exposure of infants and toddlers who were not exclusively breast fed, and who might be fed hemp food products by caregivers. We now provide data on total THC exposure in µg/kg bw of infants and toddlers, meals throughout the day, the type of food consumed based on reference data, the potential addition of hemp products to the foods, and infant and toddler weights. All data were retrieved from cited references and calculated data are found in Tables 1, 16 and 21). We assumed that non-breastfed infants up to 6 months old only receive formula that is prepared with the addition of water to powdered milk, yielding no THC exposure. Infants 6 to 11 months old could have supplementation of hemp food products into infant cereal at breakfast, lunch, dinner and two daily snacks providing a maximal total THC exposure of 6.7 (males) and 7.1 (females) µg/kg bw based on Table 1 Column B THC exposure based on consumption of all products at the Fresh Hemp Foods maximal limits of 4 µg/g for Hulled Hemp Seeds and Hemp Protein Powder and 10 µg/g for Hemp Oil. Total THC exposure based on historical THC analysis of Hemp Food products would be 0.6 µg/kg bw for this aged males and females, and based on the Monte Carlo predictions 2.5 and 2.7 µg/kg males and females, respectively.

Toddlers (12 to 24 months old) receive a larger amount of food than infants; however, no normative data were available on the amounts, so a conservative approach was to use the data for 2-5 year olds. Assuming addition of hemp food products at every meal and snack, and the maximal THC concentrations allowable in Fresh Hemp Foods Ltd. products the total THC exposure would be 12.7 µg/kg bw for male and 11.5 µg/kg bw for female toddlers. This may be an overestimation based on using food intake amounts for 2 to 5 year olds. Using the historical THC data, total exposure in the toddlers would be 3.5 and 3.3 µg/kg bw and according to the Monte Carlo predictions 6.4 and 5.9 µg/kg bw. These exposure levels are close to the µg/kg bw limits set by German, Swiss, Australian and New Zealand authorities, but exceed the limits set by the EFSA and Austrian governments. These data assume that toddlers receive maximal hemp food supplementation at every meal and snack during the day. In addition, the EFSA applied uncertainty factors of 30 for setting their exposure limit, while the Australian authorities employed an uncertainty factor of 10 for determining their limits. It is unlikely that infants and toddlers would receive this degree of hemp food supplementation, and drug metabolism in this age group is more rapid than in adults, perhaps leading to lower active THC analytes and more inactive metabolites. Based on the historical THC data from Fresh Hemp Food products and the Monte Carlo predictions, total THC exposures are less than 6.4 µg/kg bw; only the data based on the maximal allowable THC concentrations are about double the recommended µg/kg bw levels set by multiple regulatory bodies around the world.

Refer to GRN765 (Hulled Hemp Seed) Section 3.4 Dietary Exposure to Hemp Protein and to GRN778 Section 3.4 Dietary Exposure to Hemp Derived Oil. These sections discuss the safety of protein and oil derived from hemp seed and should be read concurrently with the response to Question 9. Cumulative protein exposure is about 13.3 g/day and 11.4 g/day for males and females 11 to 23 months based on hemp consumption being estimated at same level as 2 to 5 year old children (Tables 30 and 31, GRN765). Protein intake for 6 to 11 month old children is estimated at 5.4 g/day based on the protein content of Hulled Hemp Seed (Table 3 GRN765). Cumulative oil exposure is about 4.8 g/day and 4.6 g/day for males and females 11 to 23 months based on hemp consumption being estimated at same

level as 2 to 5 year old children (Tables 30 and 31, GRN778). Oil intake for 6 to 11 month old children is estimated at 7.7 g/day based on the oil content of Hulled Hemp Seed (Table 3 GRN765). The levels of protein and oil are well within the Institute of Medicine (2005) Recommended Dietary Allowance (RDA) of 13 g for children age 1 to 3 years and Adequate Intake (AI) for omega-3 at 0.7 g and 0.9 g for males and females age 1 to 3 years.

10. Health Canada's evaluation

The notices discuss the Health Canada Non-Prescription and Natural Health Products Directorate Workout Supplements Monograph. Although the notices present the monograph as a safety evaluation of hempseed protein, the monograph is not specific to hempseed protein and states that it "is not intended to be a comprehensive review of the medicinal ingredients described within." Please acknowledge that the Workout Supplements Monograph does not reflect a comprehensive safety evaluation of hempseed protein by Health Canada and is not necessarily directly applicable to general use in food.

Response:

The following statement is intended to be reviewed concurrently with the following Sections of the notices:

GRN765 (Hulled Hemp Seed) and GRN771 (Hemp Protein Powder) - Sections 3.4 Dietary Exposure to Hemp Protein and Section 5.9 Nutritional Benefits of Hemp as Food

Fresh Hemp Foods Ltd. acknowledges that the Non-Prescription and Natural Health Products Directorate Workout Supplements Monograph does not reflect a comprehensive safety evaluation of hempseed protein by Health Canada and is not necessarily directly applicable to general use in food.

GRN778 (Hemp Oil) - Section 5.9 Nutritional Benefits of Hemp as Food

Fresh Hemp Foods Ltd. acknowledges that the Non-Prescription and Natural Health Products Directorate Workout Supplements Monograph does not reflect a comprehensive safety evaluation of hempseed protein by Health Canada and is not necessarily directly applicable to general use in food.

11. Additional Requests:

11a. Allergenicity Statement

Response:

The following statement is intended to be reviewed concurrently with Section 5.8 Allergenicity of GRN765 (Hulled Hemp Seed), 771 (Hemp Protein Powder) and 778 (Hemp Oil).

A review of published literature indicates that consumption of derivatives of Cannabis sativa L seed, including those described by GRN765, 771, 778 has the potential to cause an allergic reaction in some sensitive individuals. The current prevalence rate of this allergy is low and is not anticipated to be a concern to the general population.

The Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004 is enforced by FDA to help Americans avoid the health risks posed by food allergens. There are over 160 foods that can cause allergic reactions in people with food allergies FDA (2018). US law identifies the eight most common allergenic foods which account for 90 percent of food allergic reactions and are the food sources from which many other ingredients are derived. The eight foods identified by the law are:

1. Milk
2. Eggs

3. Fish (e.g., bass, flounder, cod)
4. Crustacean shellfish (e.g., crab, lobster, shrimp)
5. Tree nuts (e.g., almonds, walnuts, pecans)
6. Peanuts
7. Wheat
8. Soybeans

These eight foods, and any ingredient that contains protein derived from one or more of them, are designated as "major food allergens" by FALCPA (FDA 2018). Hemp seed derivatives are not considered a major US food allergen.

11b. Time Frame Covered by Literature Search

Response:

No specific cut-off date was used during the literature searches performed during preparation of the notices. General search terms to identify information to assess risk from THC included but are not limited to the following: oral administration, THC, cannabis, cannabinoids, dronabinol, urine, drug test, toxicity etc.

11c. Historical Consumption of Hemp

Although this submission does not make a history of use claim for GRAS, there is a long-history and a variety of uses over a widespread geographic area that reinforces the scientific data and recognition by the scientific community of hemp seed's safety and utility as a nutritive food.

A summary of the history of consumption is provided below to further support the safety of consuming hemp.

There are three notable aspects to bear in mind when reviewing the historical consumption of hemp. First, historical consumption, which extends thousands of years, clearly pre-dates the development of modern industrial, low-THC hemp cultivars. Therefore, the historical evidence supports hemp consumption at higher levels of THC, CBD, and other Cannabinoids. Second, authors researching and writing on THC and hemp make a distinction between food use, medicinal or therapeutic use, and ritual use. Much of the summary below comes from textbooks with specific chapters on the consumption of hemp as food. Finally, the history is extensive and global. There is no way to fully summarize the entire history of hemp cultivation and use as food. It has been eaten around the world by men, women, and children for thousands of years. A timeline from *Cannabis: Evolution and Ethnobotany*, was adapted and is included on page 121.

This summary will cover:

A. History of Hemp Generally
B. Ancient Use in Asia
C. Ancient Use in the Middle East
D. Ancient Use in Europe
E. Historical Use with Children

A. History of Hemp Consumption Generally

The Cannabis sativa plant is a botanical product with origins tracing back to the mists of time. Since early humans gathered "a broad diversity of edible plant material much further back in time than has been generally accepted by scholars of prehistory" it is likely Cannabis seeds were consumed as far back as the Paleolithic era.[1] The seed of Cannabis sativa L. has been an important source of nutrition for thousands of years.[2] There is historical evidence of use in Japan[3] dating back 10,000 years ago and in modern Moldova, Ukraine and Romania[4] 6,000 years ago. Similar dates are found around the world and are briefly discussed below.

Ancient Use in Asia

Hemp seeds have an ancient history of use in China. It was regarded as an important crop in the Neolithic era with archaeo-botanical evidence found at several sites.[5] Written records from1600 to 771 BCE, show hemp listed as one of five major grains. Those included foxtail millet (chi), broomcorn millet (shu), rice (tao), barley or wheat (mai), and hemp (ma).[6] Other written records include poems and songs about growing and eating hemp. Other archeological evidence from ancient northern China found hemp among nine important grains including millets, rice, wheat, barley, soybeans, lesser beans, and hemp seed.[7] The archeological record contains much more evidence as discussed in *Cannabis Evolution and Ethnobotany*.

---

[1] *See e.g.*, Flannery, K. V. 1969. "Origins and ecological effects of early Domes- tication in Iran and the near east." In The *Domestication and Exploitation of Plants and Animals*, edited by P. J. Ucko and G. W. Dimbleby, 73–100. London: Duckworth; Weiss, e., W. Wetterstrom, D. Nadel, and O. Bar-Yosef. 2004. "The Broad spectrum Revisted: evidence from Plant Remains." *Proceedings of the National Academy Science* 101 (26): 9551–55; Dolukhanov, P.M. 2004. "Prehistoric environment, Human Migrations and Origin of Pastoralism in northern eurasia." In Impact of the Environment on Human Migration in Eurasia: Proceeding of the Nato Advanced Research Workshop, Held in St. Petersburg, 15–18 November 2003, edited by e. M. Scott, A. Y. Alekseev, and G. Zaitseva, 225–42. Dordrecht, The Netherlands: Kluwer Academic.

[2] *See, e.g.,* J.C. Callaway, Hempseed as a nutritional resource: An overview, Euphytica January 2004, Volume 140, Issue 1–2, pp 65–72)("*Cannabis sativa* L. has been an important source of food, fiber and medicine for thousands of years in the Old World."

[3] Okazaki. H., M. Kobayashi, A. Momohara, S. Eguchi, T. Okamoto, S. Yanagisawa, S. Okubo, and J. Kiyonaga. 2011. "Early Holocene coastal environment change Inferred from Deposits at Okinoshima Archeological site, Boso Peninsula, central Japan." *Quaternary International* 230:87–94; and Kudo, Y., M. Kobayashi, A. Momohara, T. Nakamura, S. Okitsu, S. Yanagisawa, and T. Okamoto. 2009. "Radiocarbon Dating of the fossil Hemp fruits in the earliest Jomon Period from the Okinoshima site, chiba, Japan." [In Japanese with English abstract.] *Japanese Journal of Historical Botany* 17, 27–32.

[4] Yanushevich, Z. V. 1989 "Agricultural evolution north of the Black sea from the Neolithic to the Iron Age." In *Foraging and Farming— The Evolution of Plant Exploitation*, edited by D. R. Harris and G. c. Hillman, 607–19. London: Unwin Hyman.

[5] (Chang, K.C. 1979. Food in Chinese Culture: Anthropological and Historical Perspectives. new Haven, cT: Yale University ; Huang, H. T. 2000. Science and Civilization in China. Volume 6: Biology and Biological Technology. Part V: Fermentations and Food Science. Cambridge: Cambridge University). (Zhimin, A. 1989 "Prehistoric Agriculture in China." In *Foraging and Farming—The Evolution of Plant Exploitation.*, edited by D. R. Harris and G. C. Hillman, 641–49.London: Unwin Hyman). (Chang, K.C. 4th ed. *The Archeology of Ancient China.* Revised, Lon- don: Yale University; Crawford, G. W., and H. Takamiya. 1990. "The Origins and Implications of Late Prehistoric Plant Husbandry in Northern Japan." *Antiquity* 64 (245): 889–911).

[6] *Id.* Huang (2000)

[7] L u, X., and R. C. Clarke. 1995. "The cultivation and Use of Hemp (*Cannabis Sativa* L.) in Ancient china." *Journal of the International Hemp Association* 2 (1): 26–30.

It's suggested based on linguistic evidence that hemp seeds were the first crop processed for oil (the Mandarin Chinese character for seed or grain mill (*mò*) is 磨, which combines 麻 (*má*) or "hemp" and 石 (*shí*) or "stone").[8] Hemp oil production became common in the sixth century which developed commercial factories that pressed oil seeds.[9] The evidence is clear this was used for cooking.

Hemps seeds continue to be pressed for their oil, and in some "areas the fruits of large-seeded varieties are quite commonly eaten raw or roasted as snacks."[10] In China, subsistence farmers living in remote mountainous regions of south-western China "still make porridge with hemp seeds" while in Tibet hemp seeds are "commonly parched, milled, and mixed into buttered tea."[11]

There is also evidence of early hemp consumption across Asia. Hemp seeds were introduced into Korea by China and remain a staple in impoverished North Korea.[12] Hemp seeds appear very early on in the archeological record of Japan, some recently discovered dating back about 10,000 years. For centuries, people living in the northwestern Himalayan foothills of India and Nepal have "roasted and eaten the [hemp] seeds.[13] Hemp is still part of Indian cuisine, a dish called *bosa* consists of the seeds of goose grass (*Eleusine indica*) and hemp, and another, referred to as *mura*, is made with parched wheat, amaranth or rice, and hemp seed.[14] The use of hemp seeds in Indian cuisine is described as making all vegetables more palatable and complete foods.[15]

Ancient Use in the Middle East

In Pakistan, Iran, and Turkey, baked hemp seeds are sold by street vendors and are very popular among children as nuts.[16] In ancient Persia (Iran), hemp seeds were consumed as a food and oil since at least the Middle Persianor Pahlavi period (about the tenth century CE).[17] Historical written records also refers to the economic value of hemp oil.

Many contemporary authors also point to the German-Hungarian scholar Immanuel Löw 's 2,600 page book titled *Die Flora der Juden* or "Flora of the Jews" for evidence of hemp seed use in the Middle East. Löw describes a sixth-century edible preparation in Persia contained hemp seeds and was called *sahdanag*, the "royal grain" or "king's grain." Löw tells us the Jewish people referred to hemp as *q'aneh-bosm*, the "root name" for *Cannabis*, and learned to make *sahdanag* from the Persians. A meal of roasted hemp seeds migrated with Jewish merchants and was well liked in the medieval period of Europe.

Ancient Use in the Europe

---

[8] *Id.* Huang (2000)
[9] *Id.*
[10] Clarke and Merlin, Cannabis Evolution and Ethnobotany, Chapter Title: Food, Feed, and Oil Uses of Hemp (Univ. of California Press, 2013).
[11] Hong, s., and R. C. Clarke. 1996. "Taxonomic studies of *Cannabis* in china." *Journal of the International Hemp Association* 3 (2): 55–60.
[12] *Id.* at 9.
[13] Watt, G. 1908. *Commercial Products of India*. Calcutta, India: E. P. Dutton.
[14] Robinson, R. 1996. *The Great Book of Hemp*. Rochester, VT: Park street.
[15] *Id.* Robinson (1996).
[16] Hayatghaibi, H., and I. Karimi. 2007. "Hypercholesterolemic effect of Drug-Type *Cannabis Sativa* L. seed (Marijuana seed) in Guinea Pig." Pakistan Journal of Nutrition 6 (1): 59–62.
[17] *Id.* at 9.

There are many examples of hemp eaten as food in Europe. For example, one author referred to the cooking and consumption of hemp seed by peoples of Eastern Europe: "Russians and Poles, even of the higher class, bruise or roast the seeds, mix them with salt, and eat them on bread."[18] There are in fact many Baltic and Eastern European references to people preparing and eating hemp seeds. The history is well documented in the Baltic and Eastern Europe. In Poland hemp seeds are stewed or made into porridge, which is common across the region.[19] In Latvia and Lithuania hemp became a staple in the Eighteenth Century and is commonly eaten as a soup or boiled with potatoes.[20] In Estonia hemp is wildly prepared as butter, milk or porridge.[21] It is also eaten in Northern Europe. In Finland hemp seeds have a history of being ground into a cereal meal and mixed with barley, buckwheat and salt.[22] This is called hempen meal. Oil derived from pressed hemp seeds was an important part of traditional societies in Finland, Russia, Poland, and other Eastern European countries.

The first literary evidence that ancient Greeks consuming hemp seed cakes appeared around the middle of the fourth century BCE. Among the foods served at a symposium were "*kannabides*," which translates as "a confection of *Cannabis* seeds and honey."[23]

Eastern European settlers in Canada, carried hemp seeds with them when they immigrated into the prairie regions, including Canada. There they grew Cannabis and utilized the seeds "for fresh oil, baking and traditional dishes," while Canadians of Chinese ancestry "have also long eaten hemp seeds for medicinal and dietary reasons."[24]

Ancient Use in the Middle East

The use of hemp has links to the Iron Age and continued through to the Romans, medieval Europe to the present day. A tomb found in 1896 in Germany dating back to the iron age contained a vase with plant remains, including hemp.[25]

---

[18] Porcher, F. P. 1863. Resources of the Southern Fields and Forests. Medical, Economical and Agricultural: Being also a Medical Botany of the Southern States. Charleston, NC: Walker, Evans & Cogswell; or Dembinska, M. 1999. Food and Drink in Medieval Poland. Translated by M. Thomas with revision by W. W. Weaver. Philadelphia: University of Pennsylvania. First published 1963 in Polish by the Polish Academy of Sciences; *See also*, Zajaczkowa, J. 2002. "Hemp and nettle: Two food/fiber/Medical Plants in Use in eastern Europe." *Slovo, the Newsletter of the Slavic Interest Group.* http//www.gallowglass.org/jadwiga/scA/ hempnettle.html.

[19] *Id.*

[20] Ambrazevicius, R., ed. 1996. "Lithuanian Roots: An Overview of Lithuanian Traditional culture." *Lithuanian Folk Culture Center*. http://thelithuanians.com/booklithuanianroots node55.html. *American Heritage Dictionary: Dictionary of the English Language*. 2000. 4th ed. Boston: Houghton Mifflin.

[21] Kokassaar, U. 2003. "Kanepiseemnetest tehti vanasti jurssi, piima ja putru" [Hemp seeds were used for making hemp butter, milk and porridge]. [In estonian.] *Eesti Looduse* 10. http:/www .loodusajakiri.ee/eesti_loodus/index.php?artikkel=485. Kokugakuin University. 1997. *Basic Terms of Shinto*. Tokyo: Kokugakuin University, Institute for Japanese culture and classics. http://www2.kokugakuin.ac.jp/ijcc/wp/bts/bts_j .html#jingu_taima.

[22] Ahokas, H. 2002. "Cultivation of *Brassica* Species and *Cannabis* by Ancient Finnic Peoples, Traced by Linguistic, Historical and Eth- nologicala Data; Revision of *Brassica Napus* as *B. Radice-Rapi*." *Acta Botanica Fennica* 172:1–32.

[23] Butrica, J. L. 2006. "The Medicinal Use of *Cannabis* among the Greeks and Romans." In *Handbook of Cannabis Therapeutics: From Bench to Bedside*, edited by Russo, Ethan B. and Franjo Grotenhermen, 23–42. New York: Haworth.

[24] CHTA/Accc. 2004. "canadian Hemp: A Plant With Opportunity." *Canadian Hemp Trade Alliance*. http://www.hemptrade.ca

[25] *Id.* Hayatghaibi (2007)

Historical Use with Children

Historical examples of children eating hemp are plentiful. In South Africa, Suto tribal women "grind up [hemp] seeds with bread or mealie pap [porridge] and give it to children when they are being weaned."[26]. As noted above, in Pakistan, Iran, and Turkey, baked hemp seeds are very popular among children as nuts.[27]

Conclusion

This summary while only touching on a deep history, shows hemp baked, boiled, roasted, milled and pressed to make a wide variety of foods. This history over thousands of years joins the evidence submitted in other parts of the submission to provide a reasonable assurance of safety.

12. Conclusion:

The standard for eligibility classification as GRAS is a, "reasonable certainty that the substance is not harmful under the conditions of its intended use" (21 C.F.R. 170.30). The original notices outlined a basis for consensus on this conclusion and this supplement underscores that conclusion. Together the GRNs establish a body of evidence and information that any expert could review and reasonably, if not comfortably, find certainty on the consumption of hemp as described. We employed an expert on cannabis and THC to contribute two summaries as part of this review – both unquestionably support the safety of consumption of hemp. In the latest report, animal studies using exceptionally high mg/kg oral THC on dogs and monkeys report little toxicity and at levels that are far above intake levels proposed in the GRNs. Animal studies examining the endocrine hormone system, immune system, intrauterine and post-natal development, genotoxicity and carcinogenicity, neurotoxicity, all concluded the risks, if any, were nominal. The lowest-observed-effect level (LOEL) was 5 mg/person, equivalent to a dose of 60 µg/kg bw. Effects at this dose, which are above the levels proposed, were minimal and reversible. The consensus of safety found in the animal studies is not surprising when considering the history of human consumption. That history shows hemp baked, boiled, roasted, milled and pressed to make a wide variety of foods enjoyed and nutritiously eaten by every age group. This history over thousands of years joins the evidence submitted in other parts of the submission to provide a reasonable assurance of safety. There is an added element of the psychoactive effects of THC, which is unique to these notices. This is shown in the animal and human studies not to be a safety concern. While other regulatory bodies, like EFSA or FSANZ, have set intake levels for hemp they have done so following their own procedures and adhering to the policies of their respective governments, in particular to authorizing the consumption of materials with minute levels of THC.

[26] Ames, f. 1958. "A clinical and Metabolic study of Acute Intoxication with *Cannabis Sativa*." *Journal of Mental Science* 104:972– 99.
[27] *Id.* Hayatghaibi (2007)

References

Note – green highlighted references were cited in a review by Health Canada (2013).

Abel EL (1984) Effects of delta-9-THC on pregnancy and offspring in rats. Neurobehav. Toxicol. Teratol. 6 29-32.

Abel EL (1985) Effects of Prenatal Exposure to Cannabinoids, from Pinkert, T.M. (ed.) Current research on the consequences of maternal drug abuse. Washington, DC: DHHS publication 85-1400.

Andre CM, Hausman J-F, Guerriero G. (2016) Cannabis sativa: The Plant of the Thousand and One Molecules. Front Plant Sci. Frontiers Media SA; 7: 19.

ANZFA Final Assessment Report [Inquiry-S.17] ApplicationA360 Use of Industrial Hemp as a Novel Food, Australia New Zealand Food Authority

Astley S, Little RE (1992) Maternal marijuana use during lactation and infant development at one year. Neurotoxicol. Teratol. 12 161-168.

Bailey JR, Cunny HC, Paule MG and Slikker Jr. W (1987) Fetal Disposition of delta-9-Tetrahydrocannabinol (THC) during Late Pregnancy in the Rhesus Monkey, Toxicol. Appl. Pharmacol., 90, 315-321.

Blevins RD & Regan JD (1976) delta-9-Tetrahydrocannabinol: Effect on macromolecular synthesis in human and other mammalian cells. Archives of Toxicology 34 127-135

Block RI, R & Schechte JA (1991) Effects of chronic marijuana use on testosterone, luteinising hormone, follicle stimulating hormone, prolactin and cortisol in men and women. Drug and Alcohol Dependence 28 121-128.

Brents LK. Marijuana, the Endocannabinoid System and the Female Reproductive System. Yale J Biol Med. 2016 Jun 27;89(2):175-91.

Bindra, G. S., Gibson, R. S., Thompson, L. U. (1986) [Phytate][calcium][zinc] ratios in asian immigrant lacto-ovo vegetarian diets and their relationship to zinc nutriture, Nutr. Res. 6, 475–483.

Citti C, Pacchetti B, Vandelli MA, Forni F, Cannazza G. J. (2018) Pharm Biomed Anal. 149: 532-540.

Cone EJ, Johnson RE, Moore JD, Roache JD. Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. Pharmacol Biochem Behav. 1986 Jun;24(6):1749-54.

D. Rotherham and S.A. Harbison (2011) Differentiation of drug and non-drug Cannabis using a single nucleotide polymorphism (SNP) assay. Forensic Science International 207: 193–197.

Downer EJ, Gowran A and Campbell VA (2007) A comparison of the apoptotic effect of Δ9-tetrahydrocannabinol in the neonatal and adult rat cerebral cortex. Brain Research, 1175, 39–47.

Ellis, R., Kelsay, J. L., Reynolds, R. D., Morris, E. R., et al., (1987) Phytate: Zinc and phytate x calcium: Zinc millimolar ratiosin self-selected diets of Americans, Asian Indians, and Nepales, Am. Diet. Assoc. 87, 1043–1047.

EFSA Journal 2015;13(6) 4141.

Escrivá Ú, Jesús Andrés-Costa M, Andreu V, Picó Y. (2018) Food Chem. 254: 391

Fitzgerald, S. L., Gibson, R. S., Serrano, J. A., Portocarrero, L. et al., (1993) Trace-element intakes and dietary phytate/zn and ca x phytate/zn millimolar ratios of periurban Gatemalan women during the 3rd trimester of pregnancy, Am. J. Clin. Nutr. 57, 195 –201.

Fontanel, Didier (2013) Unsaponifiable Matter in Plant Seed Oils. Springer-Verlag.

Fleischmann RW, Hayden DW Rosenkrantz H Braude MC (1975) Teratologic evaluation of delta-9-THC in mice, including a review of the literature. Teratology 12 47-50.

Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016.

Hansen HH, Kruzt B, Sifringer M, Stefovska V, Bittigau P, Pragst F, Mariscano G, Lutz B and Ikonomidou C (2008) Enhance Susceptibility of Immature Brain to Ethanol Neurotoxicity. Annals of Neurology, 64, 42–52.

Held, N. A., Buergel, N.,Wilson, C. A., Monsen, E. R., (1988) Constancy of zinc and copper status in adult women consuming diets varying in ascorbic acid and phytate content, Nutr. Rep. Int. 37, 1307–1317.

Hernandez ML, Garcia-Gil L, Berrendero F, Ramos JA, Fernandez-Ruiz JJ (1997) delta-9-tetrahydrocannabinol increases activity of tyrosine hydroxylase in cultured fetal mesensephalic neurons. J. Mol. Neurosci. 8 83-91.

Holler JM, Bosy TZ, Dunkley CS, Levine B, Past MR, Jacobs A. Delta9-tetrahydrocannabinol content of commercially available hemp products. J Anal Toxicol. 2008 Jul-Aug;32(6):428-32.

Hunt CA, Jones RT, Herning RI, Bachman J. J. (1981) Pharmacokinet. Biopharm;9:245.

Hutchings DE (1985) Issues of methodology and interpretation in clinical and animal behavioural teratology studies. Neurobehaviour, Toxicology & Teratology 7 639-642.

Hutchings DE, Martin BR, Gamagaris Z, Miler N, Fico T (1987) Developmental toxicity of prenatal delta-9-tetrahydrocannabinol: effects of maternal nutrition, offspring growth, and behaviour. NIDA Res. Monogr. 76 363-369.

Industrial Hemp Technical Manual Standard Operating Procedures for Sampling, Testing and Processing

Jin R. Zhou & John W. Erdman Jr. (1995) Phytic acid in health and disease, Critical Reviews in Food Science and Nutrition, 35:6, 495-508

Jorgensen K, Wulf HC, Husum B Niebuhr E Jorgensen K (1991) Sister chromatid exchange in cannabis smokers. 261 193-195.

K. Georgi, E. Mavric, K. Speer. Bestimmung von Δ9-Tetrahydrocannabinol in hanfhaltigen

K. Ridgway, S.P.D. Lalljie, R.M. Smith (2007) Sample preparation techniques for the determination of trace residues and contaminants in foods, J. Chromatogr. A1153 36–53.

Knight EM et al. (1994) Relationships of serum illicit drug concentrations during pregnancy to maternal nutritional status. In: Drug abuse, nutrition and pregnancy outcome. American Institute of Nutrition.

Lachenmeier D and Walch, S. (2005) EJEAFChe, 4(1):812-826

Landfield PW, Cadwallader LB & Vinsant S. (1988) Quantitative changes in hippocampal structure following long-term exposure to delta-9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. Brain Research 443 47-62.

Lebensmitteln. Dtsch. Lebensm.-Rdsch. 98, 363-366 (2002).

Lombaert, G. (2004). Letter to Canadian Hemp Trade Alliance regarding 2003-2004 Survey Data: Cannabinoids in Hemp Based Foods.

McElroy, A. (2018). Personal communication. 09/04/2018

Meng Q, Buchanan B, Zuccolo J, Poulin M-M, Gabriele J, Baranowski DC (2018). A reliable and validated LC-MS/MS method for the simultaneous quantification of 4 cannabinoids in 40 consumer products. PLoS ONE 13(5): e0196396

MethodologyÐCanada.ca [Internet]. Available: https://www.canada.ca/en/health-canada/services/health-concerns/reports-publications/controlled-substances-precursor- chemicals/industrial-hemp-technical-manual-standard-operating-proceduressampling-testingprocessing-methodology.html

Milica Pojić, Aleksandra Mišan, Marijana Sakač, Tamara Dapčević Hadnađev, Bojana Šarić, Ivan Milovanović, and Miroslav Hadnađev. Characterization of Byproducts Originating from Hemp Oil Processing. Journal of Agricultural and Food Chemistry 2014 62 (51), 12436-12442

Murphy, S. P., Beaton, G. H., Calloway, D. H. (1992) Estimated mineral intakes of toddlers: Predicted prevalence of inadequacy in village population in Egypt, Kenya, and Mexico, Eur. J. Clin. Nutr. 56, 565–572

Murphy LL, Steger RW, Smith MS, Bartke A. (1990) Effects of delta-9-tetrahydrocannabinol, cannabinol, and cannabidiol, alone, and in combinations, on luteinizing hormone and prolactin release and on hypothalamic neurotransmitters in the male rat. Neuroendocrinology 52 316-321.

Nadulski T, Pragst F, Weinberg G, Roser P, Schnelle M, Fronk EM, Stadelmann AM. (2005) Ther. Drug Monit;27:799.

NTP (1996) Toxicology and carcinogenesis studies of 1-trans-delta-9-tetrahydrocannabinol in F344/N rats and B6C3F1 mice. National Toxicology Program

Technical Report series no. 446.

Phillips RN, Turk RF and Forney RB (1971) Acute toxicity of Δ9-tetrahydrocannabinol in rats and mice. Proceedings of the Society for Experimental Biology and Medicine, 136, 260–263.

Raboy, V. (2003) myo-Inositol-1,2,3,4,5,6-hexakisphosphates, Phytochemistry 2003, 64, 1033 – 1043.

Rosenberg EC, Patra PH, Whalley BJ (2017) Therapeutic effects of cannabinoids in animal models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection. Epilepsy Behav. 70(PtB):319-327

Ross, S. Mehmedic, Z., Murphy, T. and ElSohly, M. (2000) Journal of Analytical Toxicology, Vol. 24, November/December 2000. 716-717.

Russo, E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br.J.Pharmacol. 163: 1344-1364.

Schlemmer U, Frølich W, Prieto RM, Grases F.(2009) Phytate in foods and significance for humans: food sources, intake, processing, bioavailability, protective role and analysis. Mol. Nutr. Food Res. 53, S330 –S375

Sidney S Bech JE, Tekawa IS Quesenberry CP Friedman GD (1997) Marijuana use and mortality. Am. J. Public Health 87 585-590.

Silva L, Zhao N, Popp S and Dow-Edwards D (2012) Prenatal tetrahydrocannabinol (THC) alters cognitive function and amphetamine response from weaning to adulthood in the rat. Neurotoxicology and Teratology, 34, 63–71.

Slikker W, Paule MG, Ali S, Scallet AC, Bailey JR (1992) Behavioural, neurochemical, and neurohistological effects of chronic marijuana smoke exposure in the nonhuman primate. In: Murphy L & Bartke A (eds.) Marijuana/Cannabinoids: neurobiology and neurophysiology. CRC Press. p 219-273.

Sirikantaramas S, Taura F, Tanaka Y, Ishikawa Y, Morimoto S, Shoyama Y. (2005) Tetrahydrocannabinolicacid synthase, the enzyme controlling marijuana psychoactivity, is secreted into the storage cavity of the glandular trichomes. Plant Cell Physiol. 46: 1578-82.

Smith CG, Asch RH. Acute, short-term, and chronic effects of marijuana on the female primate reproductive function. NIDA Res. Monogr. 1984;44:82-96.

Smith CG, Smith TM, Becsh NF, Smith RG, Asch RH (1978) Effects of delta-9-tetrahydrocannabinol (THC) on female reproductive function. Adv. Bioisci. 22-23 449-467.

Smith CG et al. (1979) Effect of tetrahydrocannabinol on the hypothalamic-pituitary axis in the ovariectomized rhesus monkey. Fertility and Sterility 31 335-339.

Steger RW et al. (1980) The effects of delta-9-tetrahydrocannabinol on the positive and negative feedback control of luteinizing hormone release. Life Sciences 27 1911-1916.

Steger RW et al. (1981) Interactions of cocaine and delta-9-tetracannabinol with the hypothalamo-hypophyseal axis of the female rat. Fertility & Sterility 35 567-572.

Steger RW, Murphy LL. Bartke A, Smith MS (1990) Effects of psychoactive and nonpsychoactives cannabinols on the hypothalamic-pituitary axis of the adult male rat. Pharmacol. Exp. Ther. 270 219-227.

Tahir SK & Zimmerman AM (1992) Cytoskeletal organisation following cannabinoid treatment in undifferentiated and differentiated PC12 cells. Biochemistry Cell Biology 70 1159-1173.

Thomas RJ (1975) The toxicologic and teratologic effects of delta-9-tetrahydrocannabinol in the zebrafish embryo. Toxicol Appl Pharmacol. 32(1):184-90.

Thompson G, Fleischman R, Rosencrantz H & Braude M (1973) Oral and intravenous toxicity of delta-9-tetrahydrocannabinol in rhesus monkeys. Toxicology and Applied Pharmacology 27; 648-665.

Trofin, G. (2012) Rev Chim. 63:3

Tyrey L & Murphy LL (1988) Inhibition of suckling-induced milk ejections in the lactating rat by delta-9-tetrahydrocannabinol. Endocrinology 123 469-472.

US Food & Drug Administration (2018). Food Allergies: What You Need to Know. Accessed 09/12/2018. https://www.fda.gov/food/resourcesforyou/consumers/ucm079311.htm

Wall. ME.; Brine. DR.; Perez-Reyes. M. (1976) The Pharmacology of Marihuana. Braude. MC.; Szara. S., editors. Raven Press; New York: 1976. p. 93

Wei, B., McGuffey J., Blount, B., and Wang, L. (2016) Sensitive Quantification of Cannabinoids in Milk by Alkaline Saponification−Solid Phase Extraction Combined with Isotope Dilution UPLC−MS/MS. ACS Omega. 1307-1313.

WHO (1997) Cannabis: a health perspective and research agenda. Programme on Substance Abuse, Division of Mental Health and Prevention of Substance Abuse, World Health Organization.

Yamaori, S., Kushihara, M., Yamamoto, I., and Watanabe, K. (2010). Characterization of major phytocannabinoids, cannabidiol and cannabinol, as isoform-selective and potent inhibitors of human CYP1 enzymes. Biochem.Pharmacol. 79: 1691-1698.

Zhu, H. J., Wang, J. S., Markowitz, J. S., Donovan, J. L. and others. (2006). Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. J.Pharmacol.Exp.Ther. 317: 850-857.

Table 1 Upper Bound Estimate of Total THC Exposure Based on Body Weight

Age & Body Weight	A - TOTAL THC EXPOSURE AT MAXIMUM SPECIFICATION LEVELS (µg/kg Body Weight)[1,2,3,4] 90% Percentile Cumulative Consumption	B - TOTAL THC EXPOSURE USING MEAN VALUES CACULATED FROM HISTORICAL DATA (µg/kg Body Weight)[1,2,3,5] 90% Percentile Cumulative Consumption	TOTAL THC EXPOSURE BASED USING MONTE CARLO PREDICTED DAILY EXPOSURE (µg/kg Body Weight)[1,2,3] 99.99% Certainty 90% Percentile Cumulative Consumption	LEVELS RECOGNIZED BY OTHER REGULATORY AUTHORITIES (µg/kg Body Weight)					
				Germany Acceptable Daily Intake	Switzerland Provisional Daily Intake	Australia and New Zealand Tolerable Daily Intake	EFSA Acute Reference Dose	Canada	Austria
Newborn - 2 months Males - 5.4 kg	0.0	0.0	0.0						
Newborn - 2 months Females - 4.8 kg	0.0	0.0	0.0						
2 - 5 months Males - 7.3 kg	0.0	0.0	0.0						
2 - 5 months Females - 6.8 kg	0.0	0.0	0.0						
6 - 11 months Males - 8.5 to 9.7 kg	6.7	0.6	2.5						
6 - 11 months Females - 8.0 to 9.3 kg	7.1	0.6	2.7						
11 to 23 months Males - 11.4 to 14.2 kg	12.7	3.5	6.4						
11 to 23 months Females - 11.2 to 13.3 kg	11.5	3.3	5.9	**5**	**7**	**6**	**1**	**Not Set**	**1-2**
2 to 5 years Males - 14.2 kg	10.2 (Table 42, GRN778)	2.8	5.1						
2 to 5 years Females - 13.3 kg	9.7 (Table 43, GRN778)	2.8	5.0						
6 to 11 years Males - 23.9 kg	6.6 (Table 44, GRN778)	2.0	3.5						
6 to 11 years Females - 23.8 kg	6.9 (Table 45, GRN778)	2.1	3.7						
2 years & older Males - 88.8 kg	2.2 (Table 41, GRN778)	0.7	1.3						
2 years & older Females - 75.48 kg	2.5 (Table 41, GRN778)	0.8	1.5						

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States. 2011-2014. National center for Health Statistics. Vital Health Stats 3(39). 2016

[2]Estimated that infants age birth to 5 months would consume no hemp and infants age 6 to 11 months could consume hemp beverage in place of fluid milk (Table 16). Estimated hemp consumption for children age 11 to 23 months based on consumption levels for 2 to 5 year old children per NHANES (Tables 17 and 18)

[3]Exposure based on body weight for infants 6 to 11 months calculated using hemp estimates from Tables 17 and 18. Other ages calculated using cumulative daily consumption of all hemp ingredients at 90% percentile taken from GRN778: 36.12 g all individuals 2 years and older (Table 14), 28.88 g boys age 2 to 5 years (Table 15), 25.33 g girls age 2 to 5 years (Table 16), 30.32 g boys age 6 to 11 years (Table17) and 31.1 g girls age 6 to 11 years (Table 17). Used lowest weight when range of body weights was cited in reference.

[4]Specification limits (µg/g THC): Hulled Hemp Seed = NMT 4, Hemp Protein Powder = NMT 4, Hemp Oil = NMT 10.

[5]Mean THC levels (µg/g): Hulled Hemp Seed = 0.3, Hemp Protein Powder = 0.6, Hemp Oil = 6.

[6]Calculated µg/kg body weight for children age 11 to 23 months using typical body weights and THC data from Tables 16 and 21.

Table 2 Summary of Historical Total THC Testing

	Hemp Oil GRN778											Hulled Hemp Seed GRN765				Hemp Protein Powder GRN771				
	Cumulative (All Years)	Cumulative (All Years Continued)	Cumulative (All Years Continued)	2011	2012	2013	2014	2015	2016	2017	2018	Cumulative (all years)	2013	2014	2016	Cumulative (all years)	2012	2013	2014	2016
Historical Data using GC-MS LOD of 0.2 µg/g	4.0	7.7	5.6	4.0	9.6	6.6	5.8	4.7	0.6	4.2	8.6	0.3	0.3	0.5	1.5	1.2	1.2	0.3	0.7	0.2
	6.0	4.3	4.5	6.0	6.7	4.4	8.0	4.9	4.7	6.9	5.4	0.3	0.3	0.3	0.2	0.3				0.5
	6.0	4.9	6.7	6.0	4.2	4.9	4.4	4.1	5.4	6.0	6.4	0.3	0.3	0.3		0.7				0.7
	9.6	4.7	5.3		8.5	4.4	7.7	7.6	8.7		6.7	0.4	0.4	0.2		0.2				
	6.7	4.9	5.2		4.0	4.3	5.2	5.6	6.0		5.6	0.4	0.4	0.2		0.5				
	4.2	4.1	6.4		8.6	5.8	4.6	6.1	0.6		6.9	0.2	0.2			0.7				
	8.5	7.6	8.0		4.2	4.5	6.9	6.6	4.9		5.8	0.2	0.2							
	4.0	5.6	9.8			5.2	4.3	4.5	6.0		8.5	0.2	0.2							
	8.6	6.1	8.9			4.3	6.1	4.0	3.1		4.3	0.2	0.2							
	4.2	6.6	9.1			4.7	4.9	4.6	8.0		5.8	0.2	0.2							
	6.6	4.5	5.9			5.8	6.5		5.7		6.6	0.2	0.2							
	4.4	4.0	8.5			9.5	5.1		5.0		5.6	0.3	0.3							
	4.9	4.6	6.9				4.0				4.5	0.3	0.3							
	4.4	0.6	6.9				7.1				6.7	0.5								
	4.3	4.7	8.0				5.2				5.3	0.3								
	5.8	5.4	5.9				6.6				5.2	0.3								
	4.5	8.7	4.7				2.6				6.4	0.2								
	5.2	6.0	4.8				7.7				8.0	0.2								
	4.3	0.6	6.9				4.3				9.8	1.5								
	4.7	4.9	5.7				4.9				8.9	0.2								
	5.8	6.0	9.1								9.1									
	9.5	3.1	6.7								5.9									
	5.8	8.0	6.7								8.5									
	8.0	5.7	8.9								6.9									
	4.4	5.0	9.9								6.9									
	7.7	4.2	8.7								8.0									
	5.2	6.9	7.5								5.9									
	4.6	6.0	6.7								4.7									
	6.9	8.6									4.8									
	4.3	5.4									6.9									
	6.1	6.4									5.7									
	4.9	6.7									9.1									
	6.5	5.6									6.7									
	5.1	6.9									6.7									
	4.0	5.8									8.9									
	7.1	8.5									9.9									
	5.2	4.3									8.7									
	6.6	5.8									7.5									
	2.6	6.6									6.7									
MEAN	**6.0**			**5.3**	**6.5**	**5.4**	**5.6**	**5.3**	**4.9**	**5.7**	**6.9**	**0.3**	**0.3**	**0.3**	**0.9**	**0.6**	**1.2**	**0.3**	**0.7**	**0.5**
MAX	**9.9**			**6.0**	**9.6**	**9.5**	**8.0**	**7.6**	**8.7**	**6.9**	**9.9**	**1.5**	**0.4**	**0.5**	**1.5**	**1.2**	**1.2**	**0.3**	**0.7**	**0.7**
MIN	**0.6**			**4.0**	**4.0**	**4.3**	**2.6**	**4.0**	**0.6**	**4.2**	**4.3**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**1.2**	**0.3**	**0.7**	**0.2**
STD DEV	**1.8**			**1.2**	**2.4**	**1.5**	**1.4**	**1.2**	**2.5**	**1.4**	**1.5**	**0.3**	**0.1**	**0.1**	**0.9**	**0.4**	**n/a**	**n/a**	**n/a**	**0.2**
COUNT	**106.0**			**3.0**	**7.0**	**12.0**	**20.0**	**10.0**	**12.0**	**3.0**	**39.0**	**20.0**	**13.0**	**5.0**	**2.0**	**6.0**	**1.0**	**1.0**	**1.0**	**3.0**

Table 3 Cannabinoid Testing – Hemp Protein Powder

Date	Lot Code	CBC (Cannabichromene)	CBD (Cannabidiol)	CBDA (Cannabidioloc Acid)	CBG (Cannabigerol)	CBN (Cannabinol)	THCV (Tetrahydrocannabivarin)	D8-THC	D9-THC	D9-THCA	Method	LOQ (µg/g)
15-Jun-18	LYQU17FC	<10	<10	20	<10	<10	<10	<10	<10	<10	HPLC-UV	10

Table 4 Cannabinoid Testing – Hemp Oil

Date	Lot Code	CBC (Cannabichromene)	CBD (Cannabidiol)	CBDA (Cannabidioloc Acid)	CBG (Cannabigerol)	CBN (Cannabinol)	THCV (Tetrahydrocannabivarin)	D8-THC	D9-THC	D9-THCA	Method	LOQ (µg/g)
23-Dec-15	KRFA15SO	n/a	n/a	30.4	n/a	n/a	n/a	n/a	n/a	n/a	GC/FID	1
12-Mar-17	BRSK13FO	n/a	n/a	20.3	n/a	n/a	n/a	n/a	n/a	n/a	GC/MS	1
18-Jul-17	ROSH15FC	n/a	n/a	30	n/a	n/a	n/a	n/a	n/a	n/a	HPLC-UV	1
23-Jan-18	KRFA17FOA	<1	10	50	<1	<1	<1	<1	<1	10	HPLC-UV	1
23-Jan-18	COGR27FOA	10	<1	60	10	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	ESKL17FOA	<1	<1	40	<1	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	GEWI85SCB	10	<1	20	10	<1	<1	<1	<1	<1	HPLC-UV	1
30-May-18	ROSH15FC	n/a	<1	30	n/a	n/a	n/a	n/a	n/a	n/a	HPLC-UV	1
30-May-18	ROSE67FO	n/a	20	60	n/a	n/a	n/a	n/a	n/a	n/a	HPLC-UV	1
30-May-18	LYQU17FC	n/a	10	150	n/a	n/a	n/a	n/a	n/a	n/a	HPLC-UV	1

Table 5 Cannabinoid Testing -Hulled Hemp Seed

Date	Lot Code	CBC (Cannabichromene)	CBD (Cannabidiol)	CBDA (Cannabidioloc Acid)	CBG (Cannabigerol)	CBN (Cannabinol)	THCV (Tetrahydrocannabivarin)	D8-THC	D9-THC	D9-THCA	Method	LOQ (µg/g)
12-Mar-14	BRCO93FC	n/a	n/a	1	n/a	n/a	n/a	n/a	0.51	n/a	GC/MS	1
23-Jan-18	TEAB15NCJ	<1	<1	10	<1	10	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	KRFA16SOE	<1	<1	10	<1	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	LAWA15FCI	<1	<1	20	<1	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	ARFR15XCI	<1	<1	10	<1	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	BRMU16FOT	<1	<1	20	<1	<1	<1	<1	<1	<1	HPLC-UV	1
24-Feb-18	180208B	<1	<1	<1	<1	<1	<1	<1	<1	<1	HPLC-UV	1
24-Feb-18	180214B	<1	<1	<1	<1	<1	<1	<1	<1	<1	HPLC-UV	1
15-Jun-18	WAPA17FC	<10	<10	120	<10	<10	<10	<10	<10	<10	HPLC-UV	10
15-Jun-18	180527BB-BJ	<10	<10	10	<10	<10	<10	<10	<10	<10	HPLC-UV	10
15-Jun-18	180510BC	<10	<10	10	<10	<10	<10	<10	<10	<10	HPLC-UV	10
08-Aug-18	NADI147FC	30	20	<10	20	10	<10	<10	<10	<10	HPLC-UV	10

Table 6 Upper Bound Exposure Estimate To Other Cannabinoids - All Individuals Age 2 Years and Older, 2 to 5 Year Old Children and 6 to 11 Year Old Children

ESTIMATED EXPOSURE TO OTHER CANNABINOIDS AT UPPER BOUND HEMP CONSUMPTION LEVELS																																		
	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) 90% Percentile Consumption Level (NHANES 2013-2014)[1]					CBDA EXPOSURE (µg/Day) Based on 150 µg/g value determined in historical testing[2]					CBD EXPOSURE (µg/Day) Based on 20 µg/g value determined in historical testing[2]					CBG EXPOSURE (µg/Day) Based on 20 µg/g value determined in historical testing[2]					CBC EXPOSURE (µg/Day) Based on 30 µg/g value determined in historical testing[2]					CBN EXPOSURE (µg/Day) Based on 10 µg/g value determined in historical testing[2]					CUMMULATIVE EXPOSURE (µg/Day) CBDA, CBD, CBG, CBC, CBN				
	2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years	
	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F
HULLED HEMP SEED	14.1	11.7	10.2	12.1	12.1	2111	1757	1530	1818	1821	281.4	234	204	242	243	281.4	234	204	242	243	422.1	351	306	364	364	140.7	117	102	121	121	3236	2705	2356	2800	2804
HEMP PROTEIN POWDER	13.8	12.4	10.6	12.1	12.5	2076	1854	1583	1821	1871	276.8	247	211	243	249	276.8	247	211	243	249	415.2	371	317	364	374	138.4	124	106	121	125	3183	2855	2437	2804	2881
HEMP OIL	8.2	4.8	4.6	6.1	6.5	1233	722	687	909	972	164.4	96	92	121	130	164.4	96	92	121	130	246.6	144	137	182	194	82.2	48	46	61	65	1891	1111	1058	1400	1497
CUMMULATIVE	**36.1**	**28.9**	**25.3**	**30.3**	**31.1**	**5420**	**4332**	**3800**	**4548**	**4664**	**722.6**	**578**	**507**	**606**	**622**	**722.6**	**578**	**507**	**606**	**622**	**1084**	**866**	**760**	**910**	**933**	**361.3**	**289**	**253**	**303**	**311**	**8310**	**6671**	**5851**	**7004**	**7182**

M - Males, F – Females

[1]Refer to Tables 14 to 18 in GRN765 for summary of hemp consumption per age group.

[2]Refer to Tables 3 to 5 for cannabinoid test results.

Table 7 Upper Bound Exposure Estimate To Other Cannabinoids - Infants and Children Age 12 to 23 Months

ESTIMATED EXPOSURE TO OTHER CANNABINOIDS AT UPPER BOUND HEMP CONSUMPTION LEVELS																																	
	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) Highest Level of Inclusion per Food Category and 90% Percentile Consumption Level (NHANES 2013-2014)[1]					CBDA EXPOSURE (cgg/Day) Based on 150 µg/g value determined in historical testing[2]					CBD EXPOSURE (µg/Day) Based on 20 µg/g value determined in historical testing[2]					CBG EXPOSURE (µg/Day) Based on 20 µg/g value determined in historical testing[2]					CBC EXPOSURE (µg/Day) Based on 30 µg/g value determined in historical testing[1]					CBN EXPOSURE (µg/Day) Based on 10 µg/g value determined in historical testing[1]					CUMMULATIVE EXPOSURE (µg/Day) CBDA, CBD, CBG, CBC, CBN				
	Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months	
	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F
HULLED HEMP SEED	0	14	14	11.7	10.2	0	2130	2130	1757	1530	0	284	284	234	204	0	284	284	234	204	0	426	426	351	306	0	142	142	117	102	0	3266	3266	2693	2346
HEMP PROTEIN	0	0	0	12.4	10.6	0	0	0	1854	1583	0	0	0	247	211	0	0	0	247	211	0	0	0	371	317	0	0	0	124	106	0	0	0	2843	2427
HEMP OIL	0	0	0	4.8	4.6	0	0	0	722	687	0	0	0	96	92	0	0	0	96	92	0	0	0	144	137	0	0	0	48	46	0	0	0	1106	1053
CUMMULATIVE	0	14	14	28.9	25.3	0	2130	2130	4332	3800	0	284	284	578	507	0	284	284	578	507	0	426	426	866	760	0	142	142	289	253	0	3266	3266	6642	5826

M - Males, F - Females

[1]Refer to Table 16 for estimated hemp consumption for infants age 6 to 11 month. Hemp consumption for 11 to 23 old children was estimated using the NHANES data for children age 2 to 5 years (Tables 15 and 16 GRN765). No hemp expected to be added to infant formula since preparation instructions specify use of water. Manufacturing of foods specific to infants such as formula and infant cereal is outside the scope of GRN765, 778, 771.

[2]Refer to Tables 3 to 5 for cannabinoid test results.

Table 8 Historical Aflatoxin 3rd Party Laboratory Testing Results – Hemp Protein Powder

Aflatoxin Testing Results Summary		
Date	Lot Code	Result LOQ (5 ng/g)
29-Feb-16	LAWA14FC	< 5 ng/g
03-Aug-16	JOSE13FC	< 5 ng/g
31-Jan-17	NEKE16FO	< 5 ng/g
31-Jan-17	161114HC	< 5 ng/g
01-Mar-17	170104HB	< 5 ng/g
01-Mar-17	SHCH36NO	< 5 ng/g
09-Jun-17	ASBS16SO	< 5 ng/g
18-Sep-17	SEYO76FOT	< 5 ng/g
19-Dec-17	ROBR66FOE	< 5 ng/g
19-Dec-17	WIGE85SCB	< 5 ng/g
19-Apr-18	DAMA45XCE	< 5 ng/g
09-May-16	TOBY34XC	< 5 ng/g
17-Jan-17	ANBE15NC	< 5 ng/g
17-Feb-17	QUVE55FC	< 5 ng/g
01-Jun-17	ROSE26FO	< 5 ng/g
05-Apr-18	DAMA45XCM	< 5 ng/g
42405	NEVA14FC	< 5 ng/g
16-May-16	DABR54FO	< 5 ng/g
03-Aug-16	ROGL14XC	< 5 ng/g
31-Jan-17	NEKE16FO	< 5 ng/g
09-Jun-17	WIGE15SC	< 5 ng/g
18-Sep-17	WIGE45SCK	< 5 ng/g
19-Apr-18	ADSI37FOG	< 5 ng/g
01-Mar-17	161216XX	< 5 ng/g
19-Dec-17	170911XY	< 5 ng/g

Table 9 Historical Aflatoxin 3rd Party Laboratory Testing Results – Hemp Oil

Aflatoxin Testing Results Summary		
Date	Lot Code	Result LOQ (5 ng/g)
16-May-16	DABR24FO	< 5 ng/g
31-Jan-17	ANBE15NC	< 5 ng/g
01-Mar-17	SHCH26NO	< 5 ng/g
09-Jun-17	DAMA15XC	< 5 ng/g
18-Sep-17	MAEN75XCH	< 5 ng/g
19-Dec-17	DABR16FOJ	< 5 ng/g
19-Apr-18	KRFA27SOI	< 5 ng/g

Table 10 Historical Aflatoxin 3rd Party Laboratory Testing Results – Hulled Hemp Seed

Aflatoxin Testing Results Summary		
Date	Lot Code	Result LOQ (5 ng/g)
05-Feb-16	QUVE64FC	< 5 ng/g
16-May-16	RACO24FC	< 5 ng/g
31-Jan-17	161115AB	< 5 ng/g
31-Jan-17	PAGR15NC	< 5 ng/g
31-Jan-17	ROLO25FC	< 5 ng/g
01-Mar-17	JUDU25FC	< 5 ng/g
09-Jun-17	15B0113XA11C	< 5 ng/g
09-Jun-17	KEWI16NO	< 5 ng/g
18-Sep-17	170831BF	< 5 ng/g
18-Sep-17	ROBR26FO	< 5 ng/g
19-Dec-17	171127BA	< 5 ng/g
19-Dec-17	ROBR76FOP	< 5 ng/g
19-Apr-18	180328AA	< 5 ng/g
19-Apr-18	NIBO17NOH	< 5 ng/g

Table 11 Historical Heavy Metals 3rd Party Laboratory Testing Results – Hemp Protein Powders

Date	Lot Code	Result				Method
		Arsenic LOQ (0.05 µg/g)	Cadmium LOQ (0.01 µg/g)	Mercury LOQ (0.05 µg/g)	Lead LOQ (0.01 µg/g)	
41697.00	LANE62XC	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
41697.00	ROSY64FO	< 0.05	0.06	< 0.05	0.03	ICP-MS
41719.00	N/A	< 0.1	0.05	0.01	< 0.03	ICP-MS
41758.00	N/A	< 0.1	0.05	0.01	< 0.03	ICP-MS
42389.00	ROMA84FO	< 0.05	0.04	< 0.05	< 0.01	ICP-MS
42410.00	LAWA14FC	< 0.05	0.03	< 0.05	0.05	ICP-MS
42440.00	ROSE94FO	< 0.05	0.06	< 0.05	0.06	ICP-MS
42585.00	JOSE13FC	< 0.05	0.04	< 0.05	< 0.01	ICP-MS
42751.00	SCBE16GO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42765.00	SAMC16NO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42787.00	SHCH26NO	< 0.05	0.01	< 0.05	< 0.01	ICP-MS
42814.00	POGR46SO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42864.00	ASBS16SO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42865.00	BRSK36NO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42900.00	ROSE56FO	< 0.05	0.07	< 0.05	< 0.01	ICP-MS
42913.00	ROBA36FO	0.05	0.03	< 0.05	< 0.01	ICP-MS
42996.00	ROBR36FO	< 0.05	0.04	< 0.05	< 0.01	ICP-MS
43031.00	ROBR66FO	< 0.05	0.03	< 0.05	0.04	ICP-MS
41697.00	LANE62XC	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
42283.00	ROSE44FO	< 0.05	0.05	< 0.05	< 0.01	ICP-MS
42517.00	DABR64FO	< 0.05	0.03	< 0.05	0.01	ICP-MS
42517.00	ROSE94FO	< 0.05	0.06	< 0.05	0.06	ICP-MS
42585.00	DAW184FC	< 0.05	0.05	< 0.05	< 0.01	ICP-MS
41697.00	BROS83FO	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
41719.00	N/A	< 0.1	0.03	0.01	< 0.03	ICP-MS
41767.00	N/A	< 0.1	0.01	0.01	< 0.03	ICP-MS
42009.00	ROBR54FO	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
42017.00	ROBR74FO	< 0.05	0.07	< 0.05	0.11	ICP-MS
42065.00	ROBR84FO	< 0.05	0.07	< 0.05	0.01	ICP-MS
42068.00	ROBR94FO	< 0.05	0.08	< 0.05	0.01	ICP-MS
42124.00	ROYB64FO	< 0.05	0.08	< 0.05	0.01	ICP-MS
42131.00	ROYB44FO	< 0.05	0.08	< 0.05	0.03	ICP-MS
42263.00	DAFA14FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42275.00	LAMA54FO	0.05	0.05	< 0.05	< 0.01	ICP-MS
42275.00	ROSE44FO	0.06	0.08	< 0.05	0.02	ICP-MS
42283.00	NESC53FC	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42297.00	ROSE54FO	< 0.05	0.08	< 0.05	0.03	ICP-MS
42304.00	KRFA25SO	< 0.05	0.03	< 0.05	0.02	ICP-MS
42304.00	ROSE64FO	< 0.05	0.07	< 0.05	0.02	ICP-MS
42313.00	KRFA15SO	0.08	0.01	< 0.05	< 0.01	ICP-MS
42389.00	NEVA14FC	0.08	0.03	< 0.05	0.11	ICP-MS
42410.00	ROMA84FO	< 0.05	0.06	< 0.05	0.03	ICP-MS
42440.00	ROSE94FO	< 0.05	0.06	< 0.05	0.06	ICP-MS
42451.00	DABR14FO	< 0.05	0.05	< 0.05	0.07	ICP-MS
42479.00	DABR24FO	< 0.05	0.05	< 0.05	0.05	ICP-MS
42485.00	DABR34FO	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
42508.00	DABR54FO	< 0.05	0.05	< 0.05	0.03	ICP-MS
42515.00	DABR64FO	< 0.05	0.04	< 0.05	< 0.01	ICP-MS
42522.00	DAGL14XC	< 0.05	0.04	< 0.05	0.02	ICP-MS
42535.00	HEBA15FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42538.00	KRFA35FO	0.05	0.02	< 0.05	0.07	ICP-MS
42580.00	LAMA45FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42585.00	ROGL14XC	< 0.05	0.01	< 0.05	< 0.01	ICP-MS
42633.00	MALA55FO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42670.00	LAMA65FO	< 0.05	0.02	< 0.05	0.06	ICP-MS
42698.00	POGR16CO	0.14	0.03	< 0.05	0.03	ICP-MS
42719.00	NEKE16FO	0.06	0.03	< 0.05	0.02	ICP-MS
42751.00	LAMA16FO	< 0.05	0.03	< 0.05	0.08	ICP-MS
42774.00	SHCH16NO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42780.00	CHSH16NO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42781.00	BRSK16NO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42788.00	SHCH26NO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42795.00	HSIC16XO	< 0.05	0.01	< 0.05	< 0.01	ICP-MS
42808.00	PGTM16SO	0.06	0.02	< 0.05	< 0.01	ICP-MS
42815.00	POGR46SO	0.09	0.03	< 0.05	0.01	ICP-MS
42822.00	PGAM16NO	0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42864.00	ASBS16SO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42873.00	BRSK36NO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42886.00	ROSE26FO	< 0.05	0.07	< 0.05	0.05	ICP-MS
43013.00	BRAN16FO	< 0.05	0.03	< 0.05	0.01	ICP-MS

Table 12 Historical Heavy Metals 3rd Party Laboratory Testing Results – Hemp Oil

Date	Lot Code	Result (µg/g)				Method
		Arsenic LOQ (0.05 µg/g)	Cadmium LOQ (0.01 µg/g)	Mercury LOQ (0.05 µg/g)	Lead LOQ (0.01 µg/g)	
41697.00	BRSK13FO	< 0.05	0.07	< 0.05	< 0.01	ICP-MS
42087.00	MAGR33FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42087.00	ROBR84FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42087.00	ROBR94FO	0.12	< 0.01	< 0.05	< 0.01	ICP-MS
42087.00	ROYB14FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42131.00	QUVE43FC	0.08	< 0.01	< 0.05	0.01	ICP-MS
42131.00	ROYB64FO	< 0.05	< 0.01	< 0.05	0.01	ICP-MS
42144.00	ROYB74FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42171.00	DAVA43FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42171.00	ROYB94FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42177.00	BEWI14XO	< 0.05	< 0.01	< 0.05	0.02	ICP-MS
42226.00	DAVA53FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42234.00	LAMA54FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42234.00	MAGR53FC	< 0.05	< 0.01	< 0.05	0.02	ICP-MS
42255.00	NESC53FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42261.00	DAFA14FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42261.00	ROSE44FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42283.00	DAVA63FC	< 0.05	< 0.01	< 0.05	0.16	ICP-MS
42292.00	ROSE54FO	< 0.05	< 0.01	< 0.05	0.07	ICP-MS
42311.00	ROSE64FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42311.00	KRFA25SO	< 0.05	< 0.01	< 0.05	0.03	ICP-MS
42313.00	KRFA15SO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42339.00	MAHA35	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42376.00	LAWA44FC	< 0.05	< 0.01	< 0.05	0.06	ICP-MS
42376.00	NEVA14FC	< 0.05	< 0.01	< 0.05	0.12	ICP-MS
42389.00	ROMA84FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42433.00	RRMH14FO	< 0.05	< 0.01	< 0.05	0.02	ICP-MS
42451.00	DABR14FO	< 0.05	< 0.01	< 0.05	0.09	ICP-MS
42507.00	DABR54FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42515.00	DABR64FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42519.00	DABR44FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42522.00	DAGL14XC	< 0.05	< 0.01	< 0.05	0.04	ICP-MS
42535.00	TOBY34XC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42564.00	DABR74FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42565.00	HEBA15FO	< 0.05	< 0.01	0.06	< 0.01	ICP-MS
42580.00	LAMA45FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42585.00	WIVA74FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42629.00	MHRB45FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42633.00	MALA55FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42669.00	MHRS75FO	< 0.05	< 0.01	< 0.05	0.08	ICP-MS
42670.00	LAMA65FO	< 0.05	< 0.01	< 0.05	0.08	ICP-MS
42698.00	POGR16CO	< 0.05	< 0.01	< 0.05	0.02	ICP-MS
42713.00	NEKE16FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42726.00	KELE16FO	< 0.05	< 0.01	< 0.05	0.08	ICP-MS
42745.00	SCBE16GO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42751.00	LAMA16FO	0.06	< 0.01	< 0.05	< 0.01	ICP-MS
42766.00	SAMC16NO	0.07	< 0.01	< 0.05	< 0.01	ICP-MS
42774.00	SHCH16NO	0.06	< 0.01	0.08	< 0.01	ICP-MS
42780.00	CHSH16NO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42788.00	SHCH26NO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42795.00	HSIC16XO	0.07	< 0.01	< 0.05	0.10	ICP-MS
42808.00	PGTM16SO	< 0.05	< 0.01	< 0.05	0.07	ICP-MS
42815.00	POGR46SO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42822.00	PGAM16NO	0.08	< 0.01	< 0.05	0.02	ICP-MS
42864.00	ASBS16SO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42873.00	BRSK36NO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42886.00	ROSE26FO	< 0.05	< 0.01	0.08	0.08	ICP-MS
42900.00	ROSE56FO	<0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42913.00	ROBA36FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42927.00	ROSE66FO	< 0.05	< 0.01	< 0.05	0.01	ICP-MS
43004.00	GRRS16FO	< 0.05	< 0.01	0.05	0.01	ICP-MS
43013.00	BRAN16FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
43021.00	NABR16FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
43054.00	DABR16FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
43174.00	RORD47SO	< 0.05	< 0.01	< 0.05	0.09	ICP-MS

Table 13 Historical Heavy Metals 3rd Party Laboratory Testing Results – Hulled Hemp Seed

Date	Lot Code	Result (µg/g)				Method
		Arsenic LOQ (0.05 µg/g)	Cadmium LOQ (0.01 µg/g)	Mercury LOQ (0.05 µg/g)	Lead LOQ (0.01 µg/g)	
41697.00	BRCO73FC	< 0.05	0.07	< 0.05	< 0.01	ICP-MS
41747.00	N/A	< 0.1	<0.01	< 0.005	< 0.03	ICP-MS
41777.00	N/A	< 0.1	0.01	0.01	0.03	ICP-MS
41802.00	N/A	< 0.1	0.03	< 0.005	< 0.03	ICP-MS
41802.00	N/A	< 0.1	0.01	< 0.005	< 0.03	ICP-MS
41802.00	N/A	< 0.1	< 0.01	< 0.005	< 0.03	ICP-MS
41802.00	N/A	< 0.1	0.04	< 0.005	0.03	ICP-MS
41933.00	DAWI64FC	< 0.05	0.01	< 0.05	< 0.01	ICP-MS
42047.00	IACU14XO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42125.00	TOBY14FC	< 0.05	0.02	< 0.05	0.02	ICP-MS
42283.00	LAWA24FC	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42410.00	JOKL24FC	0.06	0.02	< 0.05	0.03	ICP-MS
42410.00	QUVE44FC	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42522.00	GABA24FC	< 0.05	0.04	< 0.05	0.05	ICP-MS
42585.00	LACK15FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42599.00	160519.00	< 0.1	0.02	< 0.005	< 0.03	ICP-MS
42975.00	ROBR16FO	< 0.05	0.04	0.06	0.03	ICP-MS

Table 14 Phytate Exposure from Hemp Material

ESTIMATED EXPOSURE TO OTHER CANNABINOIDS AT UPPER BOUND HEMP CONSUMPTION LEVELS		
	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) 90% Percentile Consumption Level (NHANES 2013-2014)[1]	**PHYTATE EXPOSURE FROM HEMP MATERIAL CONSUMED AT CONSERVATIVE ESTIMATE (mg/Day)**
	2 Years & Older Males & Females	**2 Years & Older Males & Females**
HULLED HEMP SEED	14.1	450.7
HEMP PROTEIN POWDER	13.8	505.1
CUMMULATIVE	**27.9**	955.8

Table 15 Phytates Found in Other Common Foods

Food	Reported Phytate Content (g/100g) Schlemmer et al. 2009		Range of Phytate Content (mg/Reference Amount Customarily Consumed)	
	Low	High	Low	High
Almonds	0.4	9.4	105	2826
Peanuts	0.2	4.5	51	1341
Walnuts	0.2	6.7	60	2007
cashews	0.2	5	57	1494
Pecans	0.2	4.5	54	1356
Wheat Bran	2.1	7.3	315	1095

Table 16 Estimated Hemp Consumption and THC Exposure Levels - Infant Birth to 11 Months

Age	# Meals per Day[1]	Type of Food per Meal[1]	Quantity of food per Meal	Estimated Quantity of Hemp per Food Based on Levels of Usage[2]	Total ?-9-THC Exposure (µg/Day)6 *At NMT 4 µg/g ?-9-THC limit in hulled hemp seed per FHF specifications
Newborn - 2 months	5 - 6 (all meals)	Formula	28.35 g - 85.05 g (1 - 3 oz)	0[3,7]	0.0
				TOTAL ?-9-THC Exposure - Newborn to 2 months	**0.0**
2 - 5 months	5 - 6 (all meals)	Formula	85.05 g - 170.1 g (3 - 6 oz)	0[3,7]	0.0
				TOTAL ?-9-THC Exposure - 2 to 5 months	**0.0**
6 - 11 months	1 (breakfast)	Formula	170.1 g - 226.8 g (6 - 8 oz)	0[3,7]	0.0
		Infant Cereal	56.8 g (4 tbsp)	2.84 g hulled hemp seed from 2 tbsp hemp based milk alternative[5,7]	11.4
		Meat/Meat Alternative (egg, cheese, meat, beans etc.)	56.7 g (2 oz)	0[4]	0.0
	1 (lunch)	Formula	170.1 g - 226.8 g (6 - 8 oz)	0[3,7]	0.0
		Infant Cereal	56.8 g (4 tbsp)	2.84 g hulled hemp seed from 2 tbsp hemp based milk alternative[5,7]	11.4
		Meat/Meat Alternative (egg, cheese, meat, beans etc.)	56.7 g (2 oz)	0[4]	0.0
	1 (dinner)	Formula	170.1 g - 226.8 g (6 - 8 oz)	0[3,7]	0.0
		Meat/Meat Alternative (egg, cheese, meat, beans etc.)	56.7 g (2 oz)	0[4]	0.0
		Infant Cereal	56.8 g (4 tbsp)	2.84 g hulled hemp seed from 2 tbsp hemp based milk alternative[5,7]	11.4
	2 (snacks)	Formula	56.7 g - 113.4 g (2 - 4 oz)	0[3,7]	0.0
		Infant Cereal	56.8 g (4 tbsp)	5.68 g hulled hemp seed from 2 tbsp hemp based milk alternative[5,7]	22.7
				TOTAL ?-9-THC Exposure - 6 to 11 months	**56.8**

[1]Number of meals per day and meal composition selected from choices recommended by United States Department of Agriculture Infant Meal Pattern, 11/29/2016. Accessed 09/04/2018.
https://fns-prod.azureedge.net/sites/default/files/cacfp/CACFP_infantmealpattern.pdf
[2]Refer to Table 1 Usage Levels per Food Category in GRN765 (Hulled Hemp Seed). Maximum level used. to estimate hemp content.
[3]No hemp expected to be added to formula since preparation instructions specify use of water. [4]No hemp expected to be added

to cheese, meat, eggs or beans due to physical form of the food.
[5]Estimated that infant cereal could be prepared with a milk substitute comprised of up to 10% by weight hulled hemp seed.
[6]Upper bound exposure to Δ-9-THC estimated using FHF specification Limits. No difference based on gender is anticipated.
[7]Manufacturing of foods specific to infants such as formula and infant cereal is outside the scope of GRN 765, 778, 771.

Table 17 Daily Intake of Hemp - Males 11-23 Months based on NHANES for Males 2-5 Years

Hemp Ingredient	Minimum Daily intake (g/person)[1] Males 11 to 23 Months		Mid-Point Daily intake (g/person)[1] Males 11 to 23 Months		Maximum Daily intake (g/person)[1] Males 11 to 23 Months	
	Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	0.4	0.9	2.7	5.4	5.9	**11.7**
Protein Powders (inc. concentrate)	0.3	0.6	3.0	5.9	6.2	**12.4**
Oil	0.2	0.3	1.1	2.2	2.4	**4.8**
TOTAL	**0.9**	**1.7**	**6.8**	**13.6**	**14.4**	**28.9**

[1]Highly conservative - estimates hemp consumption at same levels as a child 2 to 5 years old (refer to Table 15 GRN765).

Table 18 Daily Intake of Hemp - Females 11-23 Months based on NHANES for Females 2-5 Years

Hemp Ingredient	Minimum Daily intake (g/person)[1] Females 2-5 Yrs		Mid-Point Daily intake (g/person)[1] Females 2-5 Yrs		Maximum Daily intake (g/person)[1] Females 2-5 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.4	0.7	2.4	4.7	5.1	10.2
Protein Powders (inc. concentrate)	0.2	0.5	2.5	5.0	5.3	10.5
Oil	0.2	0.3	1.1	2.1	2.3	4.6
TOTAL	**0.8**	**1.5**	**6.0**	**11.9**	**12.7**	**25.3**

[1]Highly conservative - estimates hemp consumption at same levels as a child 2 to 5 years old (refer to Table 16 GRN765).

Table 19 Daily Intake of THC - Males 11-23 Months based on NHANES for Males 2-5 Years (using Specification THC Limits)

Hemp Ingredient	Quality Specification THC µg/g	Minimum Daily Intake delta-9-THC[1] (µg/person)		Mid-Point Daily Intake delta-9-THC[1] (µg/person)		Maximum Daily Intake delta-9-THC[1] (µg/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	4.0	1.7	3.4	10.9	21.7	23.4	46.8
Protein Powders (inc. concentrate)	4.0	1.1	2.2	11.8	23.6	24.7	49.4
Oil	10.0	1.6	3.2	11.2	22.4	24.0	48.1
TOTAL		**4.4**	**8.8**	**33.9**	**67.8**	**72.2**	**144.4**

[1]Highly conservative - estimates hemp consumption at same levels as a child 2 to 5 years old

Table 20 Daily Intake of THC - Females 11-23 Months based on NHANES for Females 2-5 Years (using Specification THC Limits)

Hemp Ingredient	Quality Specification THC µg/g	Minimum Daily Intake delta-9-THC[1] (µg/person)		Mid-Point Daily Intake delta-9-THC[1] (µg/person)		Maximum Daily Intake delta-9-THC[1] (µg/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	4.0	1.5	3.0	9.4	18.9	20.4	40.8
Protein Powders (inc. concentrate)	4.0	0.9	1.8	10.1	20.2	21.1	42.2
Oil	10.0	1.5	3.1	10.7	21.4	22.9	45.8
TOTAL		**3.9**	**7.9**	**30.2**	**60.5**	**64.4**	**128.8**

[1]Highly conservative - estimates hemp consumption at same levels as a child 2 to 5 years old

Table 21 Exposure to THC at Maximum Hemp Consumption Levels Using Historical Mean Total THC Data

Age and Body Weight	Hulled Hemp Seed (g/Day)[1]	Total THC from Hulled Hemp Seed (µg)[2]	Exposure based on Body Weight (µg/kg bw)[3]	Hemp Protein Powder (g/Day)[1]	Total THC from Hemp Protein Powder (µg)[2]	Exposure based on Body Weight (µg/kg bw)[3]	Hemp Oil (g/Day)[1]	Total THC from Hemp Oil (µg/Day)[2]	Exposure based on Body Weight (µg/kg bw)[3]	Cumulative Hemp (g/Day)[1]	Cumulative Total THC (µg)	Cumulative Total THC Exposure from Hemp based on Body Weight (µg/kg bw)[3]
6 - 11 months Males - 8.5 to 9.7 kg	14.2	4.3	0.5	n/a	n/a	n/a	n/a	n/a	n/a	14.2	4.3	0.5
6 - 11 months Females - 8.0 to 9.3 kg	14.2	4.3	0.5	n/a	n/a	n/a	n/a	n/a	n/a	14.2	4.3	0.5
11 to 23 months Males - 11.4 to 14.2 kg	11.7	4.0	0.3	12.4	7.4	0.7	4.8	28.8	2.5	28.9	40.2	3.5
11 to 23 months Females - 11.2 to 13.3 kg	10.2	3.5	0.3	10.6	6.3	0.6	4.6	27.4	2.4	25.3	37.2	3.3
2 to 5 years Males - 14.2 kg	11.7	4.0	0.3	12.4	7.4	0.5	4.8	28.8	2.0	28.9	40.2	2.8
2 to 5 years Females - 13.3 kg	10.2	3.5	0.3	10.6	6.3	0.5	4.6	27.4	2.1	25.3	37.2	2.8
6 to 11 years Males - 23.9 kg	12.2	4.1	0.2	12.1	7.3	0.3	6.1	36.3	1.5	30.3	47.7	2.0
6 to 11 years Females - 23.8 kg	12.1	4.1	0.2	12.5	7.5	0.3	6.5	38.8	1.6	31.1	50.4	2.6
2 years & older Males - 88.8 kg	14.1	4.8	0.1	13.8	8.3	0.1	8.2	49.2	0.6	36.1	62.3	0.7
2 years & older Females - 75.5 kg	14.1	4.8	0.1	13.8	8.3	0.1	8.2	49.2	0.7	36.1	62.3	0.8

[1]Upper bound estimates of hemp consumption taken from GRN778 Tables 14 to 18. Used consumption levels for 2 to 5 years to conservatively estimate exposure for 11 to 23 month children. Refer to Table 16 for estimated hemp consumption by infants age 6 to 11 months.

[2]Mean Total THC levels based on historical data: Hulled Hemp Seed 0.3 µg/g, Hemp Protein Powder 0.6 µg/g, Hemp Oil 6 µg/g (Table 2).

[3]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016. Used lower body weight when a range is provided.

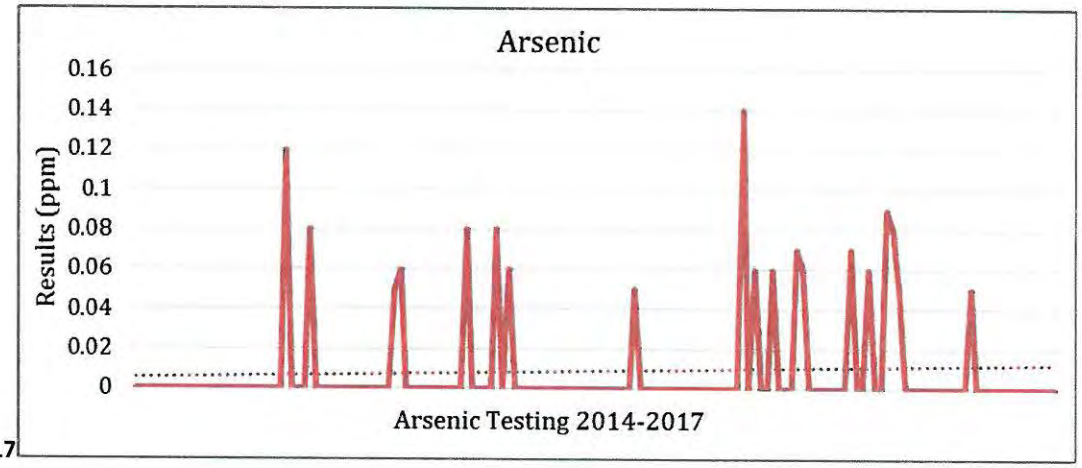


Figure 1 Arsenic Testing Results Trend 2014-2017

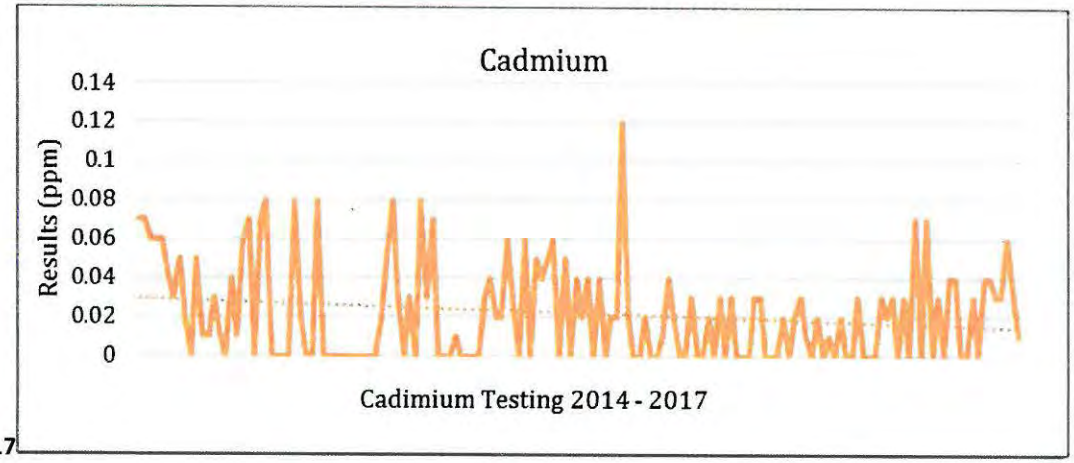


Figure 2 Cadmium Testing Results Trend 2014-2017

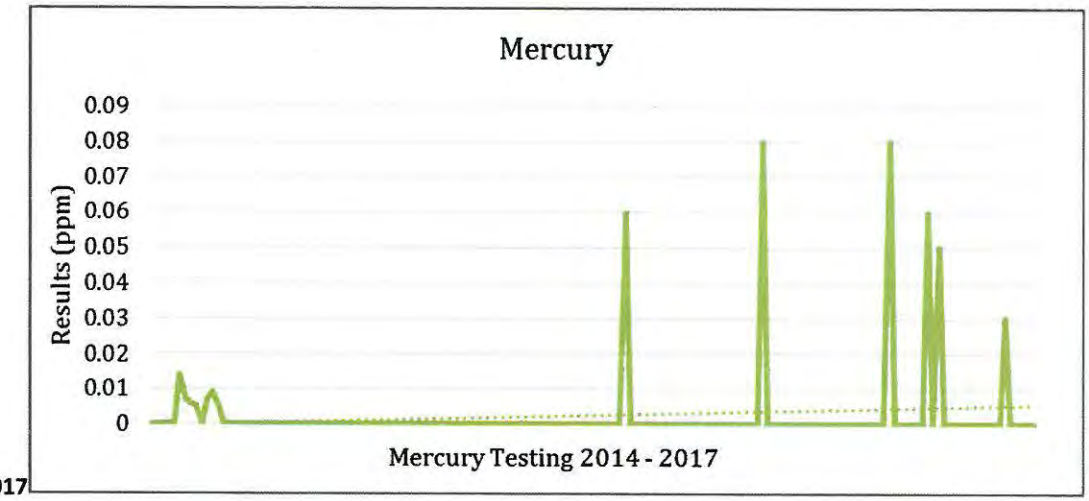


Figure 3 Mercury Testing Results Trend 2014-2017

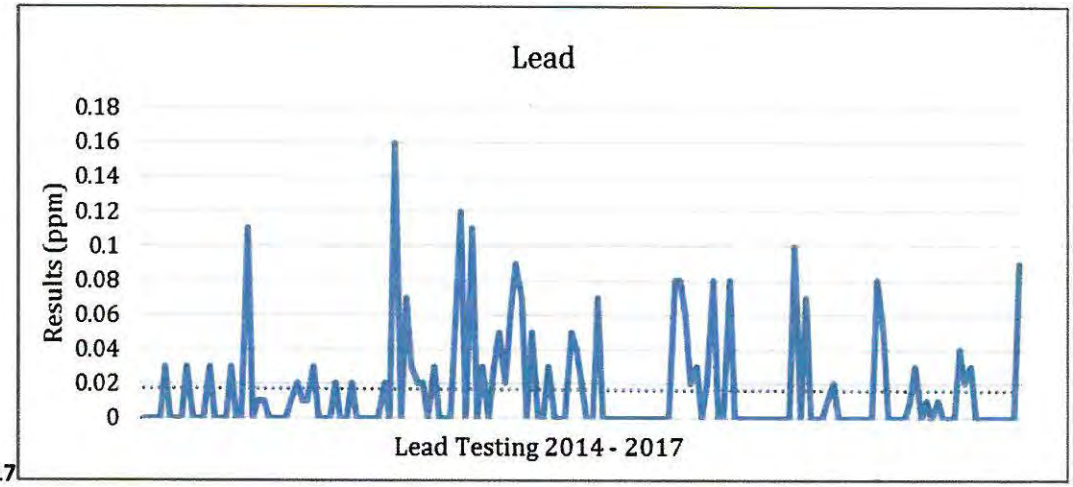


Figure 4 Lead Testing Results Trend 2014-2017

Figure 5 Crystal Ball Key Assumptions for Hulled Hemp Seed

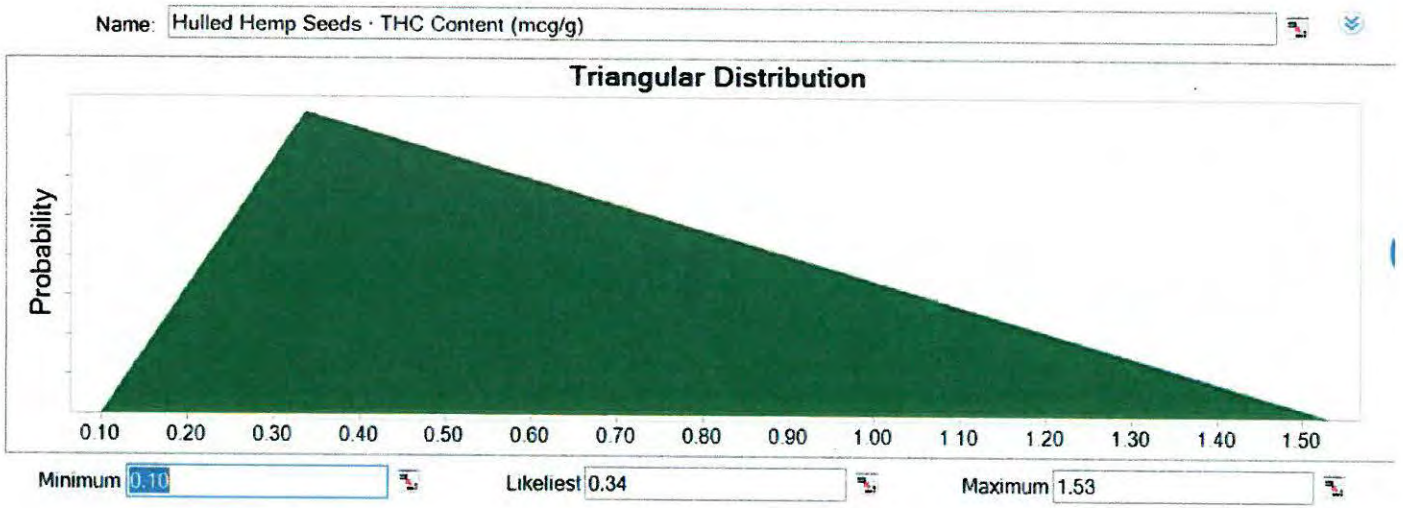


Figure 6 Crystal Ball Key Assumptions for Hemp Protein Powder

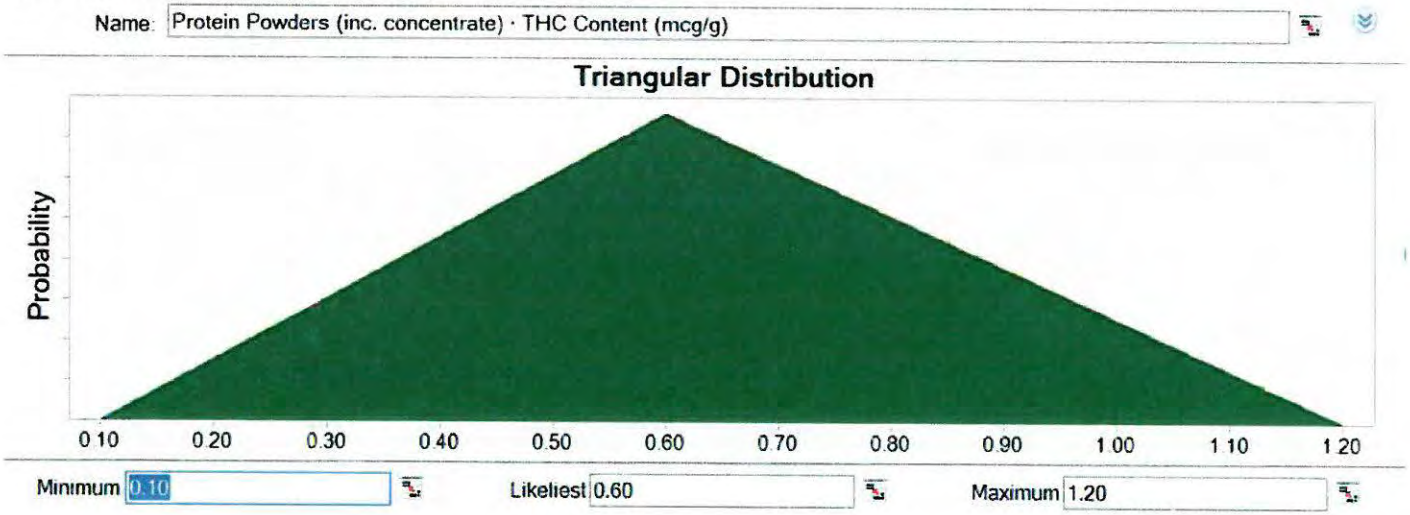


Figure 7 Crystal Ball Key Assumptions for Hemp Oil

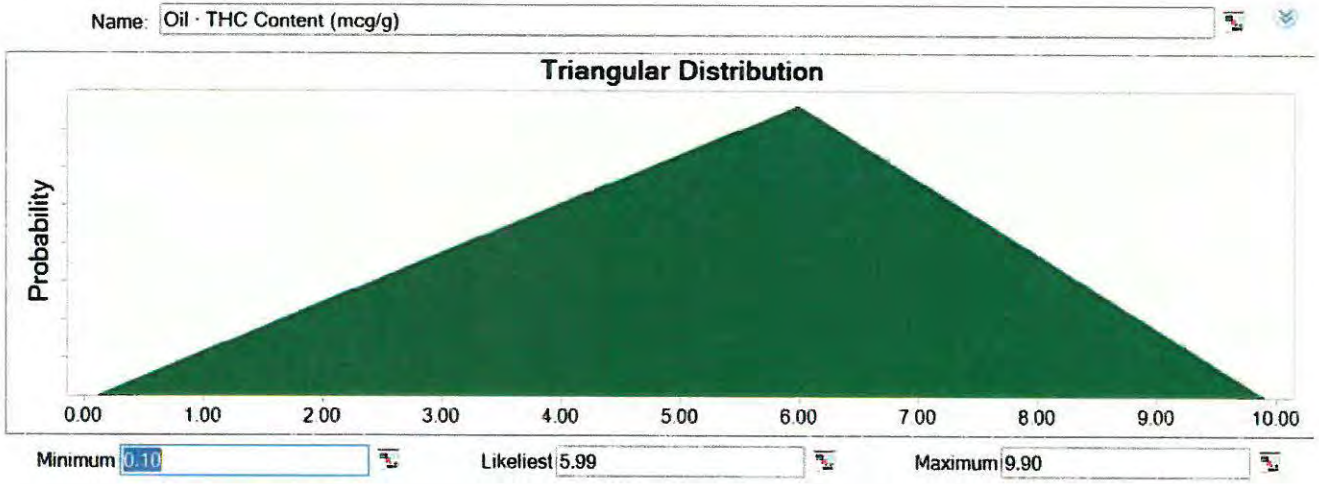
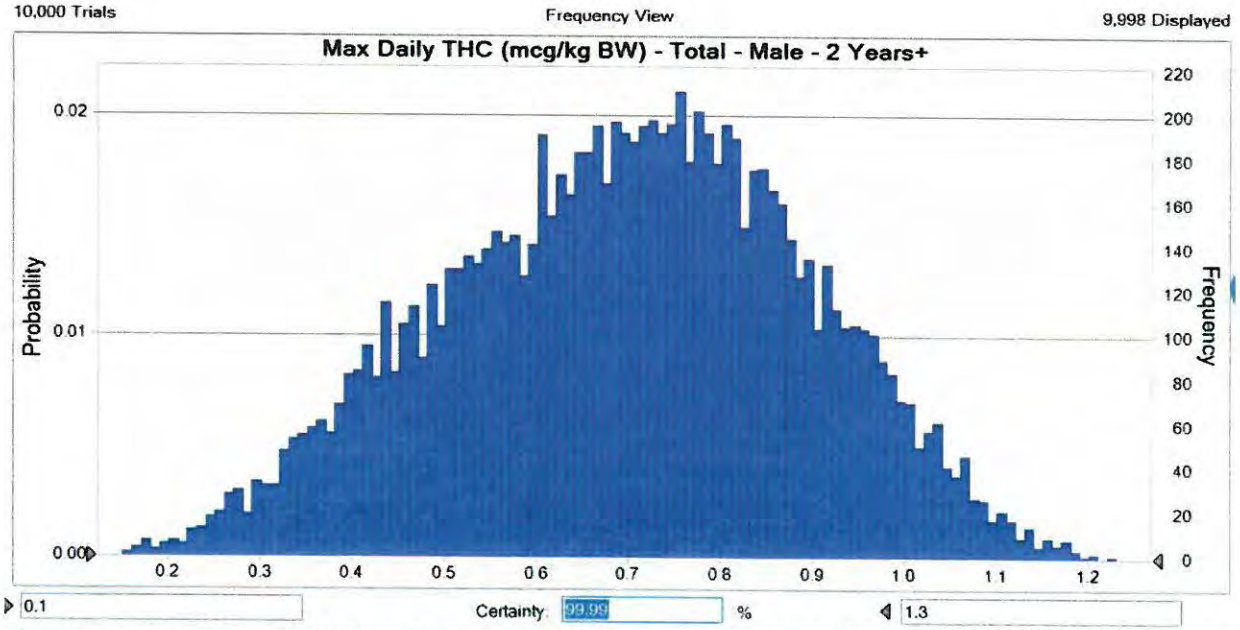


Figure 8 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Males Age 2 Years and Older

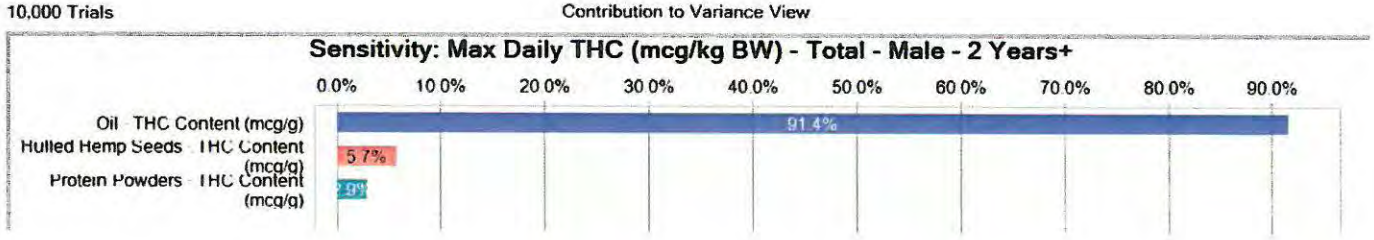


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 1.3µg/kg for males ages 2 years+.

Figure 9 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 Years and Older

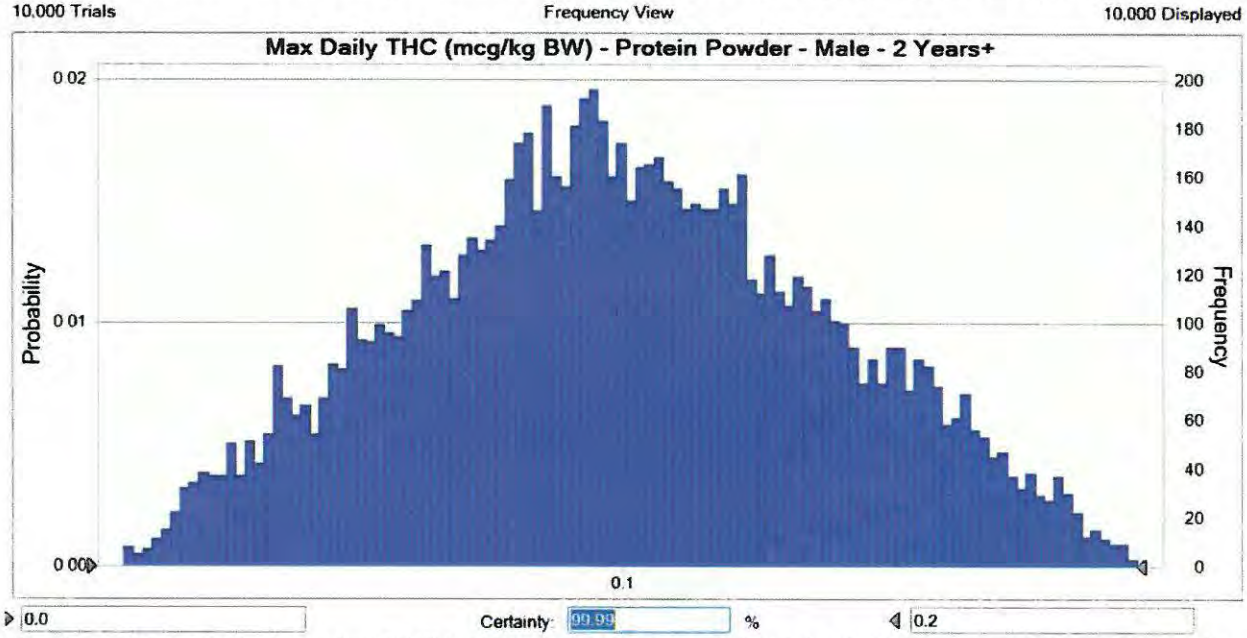
Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	0.7
Median	0.7
Mode	0.5
Standard Deviation	0.2
Variance	0.0
Skewness	-0.1329
Kurtosis	2.50
Coeff. of Variation	0.2795
Minimum	0.1
Maximum	1.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.4
20%	0.5
30%	0.6
40%	0.7
50%	0.7
60%	0.8
70%	0.8
80%	0.9
90%	0.9
100%	1.3



Variability in THC within Hemp Oil makes up 91% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 6% and Protein Powders make up 3%

Figure 10 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Males Age 2 Years and Older



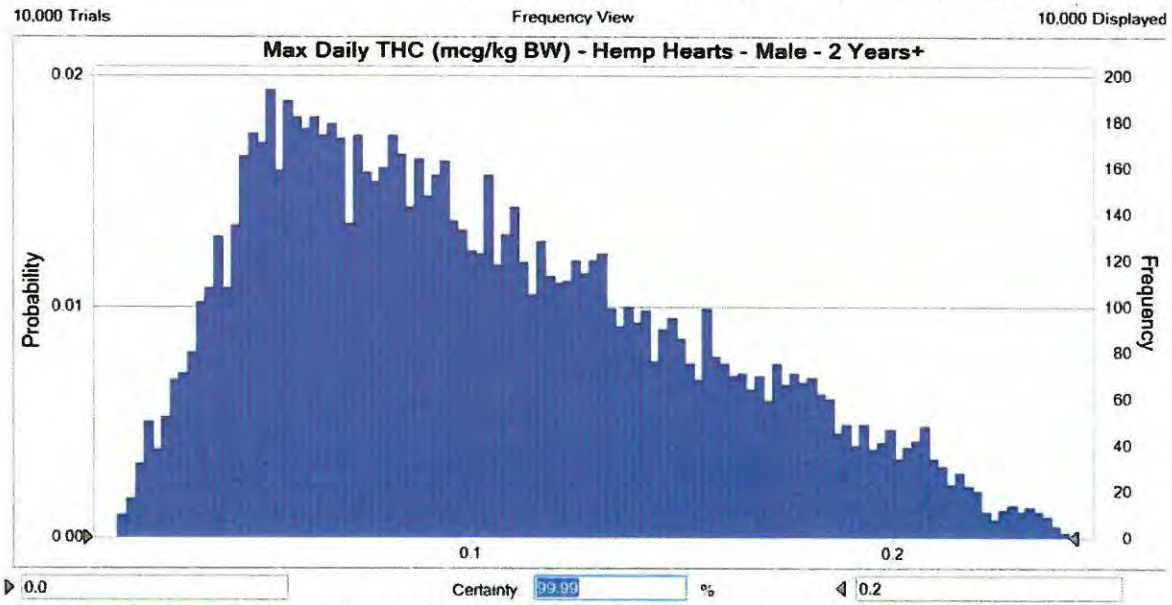
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.2µg/kg for males ages 2 years+.

Figure 11 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.0567
Kurtosis	2.42
Coeff. of Variation	0.3506
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.1
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.1
100%	0.2

Figure 12 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 2 Years and Older



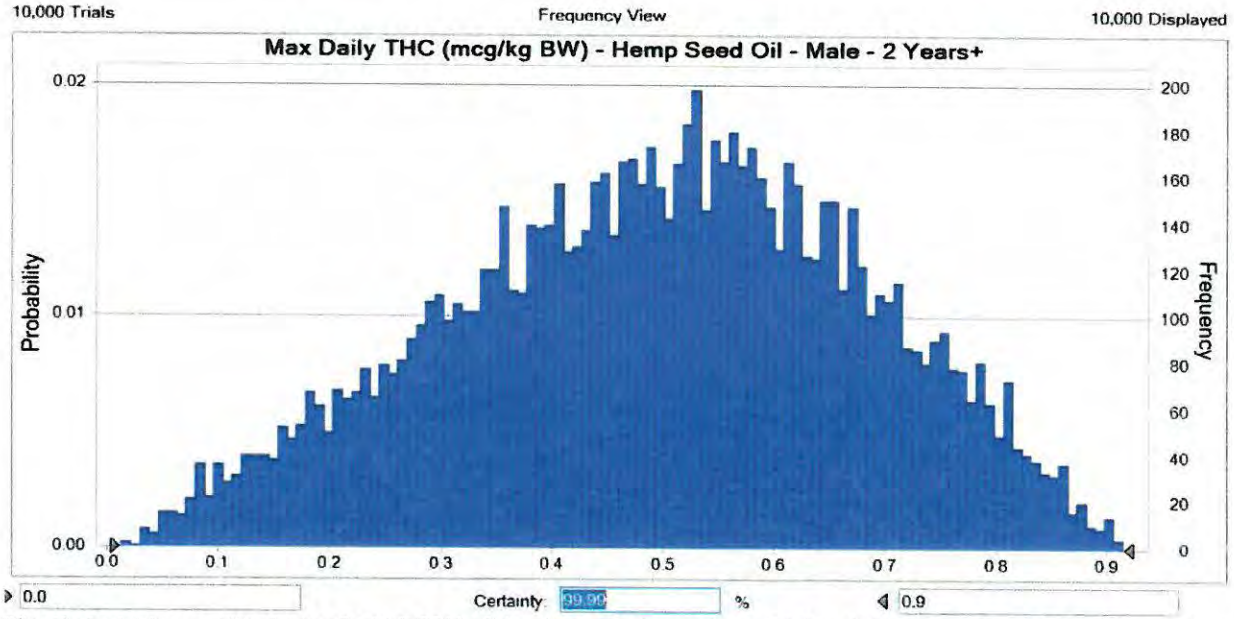
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.2µg/kg for males ages 2 years+.

Figure 13 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.5315
Kurtosis	2.43
Coeff. of Variation	0.4787
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.0
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.2
100%	0.2

Figure 14 Monte Carlo Model – Hemp Oil - THC Exposure Based on Body Weight – Males Age 2 Years and Older



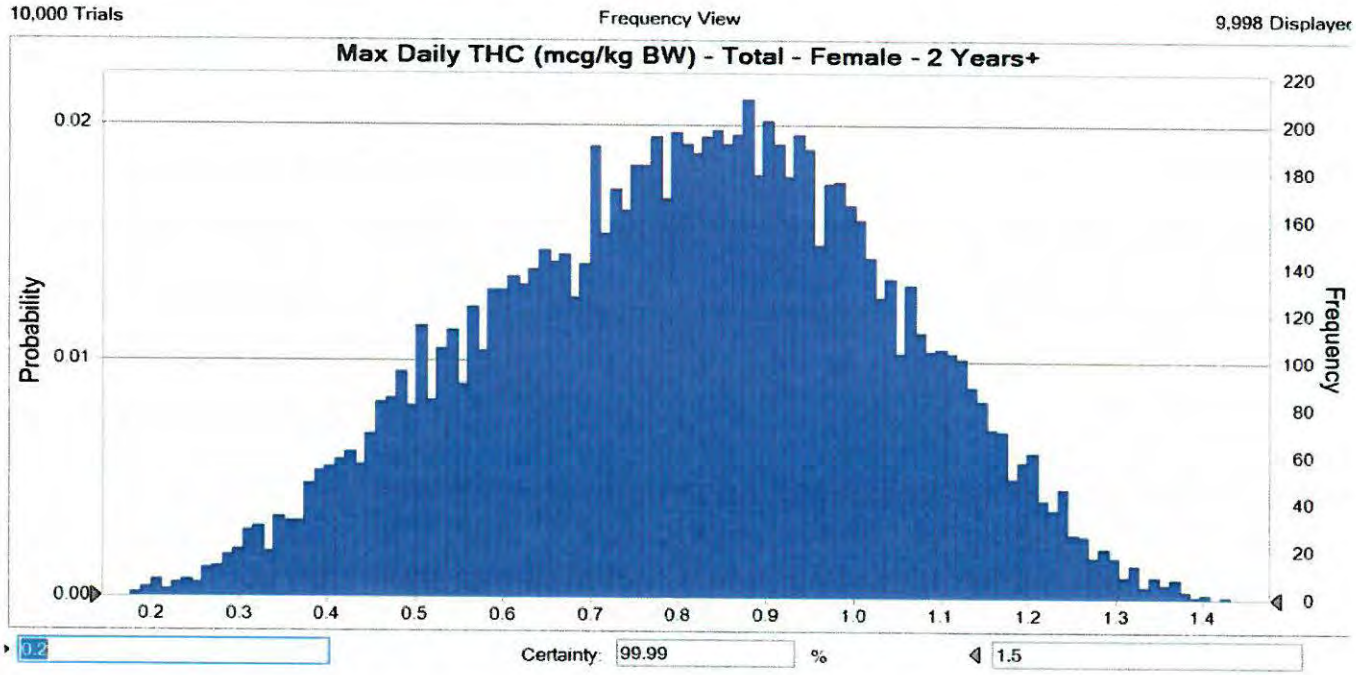
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.9µg/kg for males ages 2 years+.

Figure 15 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.5
Mean	0.5
Median	0.5
Mode	0.3
Standard Deviation	0.2
Variance	0.0
Skewness	-0.1647
Kurtosis	2.40
Coeff. of Variation	0.3752
Minimum	0.0
Maximum	0.9
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.2
20%	0.3
30%	0.4
40%	0.5
50%	0.5
60%	0.6
70%	0.6
80%	0.7
90%	0.7
100%	0.9

Figure 16 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Females Age 2 Years and Older



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 1.5µg/kg for females 2 years +.

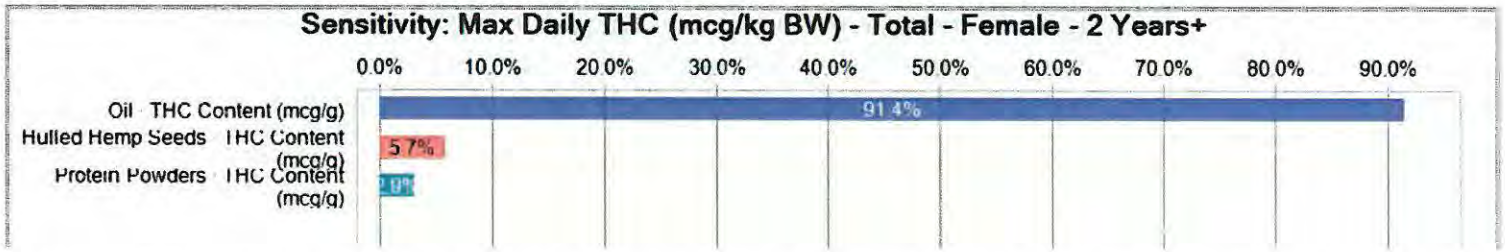
Figure 17 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	0.8
Median	0.8
Mode	0.6
Standard Deviation	0.2
Variance	0.1
Skewness	-0.1329
Kurtosis	2.50
Coeff. of Variation	0.2795
Minimum	0.2
Maximum	1.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.2
10%	0.5
20%	0.6
30%	0.7
40%	0.8
50%	0.8
60%	0.9
70%	0.9
80%	1.0
90%	1.1
100%	1.5

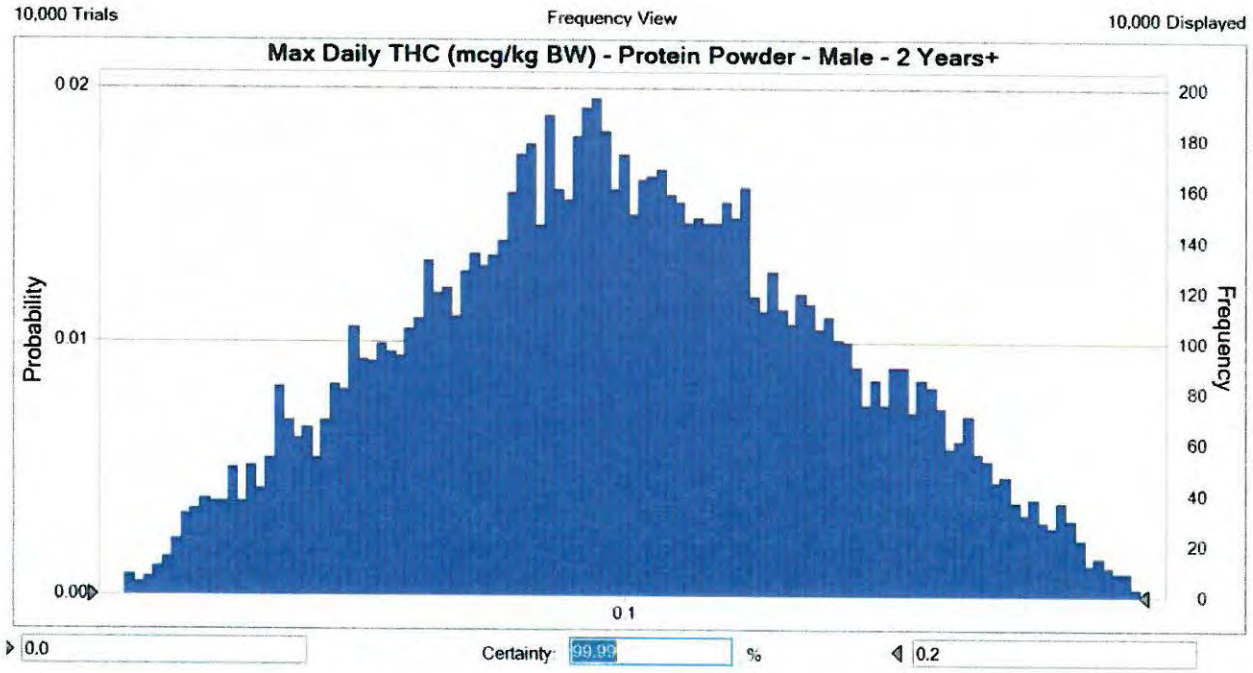
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 91% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 6% and Protein Powders make up 3%

Figure 18 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Females Age 2 Years and Older



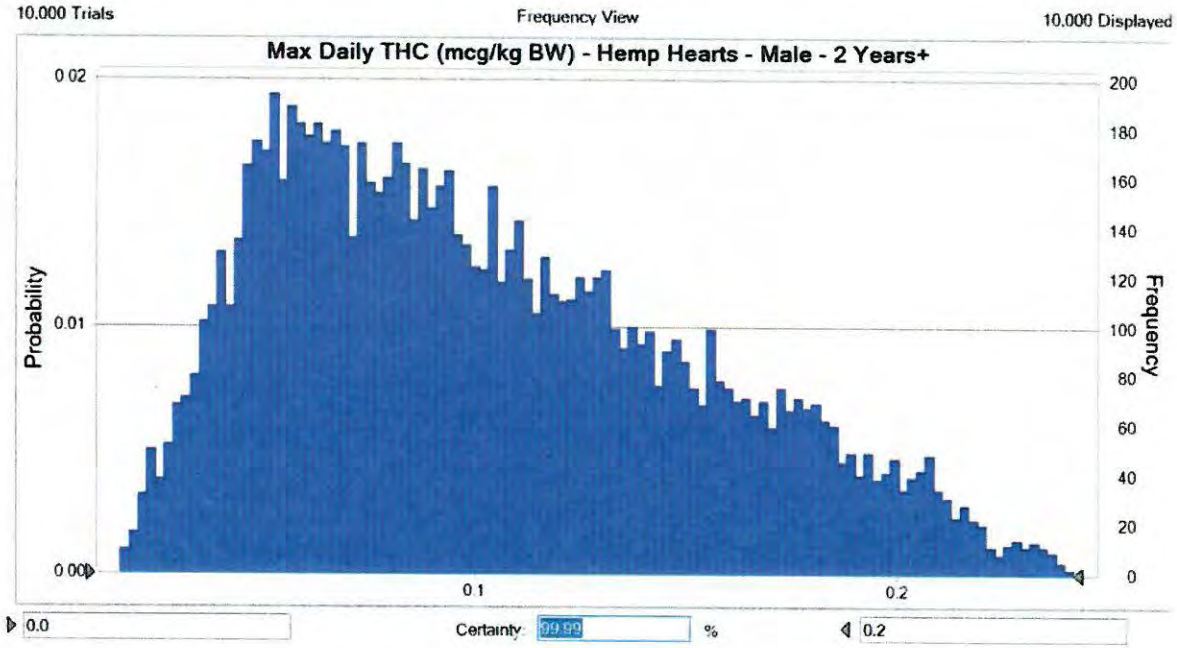
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 1.3µg/kg for males ages 2 years+.

Figure 19 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.0567
Kurtosis	2.42
Coeff. of Variation	0.3506
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.1
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.1
100%	0.2

Figure 20 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 2 Years and Older



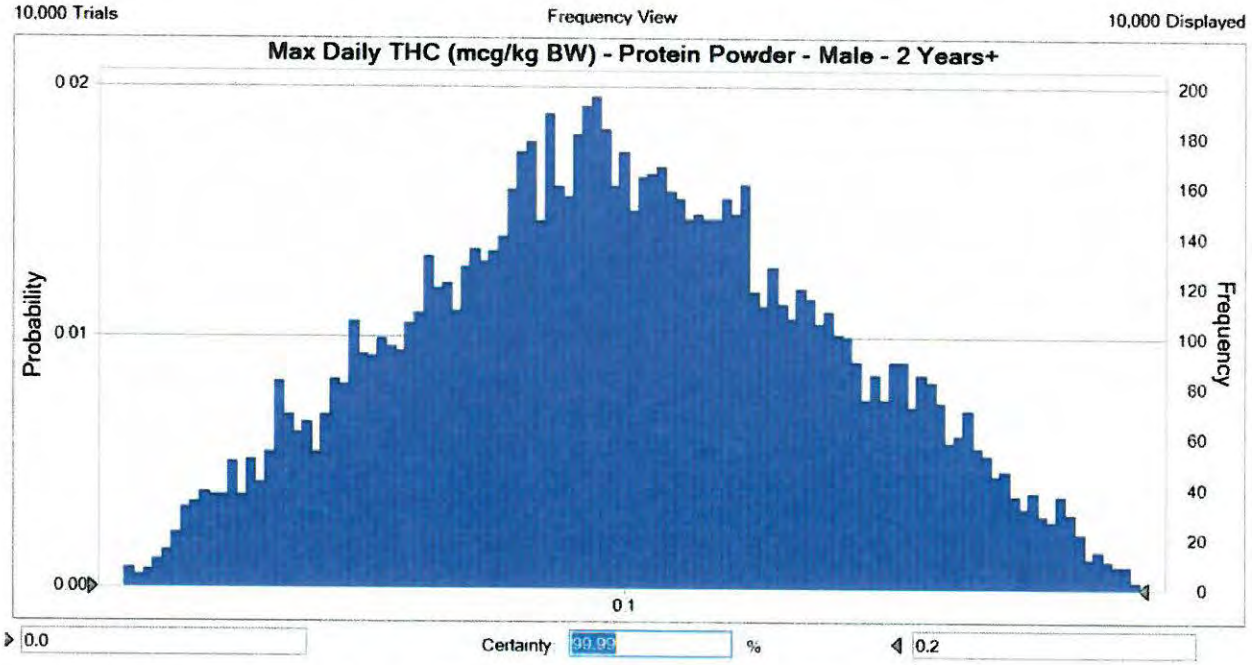
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.2µg/kg for males ages 2 years+.

Figure 21 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.5315
Kurtosis	2.43
Coeff. of Variation	0.4787
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.0
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.2
100%	0.2

Figure 22 Monte Carlo Model – Hemp Oil - THC Exposure Based on Body Weight – Females Age 2 Years and Older



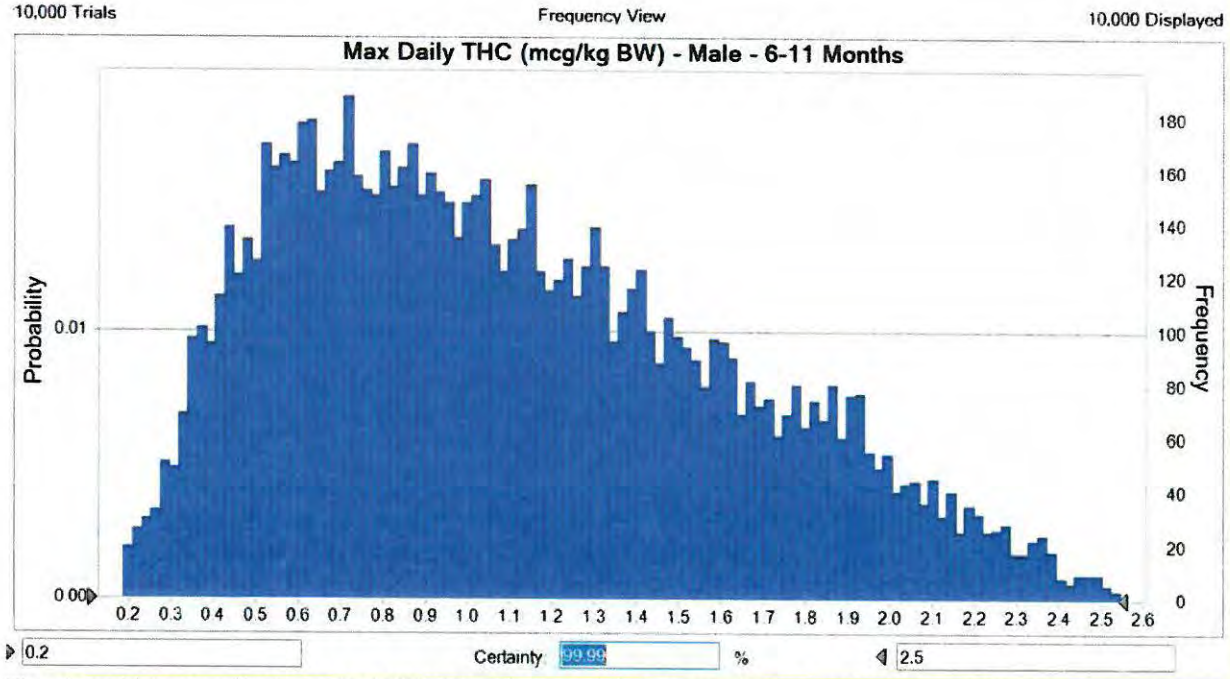
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.9µg/kg for males ages 2 years+.

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.0567
Kurtosis	2.42
Coeff. of Variation	0.3506
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Figure 23 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 Years and Older

Percentile	Forecast values
0%	0.0
10%	0.1
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.1
100%	0.2

Figure 24 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 6 to 11 Months



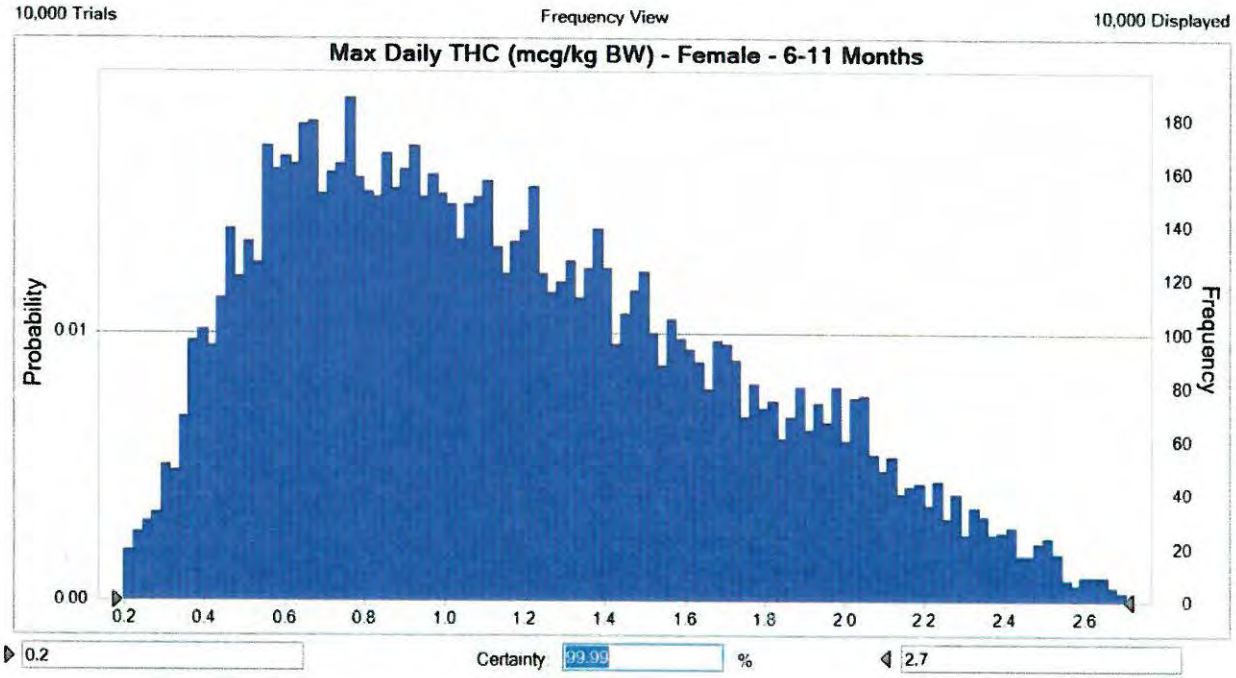
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seed will see no more than 2.5µg/kg for males age 6 to 11 months.

Figure 25 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight - Males Age 6 to 11 Months

Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	1.1
Median	1.0
Mode	—
Standard Deviation	0.5
Variance	0.3
Skewness	0.4883
Kurtosis	2.41
Coeff. of Variation	0.4699
Minimum	0.2
Maximum	2.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.2
10%	0.5
20%	0.6
30%	0.7
40%	0.9
50%	1.0
60%	1.2
70%	1.4
80%	1.6
90%	1.9
100%	2.5

Figure 26 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 6 to 11 Months



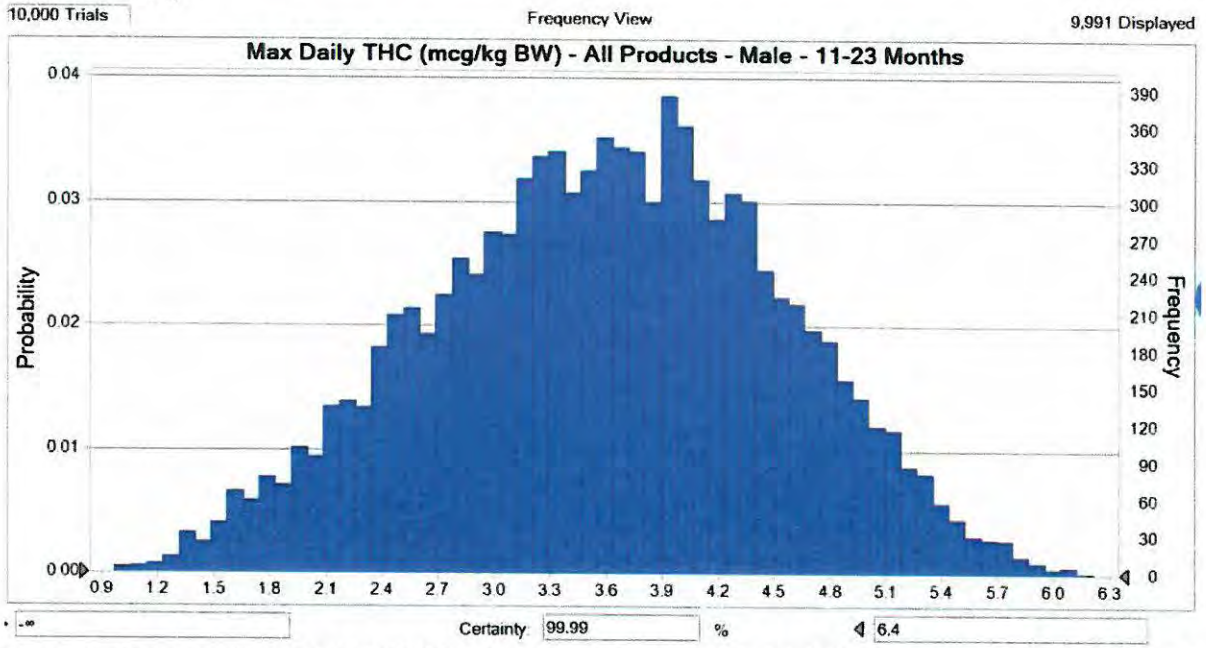
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seed will see no more than 2.7µg/kg for females age 6 to 11 months.

Figure 27 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight Females Age 6 to 11 Months

Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	1.2
Median	1.1
Mode	---
Standard Deviation	0.5
Variance	0.3
Skewness	0.4883
Kurtosis	2.41
Coeff. of Variation	0.4699
Minimum	0.2
Maximum	2.7
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.2
10%	0.5
20%	0.7
30%	0.8
40%	0.9
50%	1.1
60%	1.3
70%	1.4
80%	1.7
90%	2.0
100%	2.7

Figure 28 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 6.4µg/kg for males ages 11-23 Months.

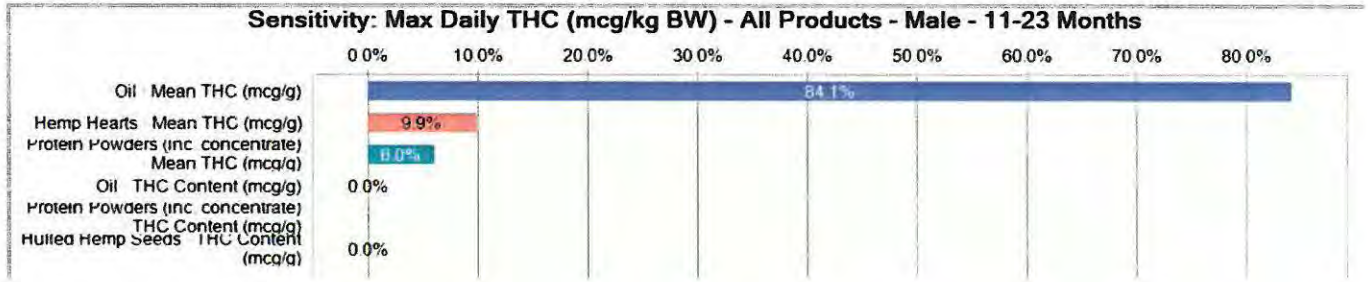
Figure 29 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	3.5
Mean	3.6
Median	3.6
Mode	—
Standard Deviation	0.9
Variance	0.9
Skewness	-0.0949
Kurtosis	2.57
Coeff. of Variation	0.2606
Minimum	0.7
Maximum	6.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.7
10%	2.3
20%	2.8
30%	3.1
40%	3.4
50%	3.6
60%	3.9
70%	4.1
80%	4.4
90%	4.8
100%	6.5

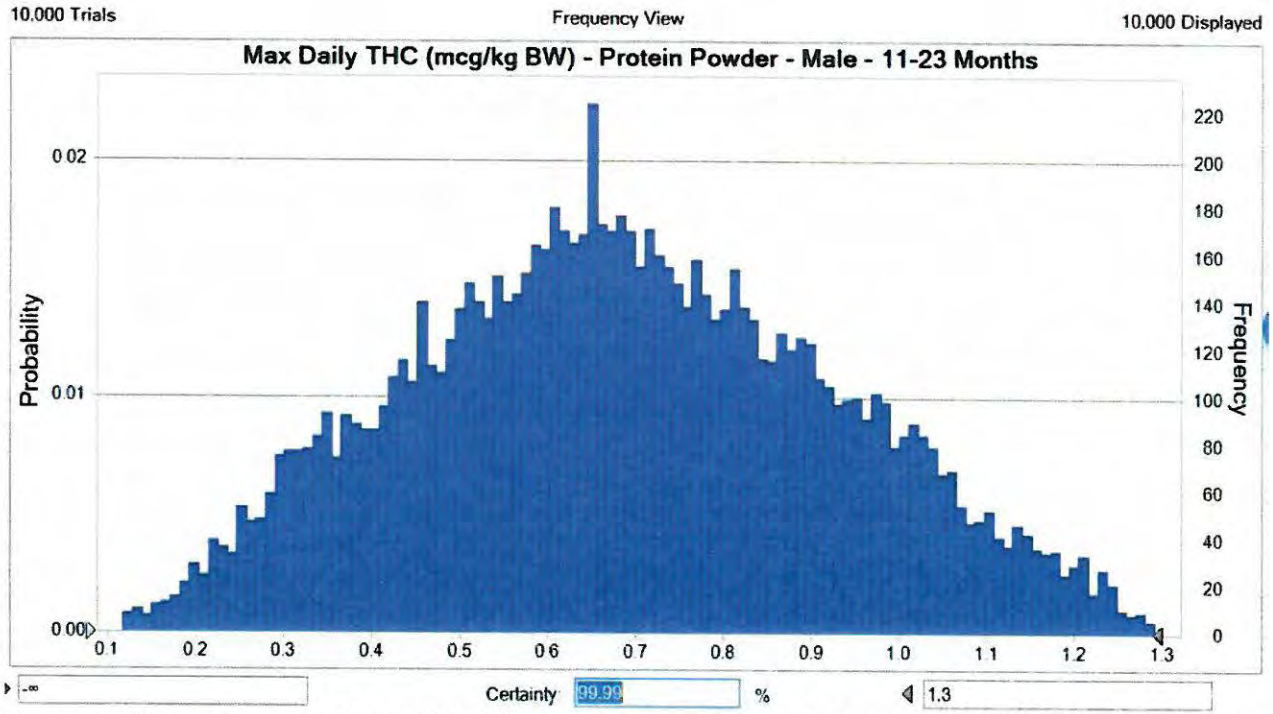
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 84% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 10% and Protein Powders make up 6%

Figure 30 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)



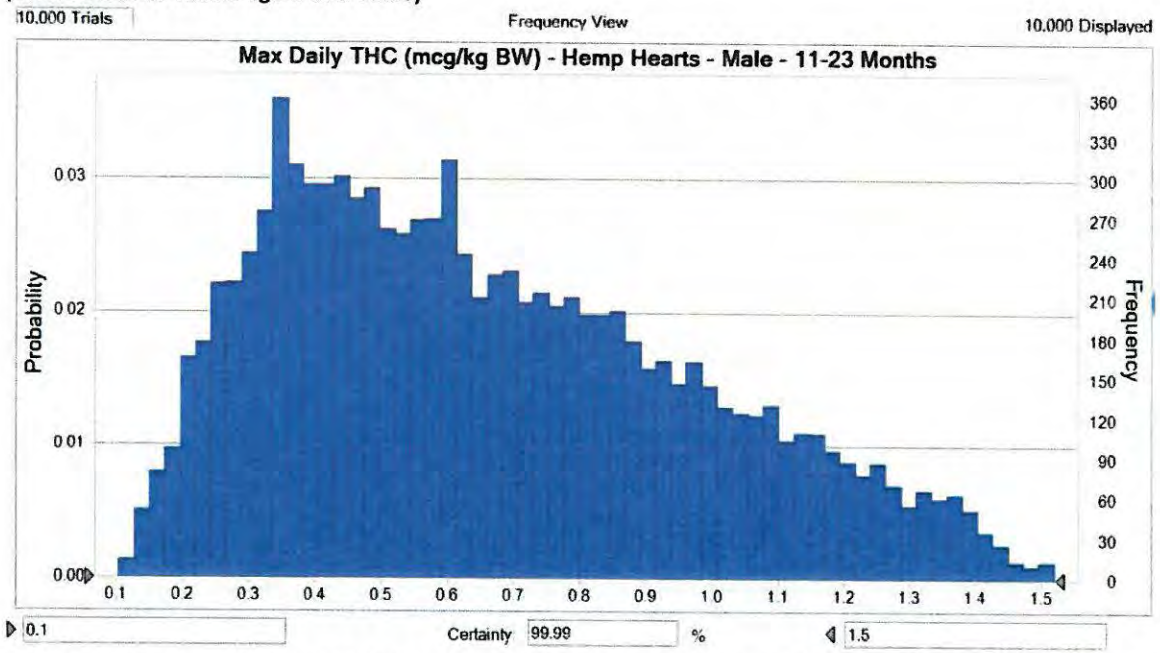
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (protein powder) of THC at a 90th percentile intake level will see no more than 1.3µg/kg for males ages 11-23 Months.

Figure 31 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.7
Mean	0.7
Median	0.7
Mode	---
Standard Deviation	0.2
Variance	0.1
Skewness	0.0999
Kurtosis	2.40
Coeff. of Variation	0.3512
Minimum	0.1
Maximum	1.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.4
20%	0.5
30%	0.6
40%	0.6
50%	0.7
60%	0.7
70%	0.8
80%	0.9
90%	1.0
100%	1.3

Figure 32 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)



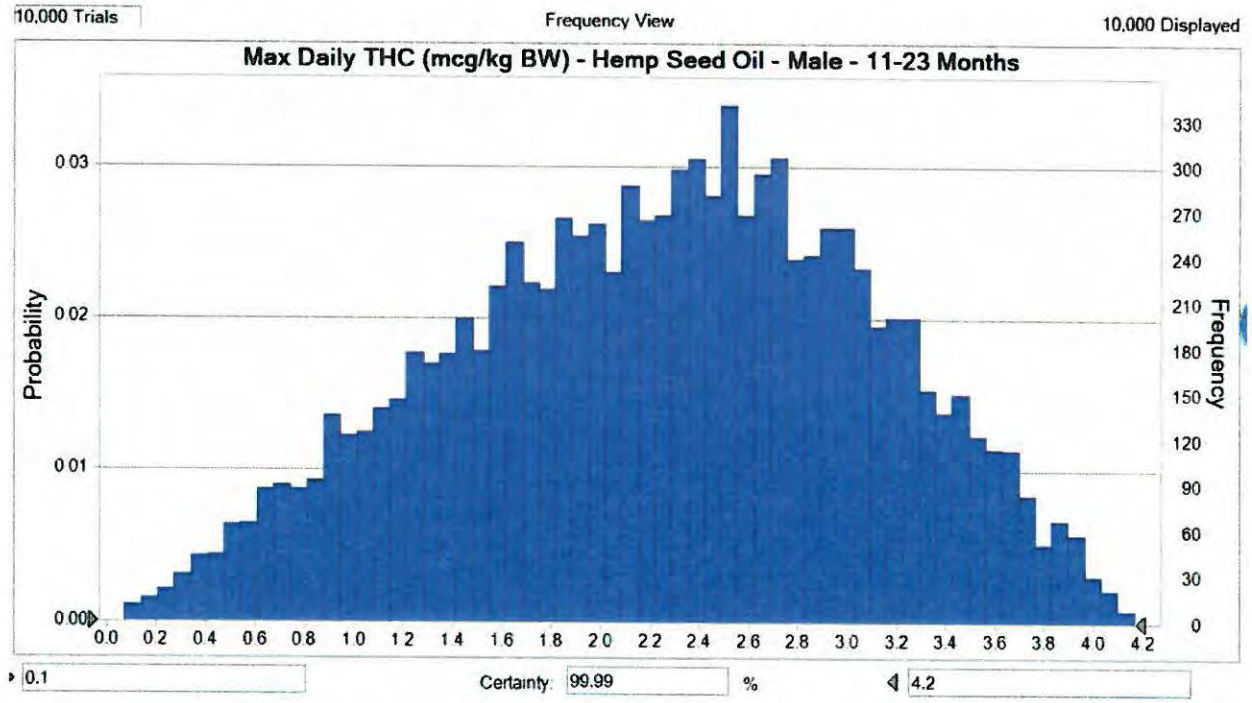
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (hemp hearts) of THC at a 90th percentile intake level will see no more than 1.5µg/kg for males ages 11-23 Months.

Figure 33 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.3
Mean	0.7
Median	0.6
Mode	—
Standard Deviation	0.3
Variance	0.1
Skewness	0.5087
Kurtosis	2.40
Coeff. of Variation	0.4761
Minimum	0.1
Maximum	1.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.4
30%	0.4
40%	0.5
50%	0.6
60%	0.7
70%	0.8
80%	1.0
90%	1.1
100%	1.5

Figure 34 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)



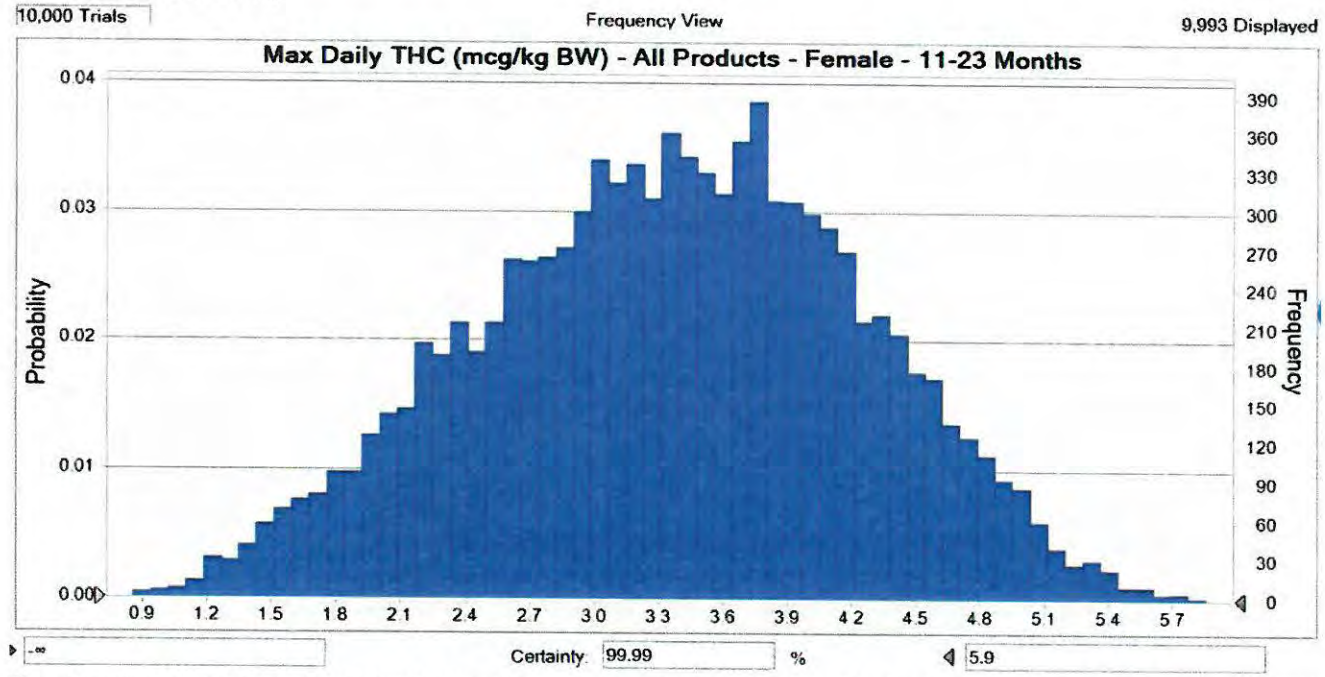
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (hemp seed oil) of THC at a 90th percentile intake level will see no more than 4.2µg/kg for males ages 11-23 Months.

Figure 35 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	2.5
Mean	2.2
Median	2.3
Mode	—
Standard Deviation	0.8
Variance	0.7
Skewness	-0.1663
Kurtosis	2.36
Coeff. of Variation	0.3788
Minimum	0.1
Maximum	4.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	1.1
20%	1.5
30%	1.8
40%	2.0
50%	2.3
60%	2.5
70%	2.7
80%	3.0
90%	3.3
100%	4.2

Figure 36 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

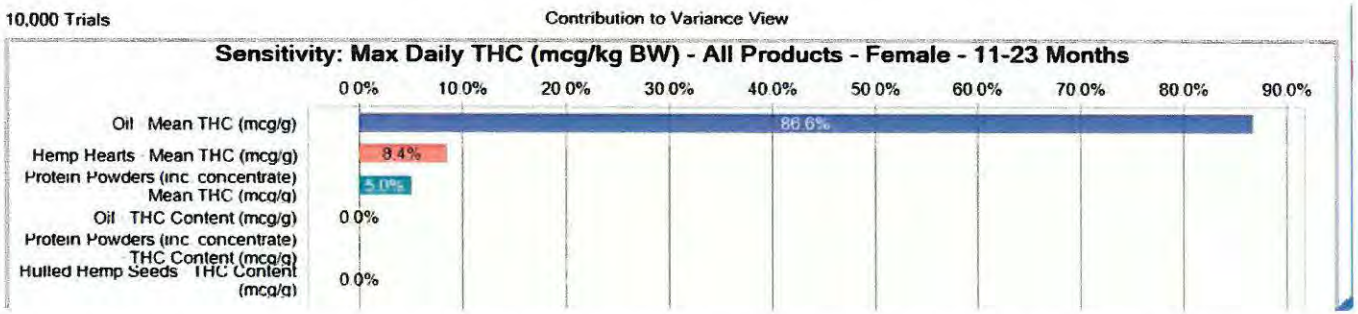


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (All Products) of THC at a 90th percentile intake level will see no more than 5.9µg/kg for females ages 11-23 Months.

Figure 37 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

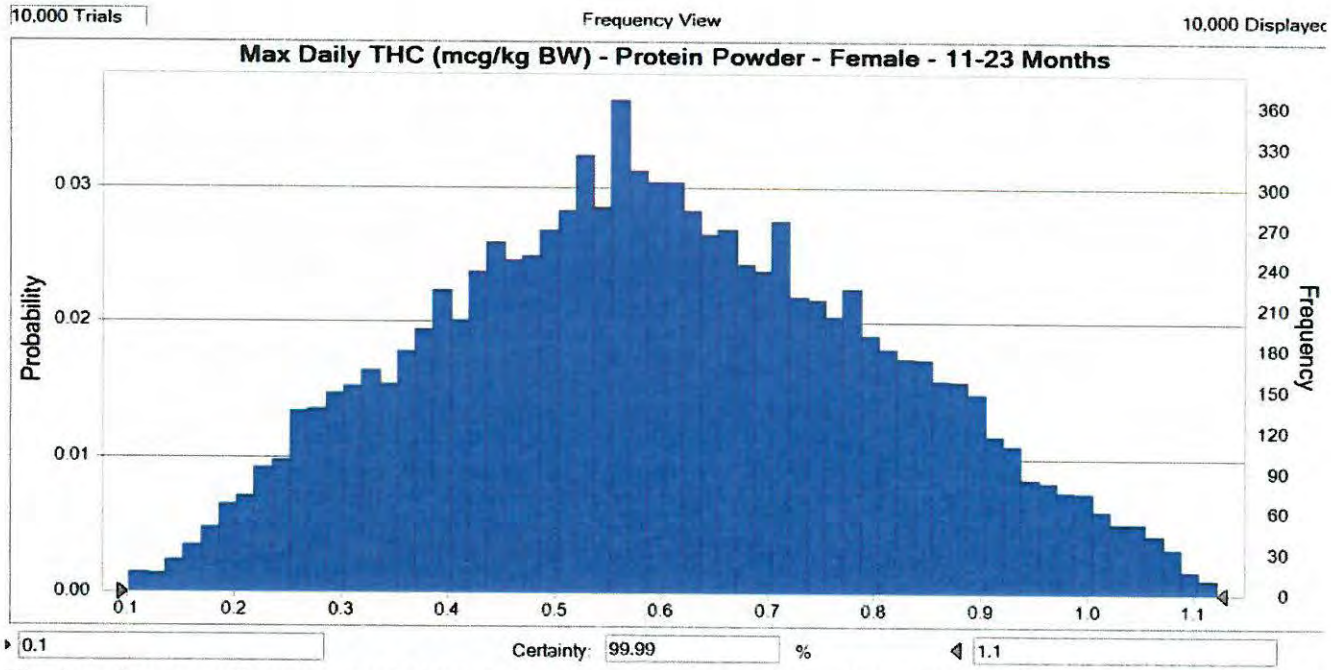
Statistic	Forecast values
Trials	10,000
Base Case	3.3
Mean	3.4
Median	3.4
Mode	—
Standard Deviation	0.9
Variance	0.8
Skewness	-0.1058
Kurtosis	2.54
Coeff. of Variation	0.2660
Minimum	0.6
Maximum	6.1
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.6
10%	2.2
20%	2.6
30%	2.9
40%	3.1
50%	3.4
60%	3.6
70%	3.9
80%	4.1
90%	4.5
100%	6.1



Variability in THC within Hemp Oil makes up 87% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 8% and Protein Powders make up 5%

Figure 38 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)



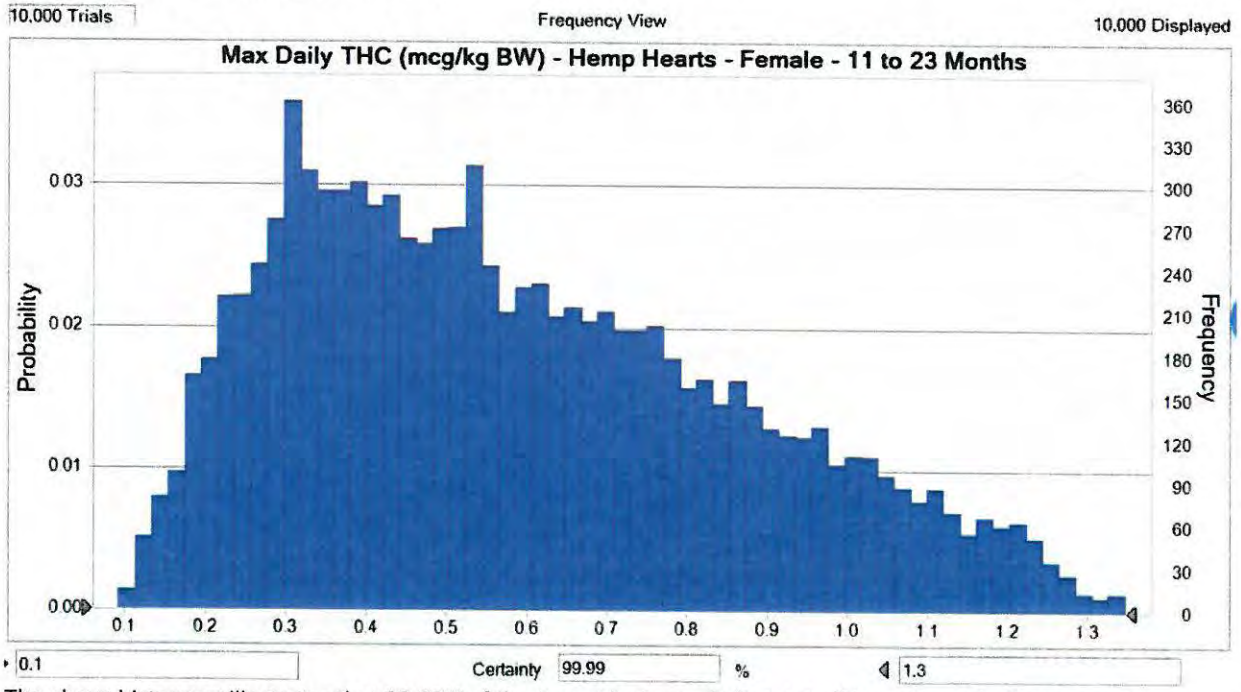
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Protein Powders) of THC at a 90th percentile intake level will see no more than 1.1µg/kg for females ages 11-23 Months.

Figure 39 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	0.6
Median	0.6
Mode	—
Standard Deviation	0.2
Variance	0.0
Skewness	0.0999
Kurtosis	2.40
Coeff. of Variation	0.3512
Minimum	0.1
Maximum	1.1
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.4
30%	0.5
40%	0.5
50%	0.6
60%	0.6
70%	0.7
80%	0.8
90%	0.9
100%	1.1

Figure 40 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)



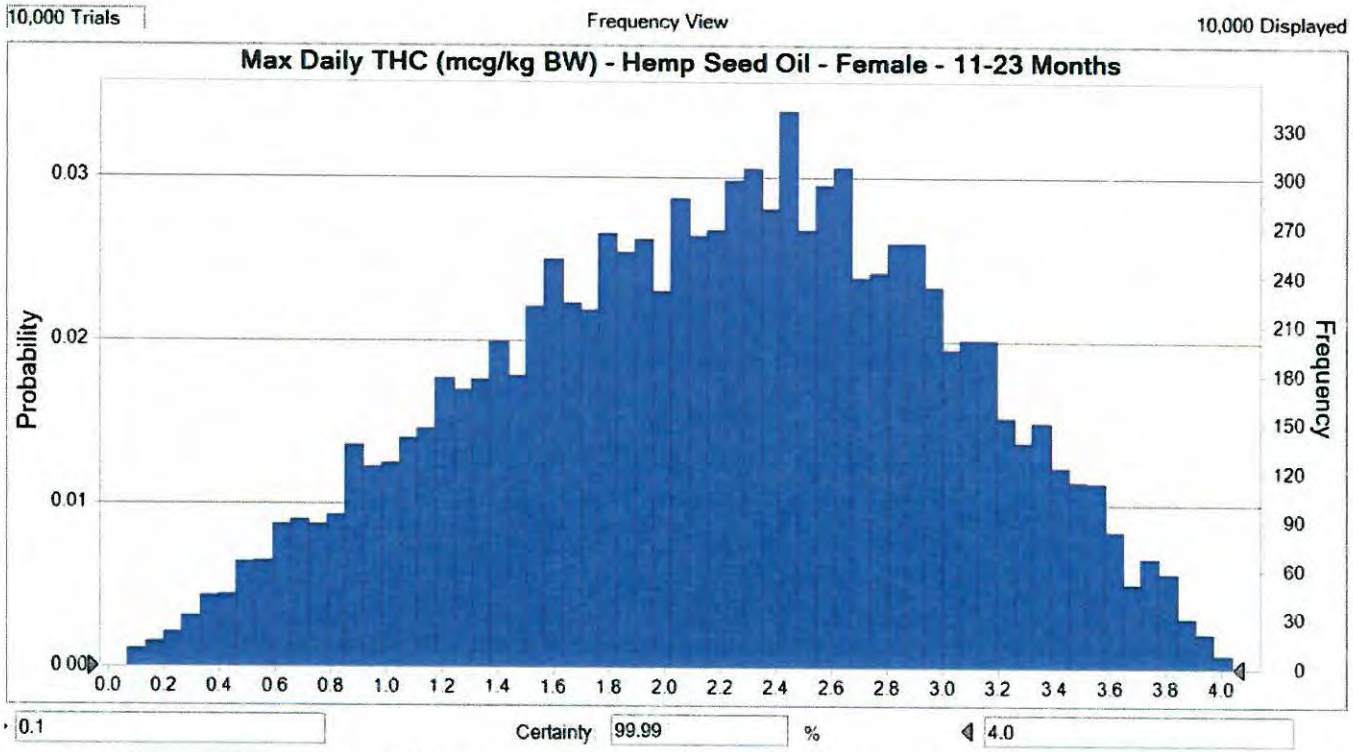
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Hemp Hearts) of THC at a 90th percentile intake level will see no more than 1.3µg/kg for females ages 11-23 Months.

Figure 41 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.3
Mean	0.6
Median	0.5
Mode	—
Standard Deviation	0.3
Variance	0.1
Skewness	0.5087
Kurtosis	2.40
Coeff. of Variation	0.4761
Minimum	0.1
Maximum	1.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.3
30%	0.4
40%	0.5
50%	0.5
60%	0.6
70%	0.7
80%	0.8
90%	1.0
100%	1.3

Figure 42 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)



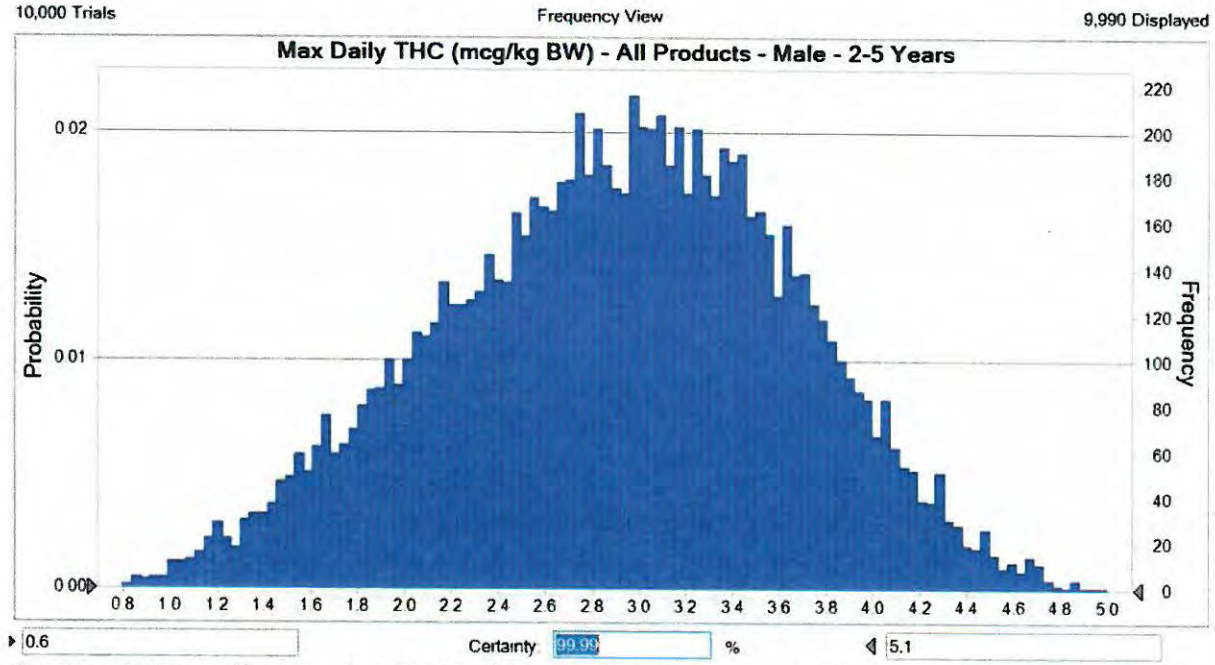
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Hemp Seed Oil) of THC at a 90th percentile intake level will see no more than 4.0µg/kg for females ages 11-23 Months.

Figure 43 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	2.5
Mean	2.2
Median	2.2
Mode	---
Standard Deviation	0.8
Variance	0.7
Skewness	-0.1663
Kurtosis	2.36
Coeff. of Variation	0.3788
Minimum	0.1
Maximum	4.0
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	1.0
20%	1.4
30%	1.7
40%	2.0
50%	2.2
60%	2.4
70%	2.7
80%	2.9
90%	3.2
100%	4.0

Figure 34 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Males Age 2 to 5 Years)



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 5.1µg/kg for males ages 2-5.

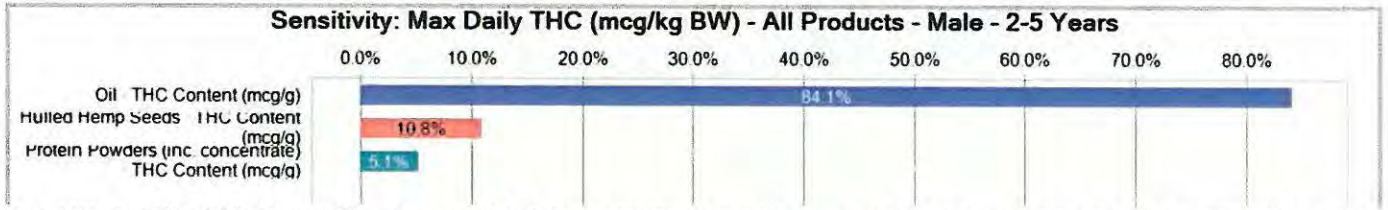
Figure 45 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	2.2
Mean	2.9
Median	2.9
Mode	---
Standard Deviation	0.7
Variance	0.6
Skewness	-0.1609
Kurtosis	2.59
Coeff. of Variation	0.2589
Minimum	0.6
Maximum	5.1
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.6
10%	1.9
20%	2.2
30%	2.5
40%	2.7
50%	2.9
60%	3.1
70%	3.3
80%	3.6
90%	3.8
100%	5.1

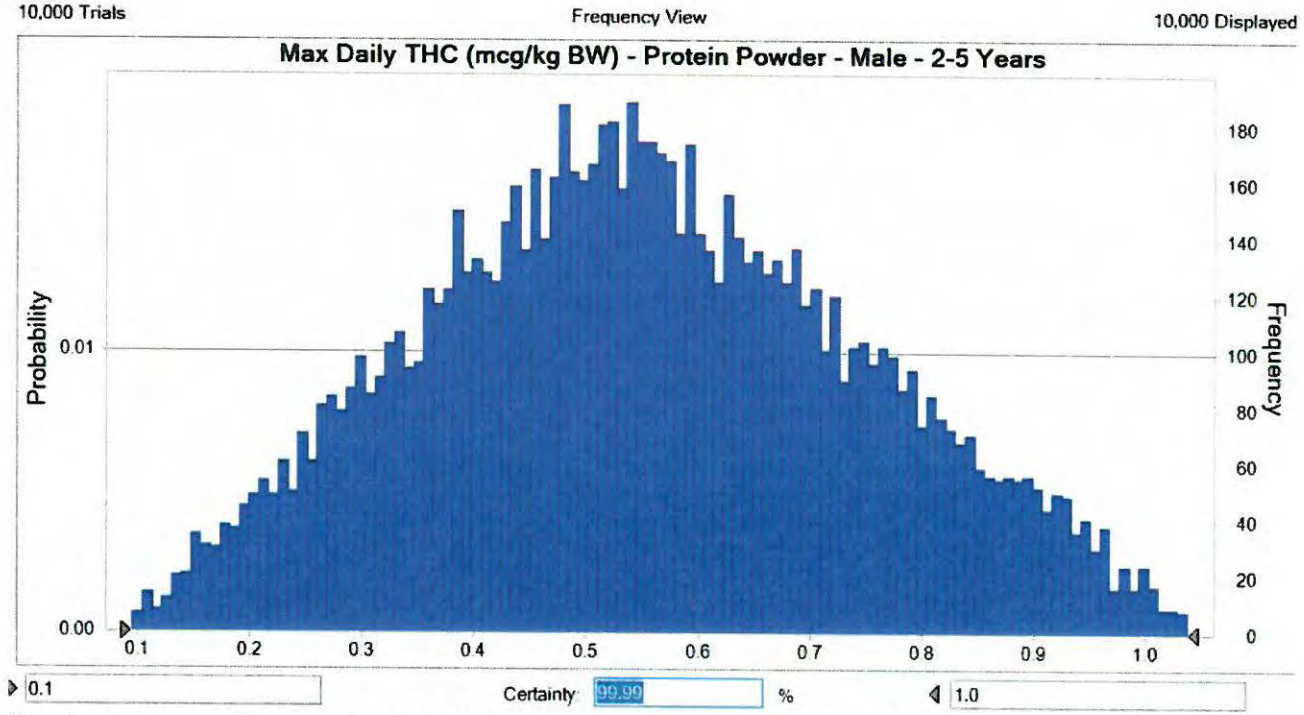
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 84% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 11% and Protein Powders make up 5%

Figure 46 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Males Age 2 to 5 Years)



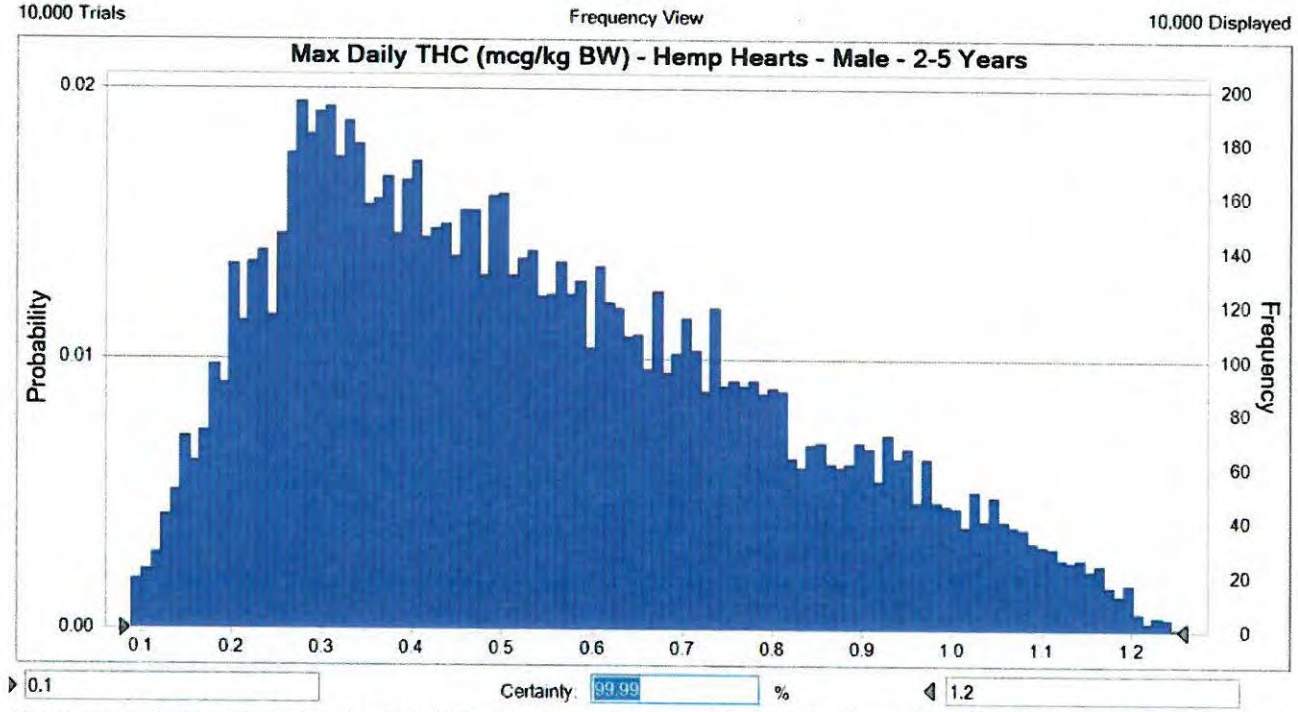
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (protein powder) of THC at a 90th percentile intake level will see no more than 1.0µg/kg for males ages 2-5.

Figure 47 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.3
Mean	0.6
Median	0.5
Mode	---
Standard Deviation	0.2
Variance	0.0
Skewness	0.1123
Kurtosis	2.41
Coeff. of Variation	0.3562
Minimum	0.1
Maximum	1.0
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.4
30%	0.4
40%	0.5
50%	0.5
60%	0.6
70%	0.7
80%	0.7
90%	0.8
100%	1.0

Figure 1 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 2 to 5 Years)



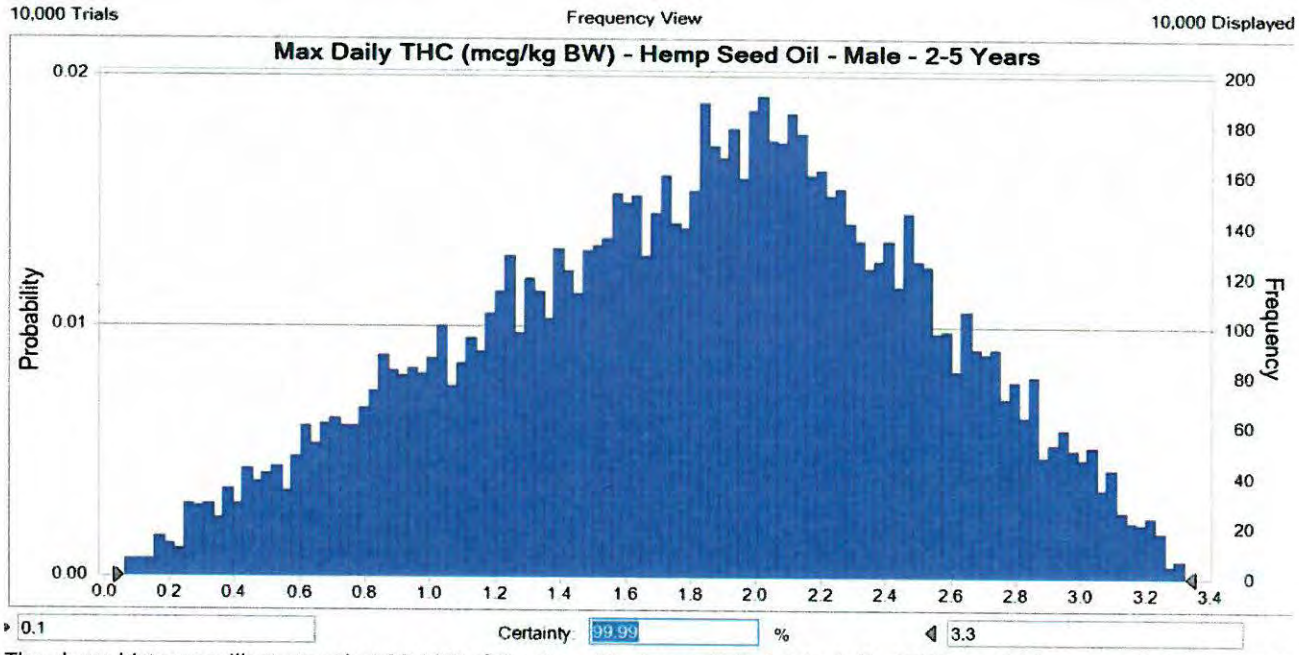
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (hemp hearts) of THC at a 90th percentile intake level will see no more than 1.2µg/kg for males ages 2-5.

Figure 49 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.5
Median	0.5
Mode	—
Standard Deviation	0.3
Variance	0.1
Skewness	0.5224
Kurtosis	2.42
Coeff. of Variation	0.4797
Minimum	0.1
Maximum	1.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.2
20%	0.3
30%	0.4
40%	0.4
50%	0.5
60%	0.6
70%	0.7
80%	0.8
90%	0.9
100%	1.3

Figure 50 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Males Age 2 to 5 Years)



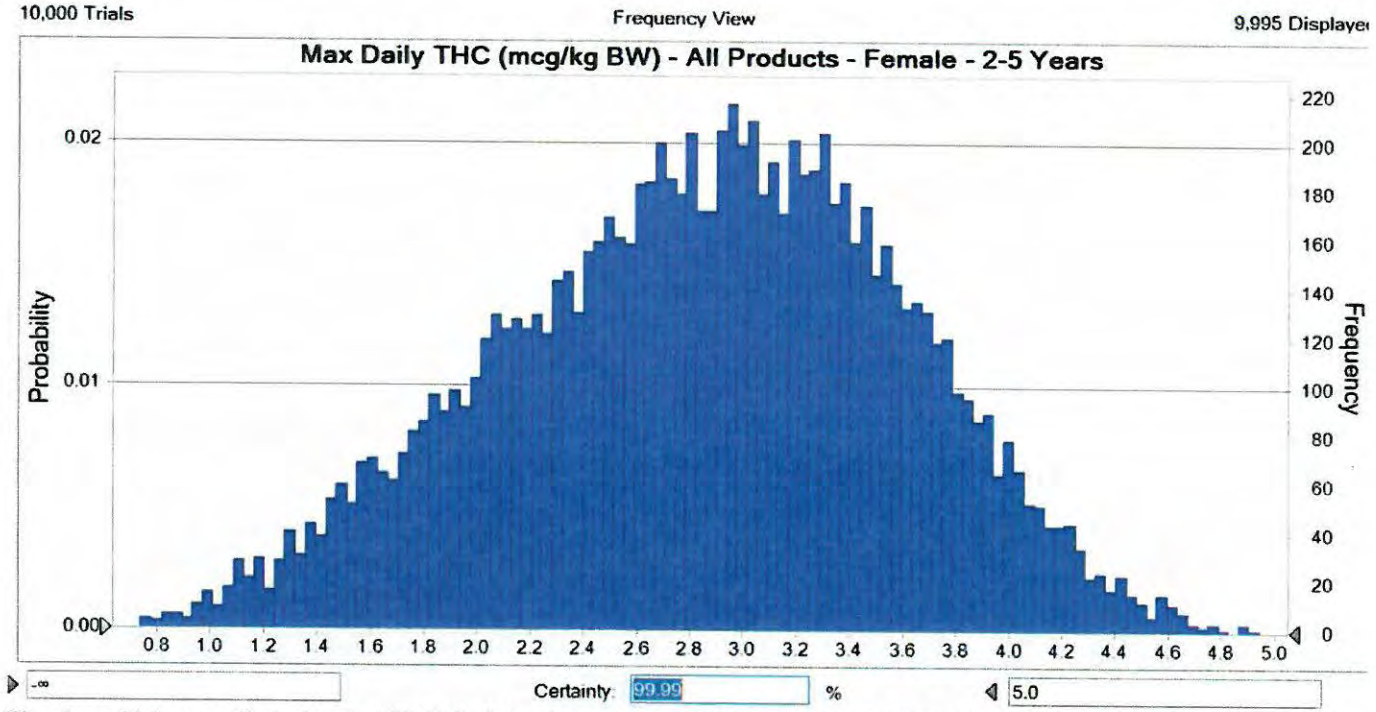
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (oil) of THC at a 90th percentile intake level will see no more than 3.3µg/kg for males ages 2-5.

Figure 51 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	1.7
Mean	1.8
Median	1.9
Mode	---
Standard Deviation	0.7
Variance	0.5
Skewness	-0.2092
Kurtosis	2.41
Coeff. of Variation	0.3772
Minimum	0.1
Maximum	3.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.8
20%	1.2
30%	1.4
40%	1.7
50%	1.9
60%	2.0
70%	2.2
80%	2.4
90%	2.7
100%	3.3

Figure 52 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Females Age 2 to 5 Years)



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (All Products) of THC at a 90th percentile intake level will see no more than 5.0µg/kg for females ages 2-5 years.

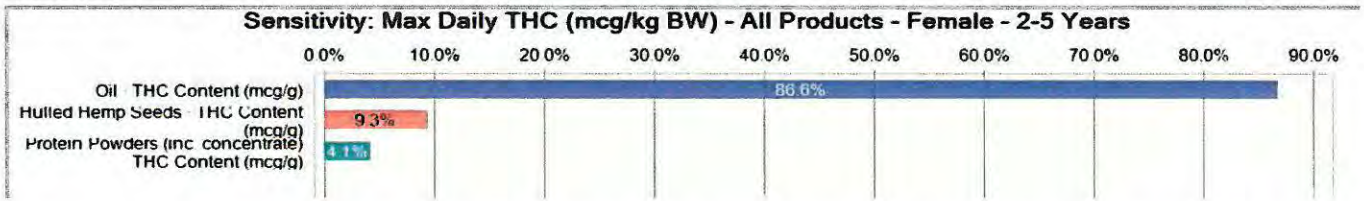
Figure 53 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	2.2
Mean	2.8
Median	2.9
Mode	---
Standard Deviation	0.8
Variance	0.6
Skewness	-0.1726
Kurtosis	2.56
Coeff. of Variation	0.2642
Minimum	0.6
Maximum	5.0
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.6
10%	1.8
20%	2.2
30%	2.4
40%	2.7
50%	2.9
60%	3.1
70%	3.3
80%	3.5
90%	3.8
100%	5.0

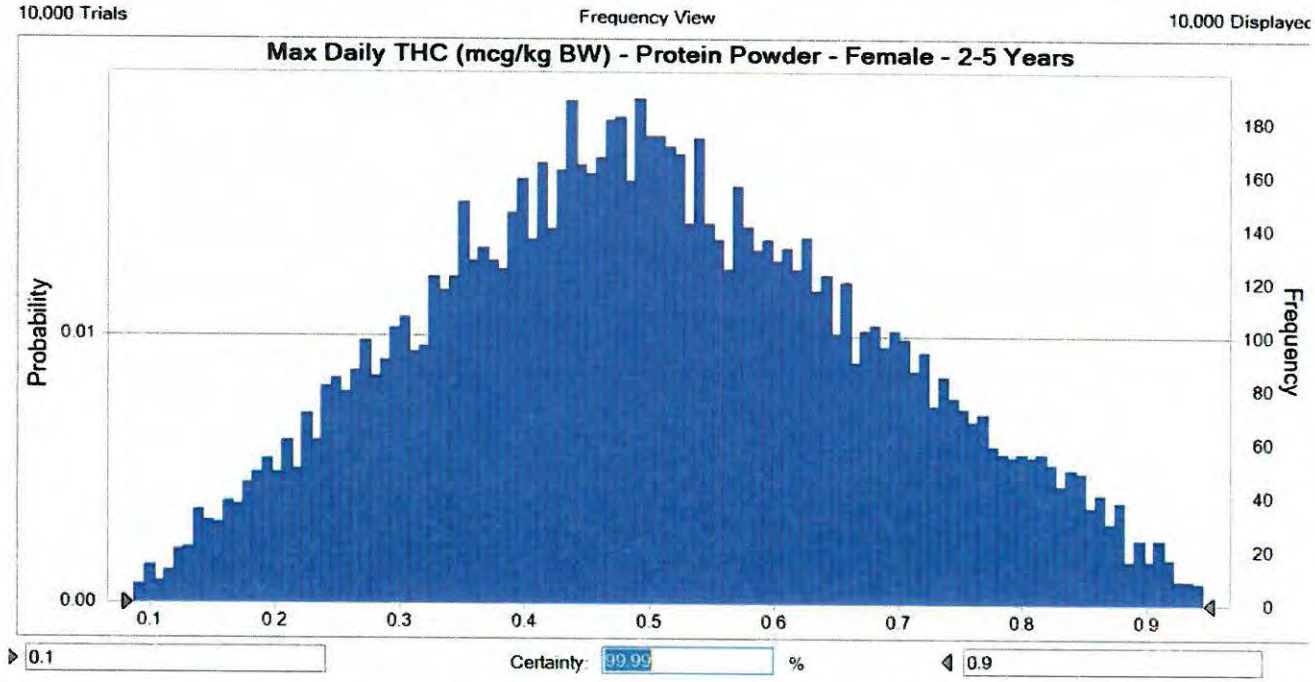
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 87% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 9% and Protein Powders make up 4%

Figure 542 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Females Age 2 to 5 Years)



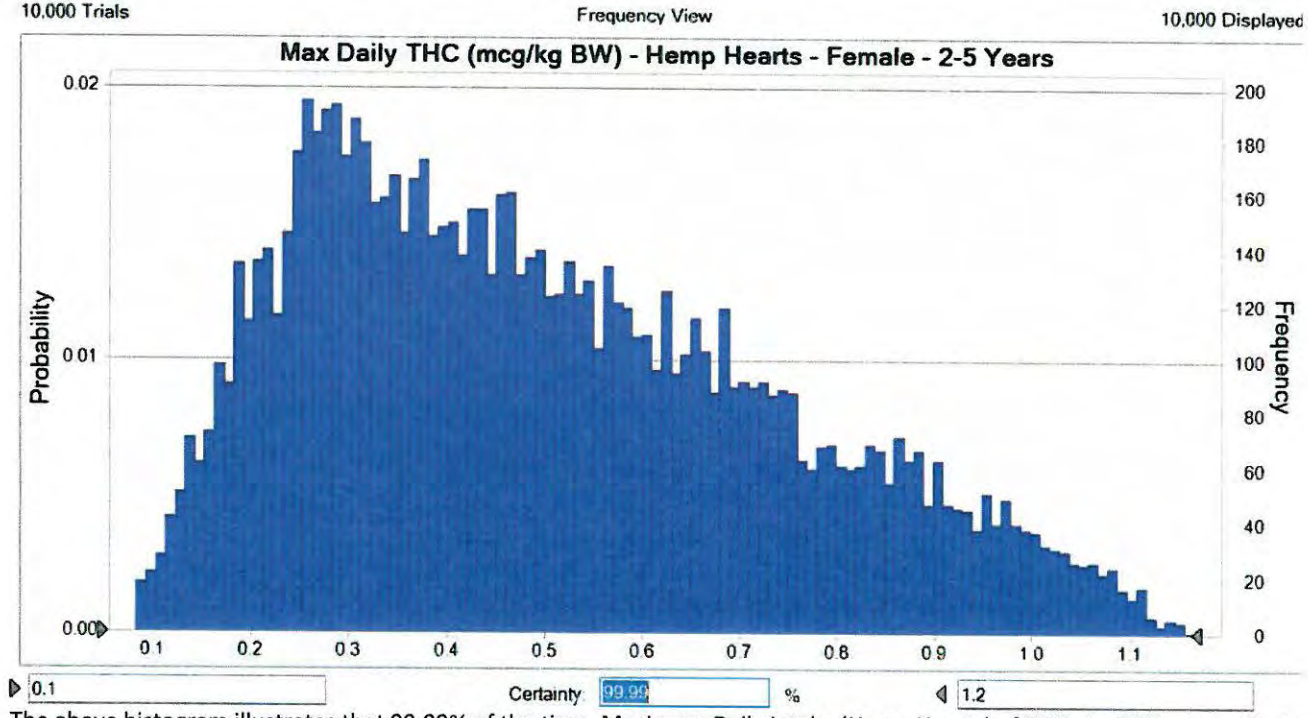
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Protein Powders) of THC at a 90th percentile intake level will see no more than 0.9µg/kg for females ages 2-5 years.

Figure 553 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.5
Median	0.5
Mode	---
Standard Deviation	0.2
Variance	0.0
Skewness	0.1123
Kurtosis	2.41
Coeff. of Variation	0.3562
Minimum	0.1
Maximum	0.9
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.3
30%	0.4
40%	0.5
50%	0.5
60%	0.5
70%	0.6
80%	0.7
90%	0.7
100%	0.9

Figure 564 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 2 to 5 Years)



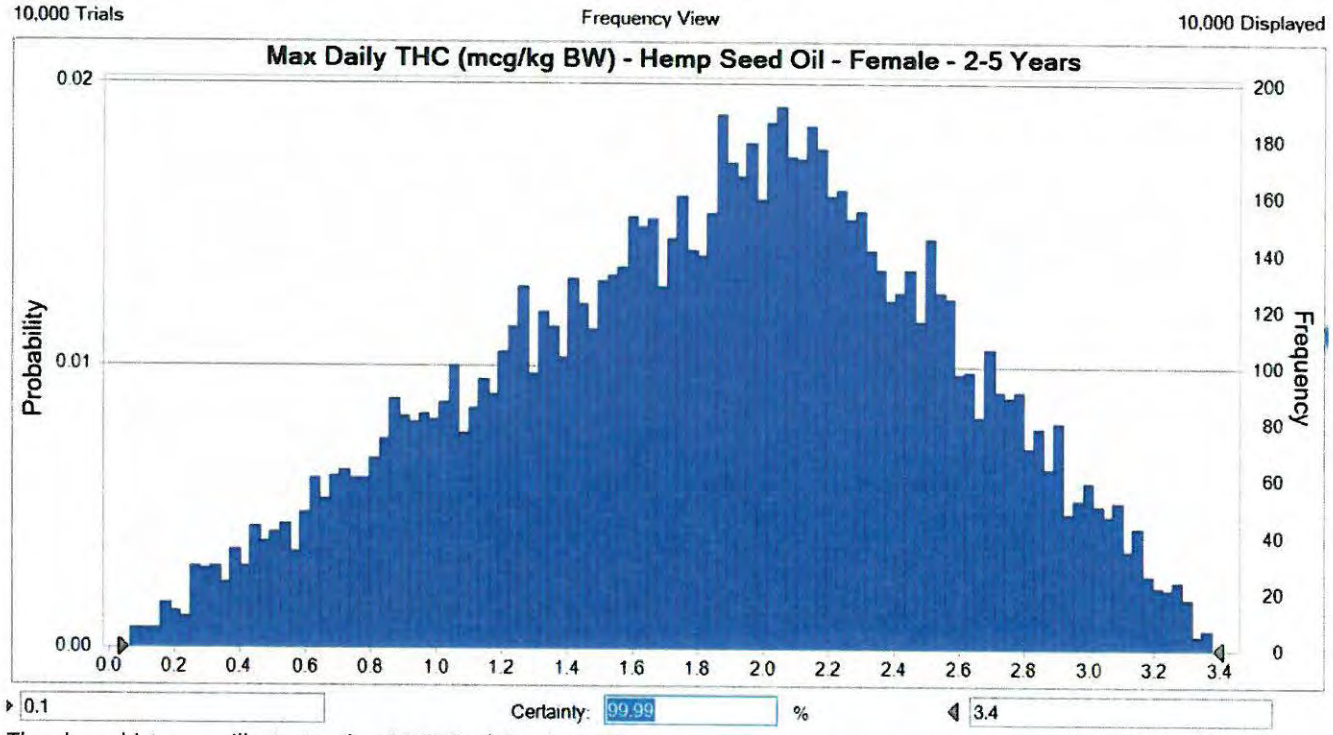
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Hemp Hearts) of THC at a 90th percentile intake level will see no more than 1.2µg/kg for females ages 2-5 years.

Figure 57 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.5
Median	0.5
Mode	—
Standard Deviation	0.2
Variance	0.1
Skewness	0.5224
Kurtosis	2.42
Coeff. of Variation	0.4797
Minimum	0.1
Maximum	1.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.2
20%	0.3
30%	0.3
40%	0.4
50%	0.5
60%	0.5
70%	0.6
80%	0.7
90%	0.9
100%	1.2

Figure 58 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Females Age 2 to 5 Years)



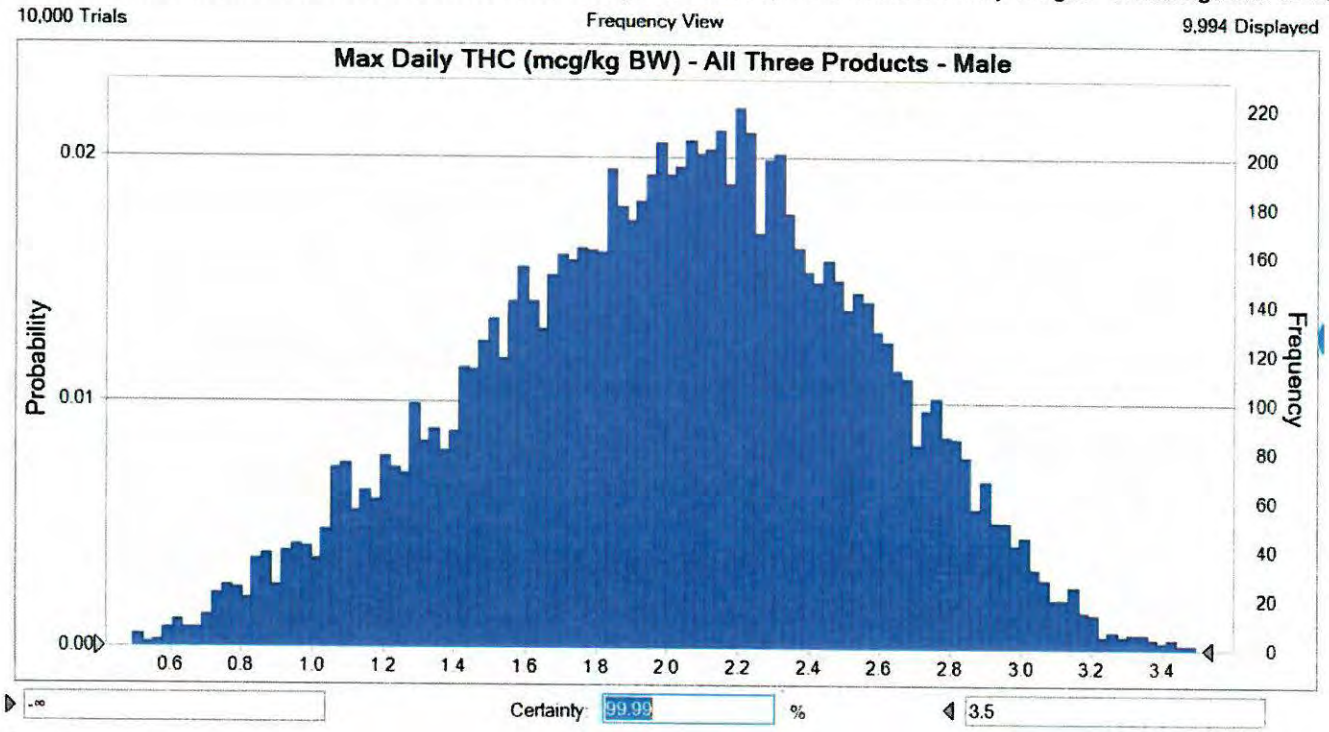
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Hemp Seed Oil) of THC at a 90th percentile intake level will see no more than 3.4µg/kg for females ages 2-5 years.

Figure 59 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	1.7
Mean	1.8
Median	1.9
Mode	—
Standard Deviation	0.7
Variance	0.5
Skewness	-0.2092
Kurtosis	2.41
Coeff. of Variation	0.3772
Minimum	0.1
Maximum	3.4
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.9
20%	1.2
30%	1.5
40%	1.7
50%	1.9
60%	2.1
70%	2.2
80%	2.5
90%	2.7
100%	3.4

Figure 60 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Males Age 6 to 11 Years



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 3.5µg/kg for males age 6-11.

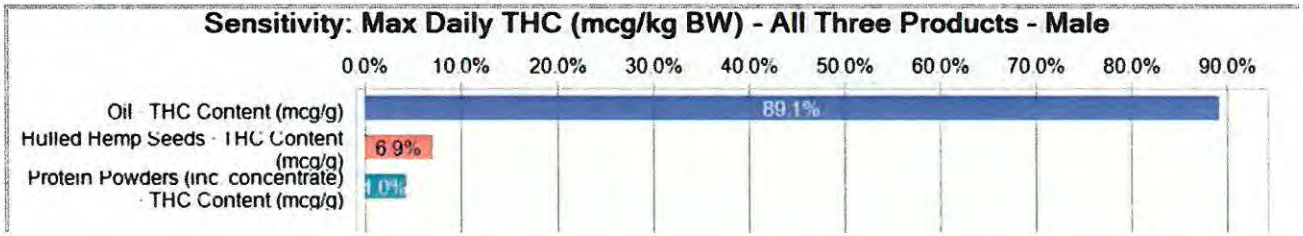
Figure 61 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	1.6
Mean	2.0
Median	2.0
Mode	---
Standard Deviation	0.5
Variance	0.3
Skewness	-0.1738
Kurtosis	2.60
Coeff. of Variation	0.2690
Minimum	0.4
Maximum	3.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.4
10%	1.3
20%	1.5
30%	1.7
40%	1.9
50%	2.0
60%	2.2
70%	2.3
80%	2.5
90%	2.7
100%	3.5

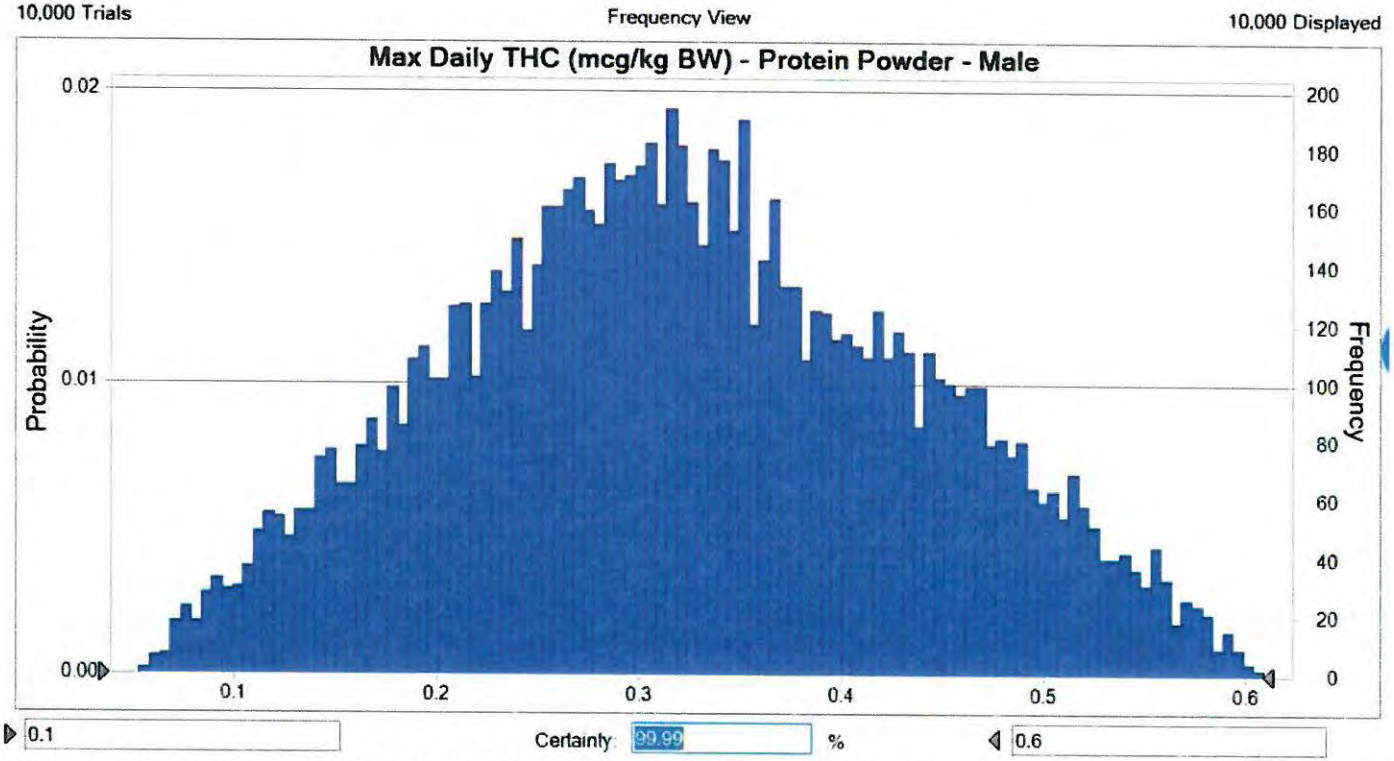
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 89% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 7% and Protein Powders make up 4%.

Figure 62 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Males Age 6 to 11 Years



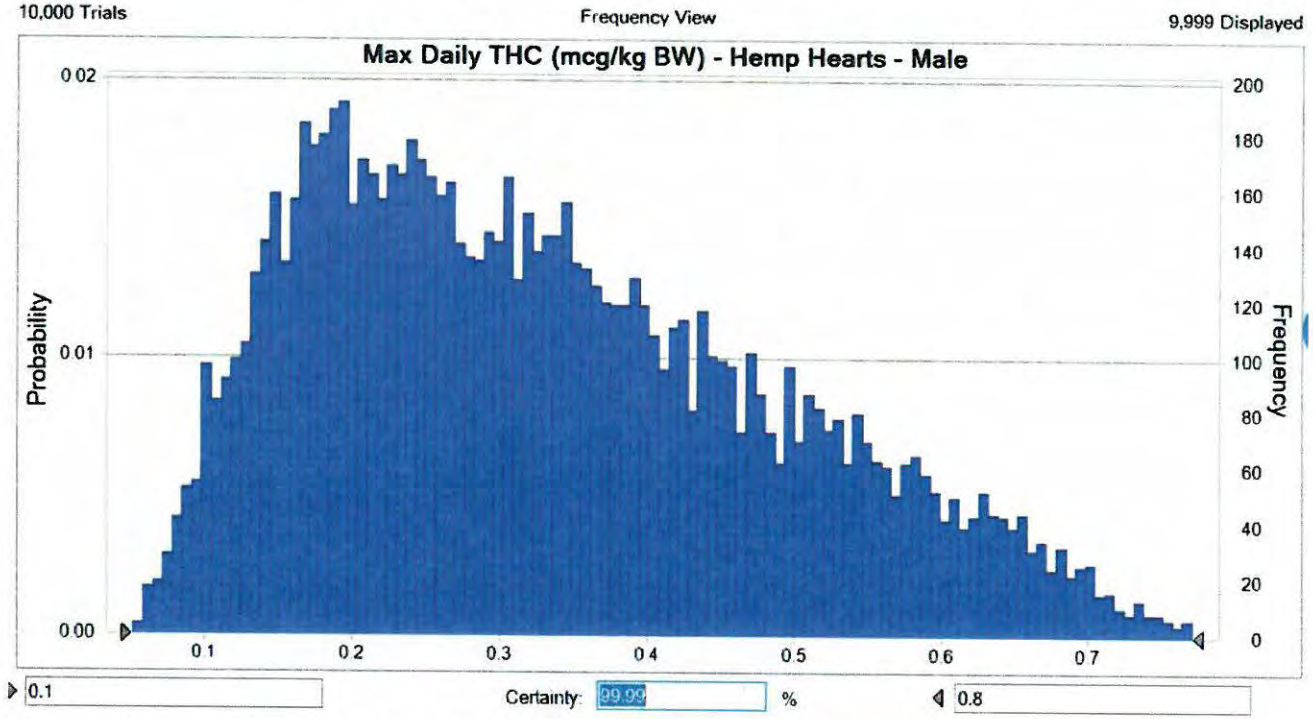
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.6µg/kg for males age 6-11.

Figure 63 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.3
Median	0.3
Mode	---
Standard Deviation	0.1
Variance	0.0
Skewness	0.0971
Kurtosis	2.39
Coeff. of Variation	0.3551
Minimum	0.1
Maximum	0.6
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.2
20%	0.2
30%	0.3
40%	0.3
50%	0.3
60%	0.3
70%	0.4
80%	0.4
90%	0.5
100%	0.6

Figure 64 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 6 to 11 Years



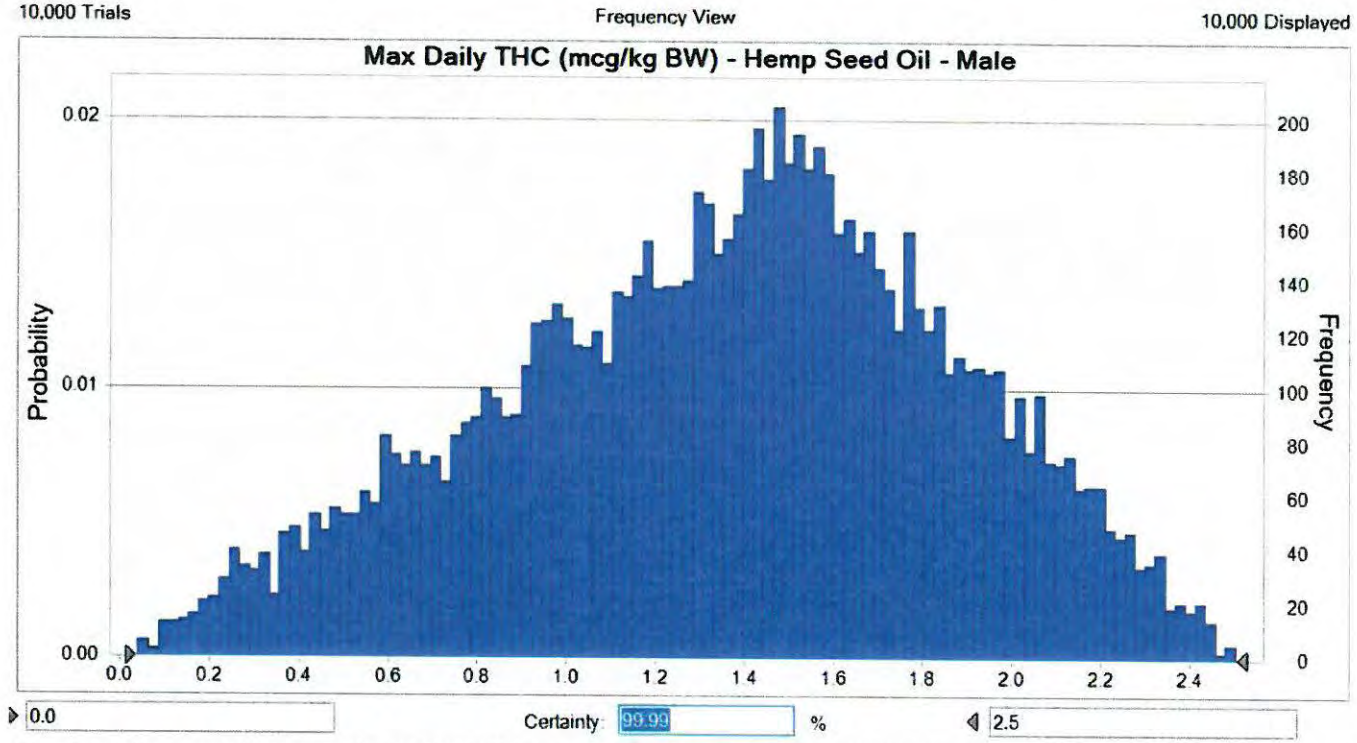
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.8µg/kg for males age 6-11.

Figure 65 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.1
Mean	0.3
Median	0.3
Mode	---
Standard Deviation	0.2
Variance	0.0
Skewness	0.5183
Kurtosis	2.44
Coeff. of Variation	0.4728
Minimum	0.1
Maximum	0.8
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.1
20%	0.2
30%	0.2
40%	0.3
50%	0.3
60%	0.4
70%	0.4
80%	0.5
90%	0.6
100%	0.8

Figure 66 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Males Age 6 to 11 Years



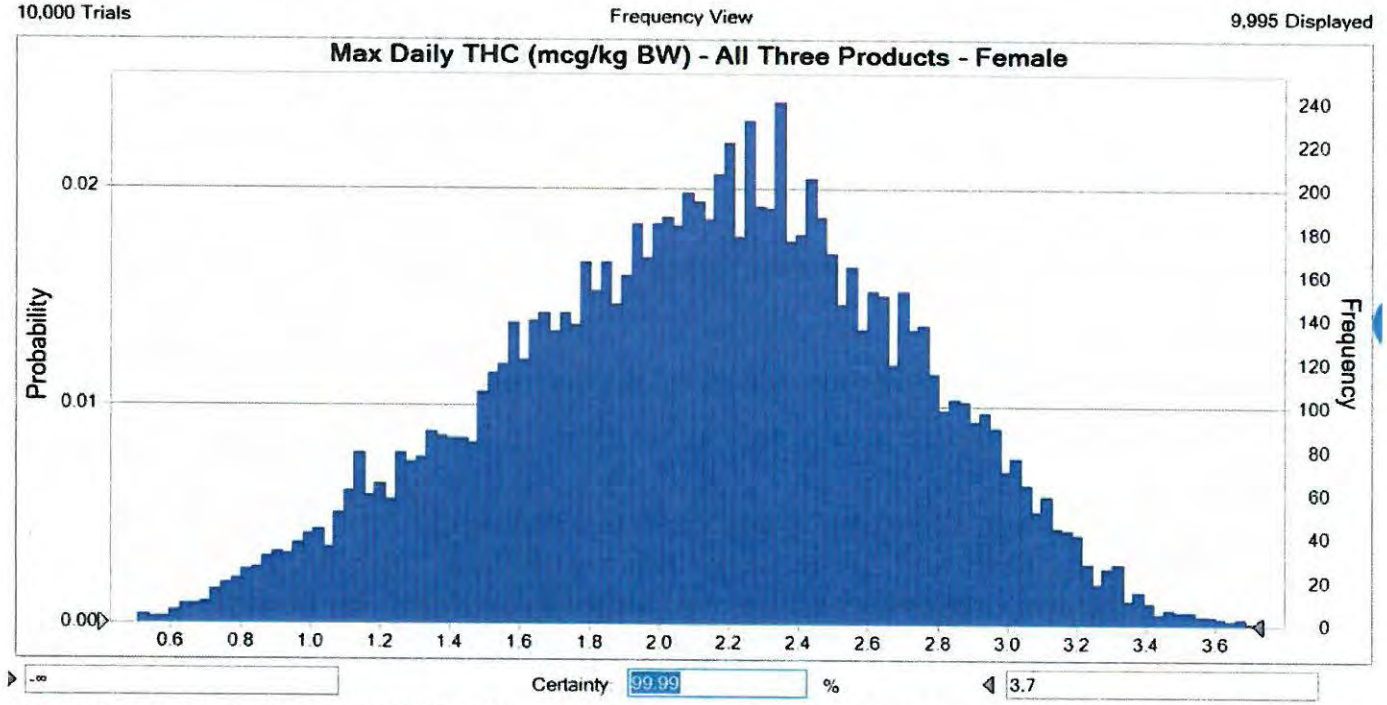
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 2.5µg/kg for males age 6-11.

Figure 67 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	1.3
Mean	1.4
Median	1.4
Mode	—
Standard Deviation	0.5
Variance	0.3
Skewness	-0.2254
Kurtosis	2.46
Coeff. of Variation	0.3744
Minimum	0.0
Maximum	2.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.6
20%	0.9
30%	1.1
40%	1.3
50%	1.4
60%	1.5
70%	1.6
80%	1.8
90%	2.0
100%	2.5

Figure 68 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Females Age 6 to 11 Years



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 3.7µg/kg for females age 6-11.

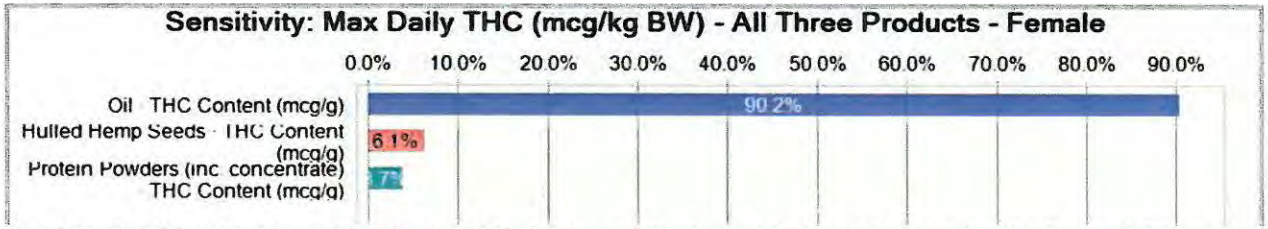
Figure 69 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	1.7
Mean	2.1
Median	2.2
Mode	—
Standard Deviation	0.6
Variance	0.3
Skewness	-0.1800
Kurtosis	2.59
Coeff. of Variation	0.2718
Minimum	0.4
Maximum	3.7
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.4
10%	1.3
20%	1.6
30%	1.8
40%	2.0
50%	2.2
60%	2.3
70%	2.4
80%	2.6
90%	2.9
100%	3.7

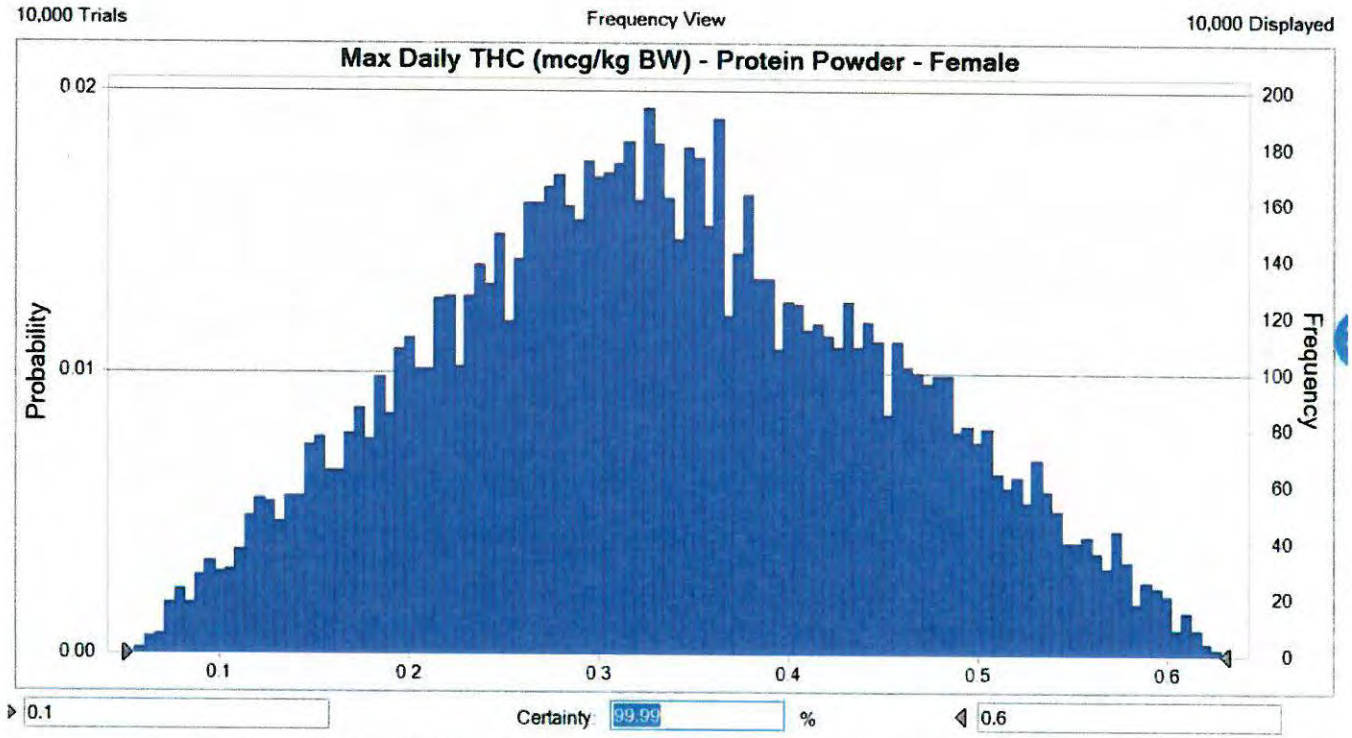
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 90% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 6% and Protein Powders make up 4%

Figure 70 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Females Age 6 to 11 Years



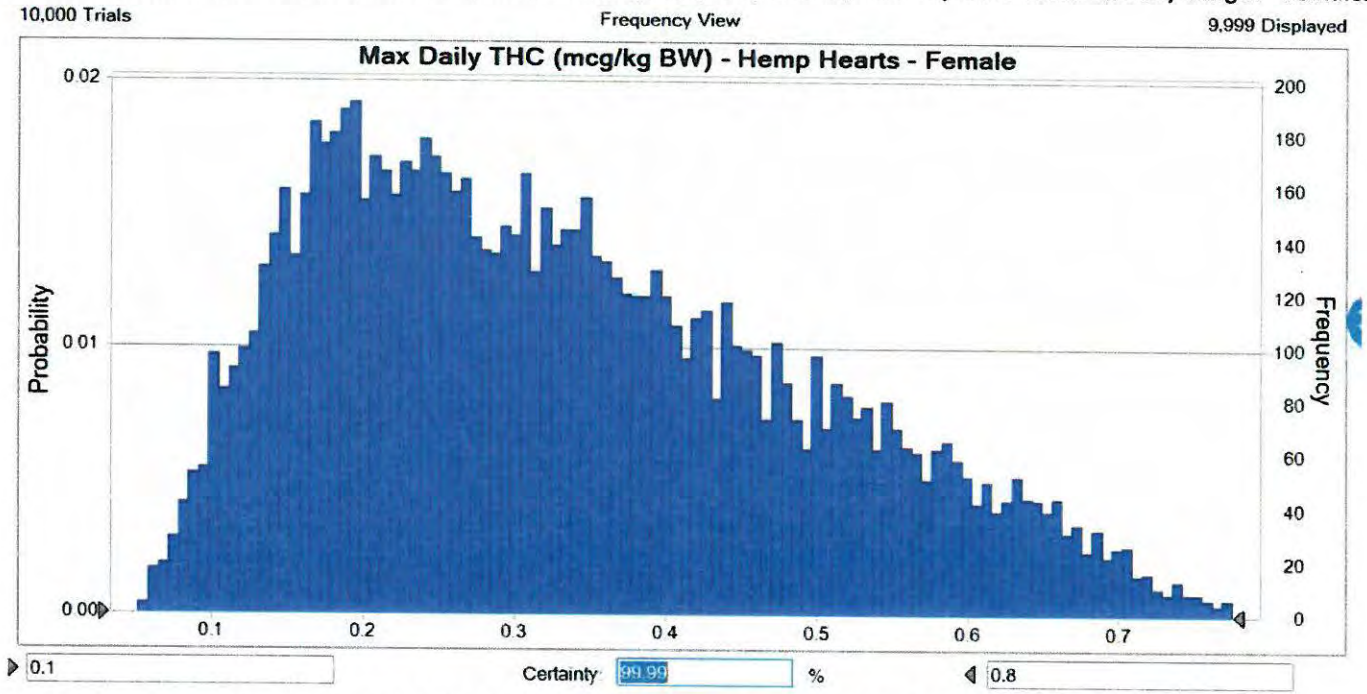
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.6µg/kg for females age 6-11.

Figure 71 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.3
Median	0.3
Mode	---
Standard Deviation	0.1
Variance	0.0
Skewness	0.0971
Kurtosis	2.39
Coeff. of Variation	0.3551
Minimum	0.1
Maximum	0.6
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.2
20%	0.2
30%	0.3
40%	0.3
50%	0.3
60%	0.4
70%	0.4
80%	0.4
90%	0.5
100%	0.6

Figure 72 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 6 to 11 Years



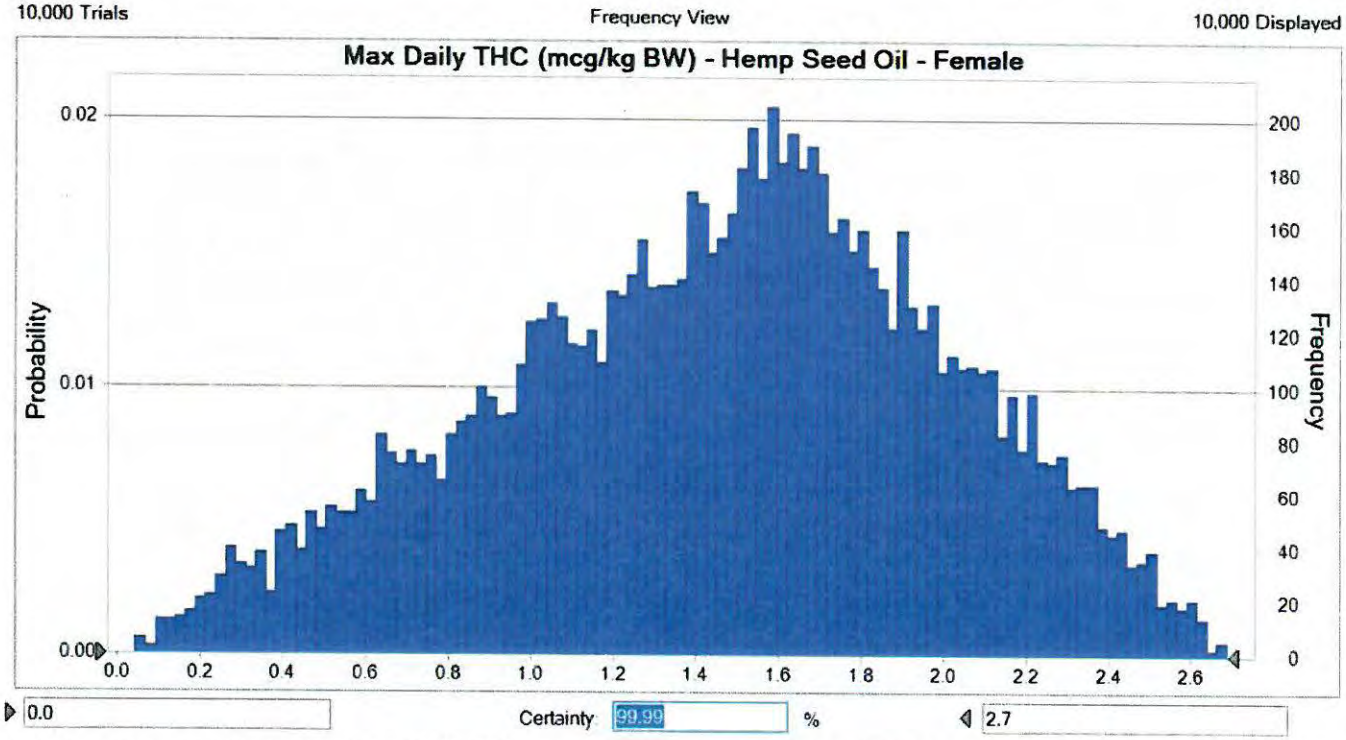
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.8µg/kg for females age 6-11.

Figure 73 Hulled Hemp Seed Consumption - THC Exposure Forecast at Based on Body Weight – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.1
Mean	0.3
Median	0.3
Mode	---
Standard Deviation	0.2
Variance	0.0
Skewness	0.5183
Kurtosis	2.44
Coeff. of Variation	0.4728
Minimum	0.1
Maximum	0.8
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.1
20%	0.2
30%	0.2
40%	0.3
50%	0.3
60%	0.4
70%	0.4
80%	0.5
90%	0.6
100%	0.8

Figure 74 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Males Age 6 to 11 Years



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 2.7µg/kg for females age 6-11.

Figure 75 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	1.3
Mean	1.5
Median	1.5
Mode	—
Standard Deviation	0.5
Variance	0.3
Skewness	-0.2254
Kurtosis	2.46
Coeff. of Variation	0.3744
Minimum	0.0
Maximum	2.7
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.7
20%	1.0
30%	1.2
40%	1.3
50%	1.5
60%	1.6
70%	1.8
80%	1.9
90%	2.2
100%	2.7

Adapted

TIMELINE

Cannabis in History

12,000 bce The earth begins to warm as the Holocene Epoch begins, and plants and animals begin to recolonize Eurasia from glacial refugia.

8000 bce Antecedents of Japanese Jōmon culture already using hemp seed and leaving remains.

5000 bce Earliest European hemp seed remains deposited in Germany.

5000–4000 bce *Cannabis* seed imprints in pottery, Dniester-Prut region, Moldova

4000 bce Ancient Egyptians build the first sailing ships.

3000 bce Hemp seed remains appear in the Baltic region.

2800 bce Earliest hemp seed remains from China, and the first assumed written record of *Cannabis* use for medicine is in the pharmacopoeia of Emperor Shen Nung, the legendary father of Chinese medicine.

2700 bce Remarkably well-preserved *Cannabis* flowers, seeds, stems, and leaves are left in a Yanghai burial tomb of a shaman in western China.

2200 bce Ancient Yellow River civilization begins to consolidate power in northern China, and *Cannabis* is an important multipurpose, cultivated plant.

2000 bce First hemp seed evidence from the Balkan region.

600 bce Phoenicians pioneer the first sea trade routes in the eastern Mediterranean and Red Seas.

500 bce *Cannabis* is described in the Persian Zoroastrian *Avesta* sacred text.

500 bce Earliest hemp seed remains from the Korean Peninsula.

420 bce Hemp seed offerings left in Scythian kurgan tombs in Central Asia.

325 bce Greek geographer and astronomer Pytheas makes first recorded sojourn to England and Scandinavia by sail.

100 bce Chinese make first paper from *Cannabis* and mulberry.

70 ce Roman physician Dioscorides records *Cannabis*'s medical properties.

600 ce Papermaking spreads to Korea.

640 ce The Koran, Islam's central religious text, tolerates *Cannabis* use but forbids alcohol.

900 ce Viking expeditions begin reaching Iceland, Greenland, and Newfoundland.

950 ce Muslim Moors introduce papermaking with *Cannabis* to Spain from North Africa.

1000 ce The English word "hempe" first listed in a dictionary.

1023 Chinese Song dynasty issues the first paper money.

1149 Oxford University is founded in Oxford, England.

1160 Hildegard von Bingen writes *Physica* describing the medicinal use of *Cannabis*.

1200s The magnetic compass commonly used on Chinese oceangoing ships.

1206 Genghis Khan leads the Mongol armies and conquers much of Eurasia.

(*continued*)

1241	Gunpowder introduced to Europe by the Mongols.
1250	European sailors begin to use the magnetic compass.
1275	Marco Polo starts on his alleged 20-year trip to China and reports use of hemp fiber for paper making, caulking of Chinese ships, and cultivation near oases in eastern Turkestan.
1315	The Great Famine begins in Europe.
1346	The bubonic plague starts in China and spreads westward through Europe killing at least one-quarter of Europe's population.
1440s	German inventor Johann Gutenberg revolutionizes knowledge transfer by combining the printing press, movable metal type, and an oil-based ink.
1492	Spanish explorer Christopher Columbus lands in the Bahamas, leading ultimately to the colonization of the New World and introduction of several Old World plants including *Cannabis*.
	First paper mill in England started.
1495	Portuguese explorer Vasco da Gama sails to India via southern Africa and the Cape of Good Hope.
1498	
1533	King Henry VIII issues his first royal decree ordering each farmer to set aside a quarter acre of land for every 60 acres he controlled to cultivate hemp as a strategic crop.
	Spanish bring hemp cultivation to Chile for cordage and cloth.
1545	The Little Ice Age strikes Europe; crops fail and many starve.
1550–1850	Queen Elizabeth I decrees that land owners must grow hemp or pay a £5 fine.
1563	King Philip orders hemp to be grown throughout the Spanish Empire from Argentina to Oregon.
1564	
1569	Mercator publishes his cylindrical projection map of the earth.
1602	Dutch United East India Company (VOC) founded.
1606	British begin to grow hemp in Canada for maritime use.
1611	British begin to grow hemp in Virginia colony.
1619	Virginia becomes first American colony to make hemp growing mandatory.
1630s	Hemp traded throughout the American Colonies.
1735	Carolus Linnaeus introduces his taxonomic system for naming species.
1750s to 1790s	George Washington and Thomas Jefferson experiment with growing hemp on their farms.
1753	*Cannabis sativa* described and classified by Linneaus.
1778	After visiting Australia, James Cook is the first European to travel to Hawai'i.
1783	*Cannabis indica* described and classified by Lamarck.
1791	President Washington imposes import duties on hemp to encourage domestic industry, and Thomas Jefferson urges farmers to grow hemp instead of tobacco.
1807	Napoleon signs treaty with Russia severing all legal Russian hemp trade with Britain. American sailors commence illegal trade in Russian Hemp.
1812	Napoleon invades Russia hoping to control the supply of hemp.
1841	Scotsman William O'Shaunghnessy learns of the medical use of *Cannabis* in India.
1845	Frenchman Jacques-Joseph Moreau de Tours documents the medical benefits of *Cannabis*.
1857	Fitz Hugh Ludlow's *The Hasheesh Eater* is published.

(continued)

1872–76	Scientific Challenger expedition makes many discoveries and established oceanography; the expedition's, mother vessel, HMS Challenger, was supplied with 291 km (181 miles) of Italian hemp for depth sounding.
1859	Charles *Darwin* publishes his classic *The Origin of Species* describing evolution by natural selection and opens the ongoing debate of "evolution versus creationism."
1860	Ohio State Medical society conducts first governmental study of *Cannabis* use and health.
1860s	Augustinian friar Gregor Mendel lays the foundation for modern genetics.
1869	University of California established.
1870	*Cannabis* is listed in the United States Pharmacopoeia as a treatment for various ailments.
1881	Charles and Sir Francis Darwin publish *The Power of Movement in Plants*, investigating fundamental aspects of plant growth.
1890	Queen Victoria's personal physician, Sir Russell Reynolds, prescribes *Cannabis* for menstrual cramps and claims that when pure preparations of *Cannabis* are administered carefully, it is a most valuable medicine.
1894	The *Indian Hemp Drugs Commission Report* concludes that *Cannabis* has medical uses, no addictive properties, and a number of positive emotional and social benefits.
1916	United States Department of Agriculture calls for expansion of hemp acreage to replace timber use by the paper pulp industry.
1925	The *Panama Canal Zone Report* concludes that there is no evidence that *Cannabis* use is habit-forming or deleterious and recommends that no action be taken to prevent its use.
1938	Popular Mechanics magazine publishes an article written before the Marijuana Transfer Tax was passed extolling the virtues of "Hemp—the New Billion Dollar Crop."
1942	United States Department of Agriculture releases the movie Hemp for Victory, encouraging American farmers to resume hemp cultivation to support the war effort.