

# Extractables and Leachables Analysis of IV Bag Systems

**Direct Thermal Extraction of the Materials and Stir Bar Sorptive Extraction of Aqueous Solutions Coupled with Thermal Desorption Gas-Chromatography with Unit Mass and High Resolution Mass Spectrometric Detection**

## Application Note

Pharmaceuticals

### Authors

Andreas Hoffmann, Thomas Albinus  
Gerstel GmbH & Co. KG,  
Eberhard-Gerstel-Platz 1,  
D-45473 Mülheim an der Ruhr,  
Germany

Elizabeth Almasi,  
Agilent Technologies, Inc.  
5301 Stevens Creek Boulevard,  
Santa Clara, CA 95051, USA

Kurt Thaxton  
Gerstel, Inc.  
701 Digital Dr. Suite J,  
Linthicum, MD 21090, USA

### Abstract

To ensure the safety of pharmaceutical products, the monitoring of potentially harmful contaminants originating from the product itself or its packaging is necessary. In this study, IV bag components were analyzed for extractables using direct thermal desorption/thermal extraction combined with unit resolution GC/MS system. The results were compared to those obtained for leachables by stir bar sorptive extraction of an aqueous solution stored in the exact same type of IV bag, again combined with GC/MS determination of the leached compounds. In addition, a high resolution GC/Q-TOF mass spectrometer was used to confirm or refute some of the analyte identifications obtained using commercial library searches with the unit resolution MSD system.



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## Introduction

Packaging or packaging systems, used for affordable, efficient transportation and storage of pharmaceutical products may contain unwanted chemicals that may come in contact with the pharmaceutical product itself, resulting in changes to it. Suitable packaging must ensure the efficacy, safety and quality of the pharmaceutical products and their delivery to the patients.

“Leachables” are organic and inorganic analytes that migrate under normal storage or usage conditions from the packaging into the pharmaceutical product or into the patient if direct contact is encountered.

“Extractables” are compounds removed from the packaging material using aggressive laboratory conditions such as elevated temperature, which would accelerate the transfer of these analytes from the packaging to the drug formulation or to the patient.

Leachables are typically a subset of extractables, or are derived from extractables.

The assessment, regulatory guidance, and safety thresholds of the so called “leachables/extractables” from packaging is addressed by the U.S. Food and Drug Administration (FDA)[1], the Product Quality Research Institute (PQRI), the United States Pharmacopeia (USP 1663 and USP 1664) [2], and the

International Organization for Standardization (ISO 10993). According to USP 1664, the highest concern and risk is associated with the packaging of inhalation aerosols and sprays, injections and injectable suspensions, inhalation and ophthalmic solutions, and transdermal ointments and patches. In these situations, rigorous qualification and low levels of quantification of the leachables/extractables must be met.

IV bags represent an increased risk as the solution from the bag is passed directly into the veins of the patient. Therefore, the study of IV bags is important and includes the analysis of the bag and its components (extractables) and also the content of the aqueous media in the bag (leachables).

To satisfy the identification and sometimes sub-ppb level detection requirements of the extracted or leached chemicals (the latter often in aqueous matrices), a unique sample preparation [3,4] and detection approach was employed as described in the experimental section. The detected leachable or extractable analytes often have significantly different (10–100+ fold) concentration levels, therefore, it is essential to ensure that no carryover occurs, ensuring accurate results. Both the sample preparation and instrumental analysis delivered true blanks, even if very high levels were detected in the previous run.

Table 1. Modified FDA/CDER/CBER Risk-Based Approach to Consideration of Leachables<sup>a</sup>, USP 1664 [1].

### Examples of packaging concerns for common classes of drug products

Degree of concern associated with the route of administration	Likelihood of packaging component-dosage form interaction		
	High	Medium	Low
Highest	Inhalation aerosols and sprays	Injections and injectable suspensions; Inhalation solutions	Sterile powders and powders for injection; Inhalation powders
High	Transdermal ointments and patches	Ophthalmic solutions and suspensions; Nasal aerosols and sprays	—
Low	Topical solutions and suspensions; Topical and lingual aerosols; Oral solutions and suspensions	—	Oral tablets and oral (hard and soft gelatin) capsules; Topical powders; Oral powders

<sup>a</sup>While this table provides a convenient overview of the general level of regulatory concern with various dosage forms regarding leachables, it should not be inferred that “low-risk” dosage forms (for example, oral tablets) carry no risk for leachables issues.

## Experimental

### Materials

Empty and sterile 250-mL capacity IV bags were provided by a customer. The bags were made from polypropylene, but some components (valve, tubing) contained DEHP-plasticized PVC.

### Sampling/sample preparation

Two simple and easy sampling and sample enrichment techniques were used for the measurement:

#### Extractables

Direct thermal desorption was applied at various temperatures to analyze the bag and its components.

Small sample pieces (between 3 and 15 mg) were taken from the IV bag at the positions indicated in Figure 1. These materials were then placed in empty, preconditioned TDU tubes for subsequent direct thermal extraction at temperatures of 80, 140, and 200 °C. During this process, volatilized analytes were purged with the carrier gas into the precooled PTV inlet, concentrating the extracted compounds in the inlet for subsequent GC/MS analysis.

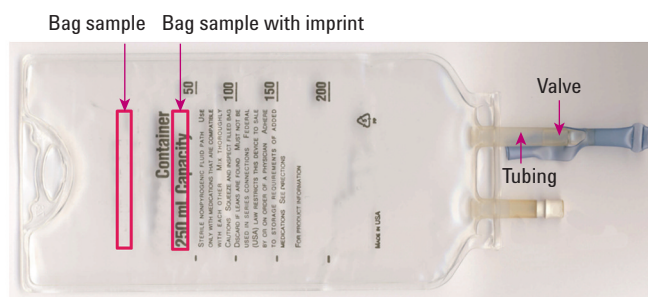


Figure 1. IV bag sampling locations.

#### Leachables

Stir Bar (Twister) Sorptive Extraction [SBSE] sampling was used to enrich the concentration of the leachates of the aqueous media within the IV bags.

SBSE is a solvent-less sample extraction technique for the enrichment of solutes from aqueous samples, first introduced by Baltussen *et al.* in 1999 [5]. It minimizes sample preparation and avoids sample contamination from organic solvents that are usually required to extract analytes from a water-based sample. In addition, there is no need for further concentration procedures, such as large volume injection of an extract, since analytes are already concentrated in the PDMS coating of the stir bar.

A 250-mL volume of deionized water was inserted into an empty IV bag and stored for 48 hours at 40 °C to allow compounds to leach into the aqueous solution. After this period, a 10-mL aliquot of the water was transferred to an empty vial. A Twister stir bar (24 µL PDMS) was added, and the vial was capped. The sample was extracted for 60 minutes by stirring with a Twister at room temperature. The stir bar was removed, rinsed with bottled water, dabbed dry, and placed into a conditioned thermal desorption tube for analysis. The Twister was desorbed at 240 °C.

The rest of the analysis was common to the extractables and leachables measurements.

#### Instrumentation

An Agilent 7890B GC coupled with an Agilent 5977A MSD equipped with a Gerstel PTV Inlet (CIS 4), thermal desorption unit (TDU), and multipurpose sampler (MPS) was used.

The SBSE experiments were performed with Gerstel Twister stir bars coated with 24 µL PDMS. After desorption of the Twister, the above-mentioned GC/MS was used for the analysis.

The confirmatory identification analyses were performed on a 7890B GC coupled with an Agilent 7200 Q-TOF, also equipped with Gerstel PTV Inlet (CIS 4), TDU, and MPS robotic sampler.

## GC/MS analysis

### Thermal desorption of extractables

#### Gerstel TDU

Tube type	Empty (3-15 mg sample)
Pneumatics mode	Splitless
Sample mode	Sample remove
Temperature	30 °C, at 60 °C/min to 80 °C/140 °C/200 °C (10 minutes)
Transfer zone temperature	280 °C

#### Gerstel CIS 4 PTV inlet

##### Liquid Nitrogen Cooling

Liner type	Packed with deactivated glass wool
Carrier gas	Helium
Pneumatics mode	Solvent venting
Vent flow	50 mL/min
Vent pressure	49 kPa until 0.1 minutes
Split flow	30 mL/min at 0.01 minutes
Temperature	-150 °C (0.1 minutes), at 16 °C/sec to 150 °C, at 12 °C/sec to 280 °C (3 minutes)

#### Agilent 7890B GC

Column	Agilent HP-5ms, 30 m × 0.25 mm, 0.25 µm
Column flow	He, 1.0 mL/min, constant flow
Temperature	40 °C (1 minute), at 10 °C/min to 200 °C, at 20 °C/min to 280 °C (5 minutes)

#### Agilent 5977A MSD

Transfer line	280 °C
MS source	230 °C
MS quad	150 °C
Scan range	19 to 350 <i>m/z</i> , 1.14 scans/sec
Threshold	40

### Stir bar sorptive extraction (SBSE) of leachables of an aqueous simulant

#### Gerstel TDU

Tube type	Empty (Twister)
Temperature	30 °C, at 60 °C/min to 240 °C (5 minutes)

#### Gerstel CIS 4 PTV inlet

Split flow	30 mL/min at 1.1 minutes
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#### Agilent 7890B GC, conditions as above

#### Agilent 7200 Q-TOF

MS source	230 °C
Electron energy	70 eV
Scan	29 to 350 <i>m/z</i>
Acq rate	10 spec/sec
Tune mode	4 GHz (high resolution)

## Results and Discussion

### Direct thermal desorption of IV bag components - extractables

Thermal extraction of solid materials at high temperatures allows detection of volatile and semivolatile species independent of their polarity. The ease-of-use and the efficiency of this technique enable fast and substantial extractables studies, as the most relevant compounds, those with relatively high mobility, are covered. For extractables analysis, this is a major advantage over solvent extraction, in which analyte extraction rates depend more on the polarity of the solvent than on their mobility [6].

This procedure minimizes sample preparation and eliminates sample contamination from solvents.

Extraction of clear bag samples were carried out at 80 °C and 200 °C, and the results were compared to bag samples with printed areas.

Compounds identified at 80 °C thermal extraction included cyclohexanone, which is often used as solvent in PVC production. A recent study of plastic tubing used in medical procedures that circulate blood outside the body suggests a link between this compound and decreased heart function, swelling, loss of taste, and short-term memory loss [7]. Almost all 2-ethylhexanol produced globally is converted into the diester *bis*(2-ethylhexyl) phthalate (DEHP), a plasticizer. Neither compound is typically related to the production of polypropylene, the material used to make this IV bag.

When the extraction temperature was elevated to 200 °C, the resulting (red) chromatographic trace shows an increase, not only in recovery of semivolatile compounds, as expected, but also in recovery of volatile compounds (compounds eluting before cyclohexanone, 0–8 minutes). Apparently, these compounds (mainly residual solvents such as acetaldehyde, acetone, *tert*-butanol, hexane, Methyl Isobutyl Ketone (MIBK), toluene, hexanal, styrene, cyclohexanone, and so forth) are only released from the material by applying high extraction temperatures.

When the sample was taken from the bag area with printed text, additional three components, originating from the ink, were detected. This kind of investigative work can identify the source of encountered contaminants.

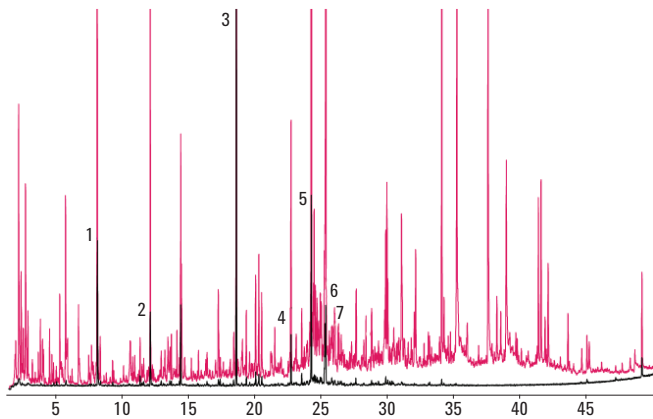


Figure 2. Overlay chromatograms following thermal extraction of 16.3 mg of IV bag material, at 80 °C (black trace) and 200 °C (red trace) at a split rate of 1:30.

Table 2. Compounds Identified at 80 °C Thermal Extraction

No.	Compound	Possible origin
1	Cyclohexanone	Residual solvent
2	2-Ethyl hexanol	DEHP breakdown product, intermediate
3	1,3-di- <i>tert</i> -Butyl benzene	Antioxidant degradation product
4	Diphenyl ether	Intermediate in the production of surface active agents and high-temperature lubricants
5	2,6-di- <i>tert</i> -Butyl- <i>p</i> -benzoquinone	BHT breakdown product, intermediate
6	Butylated hydroxytoluene (BHT)	Antioxidant
7	2,4-di- <i>tert</i> -Butyl phenol	Antioxidant degradation product

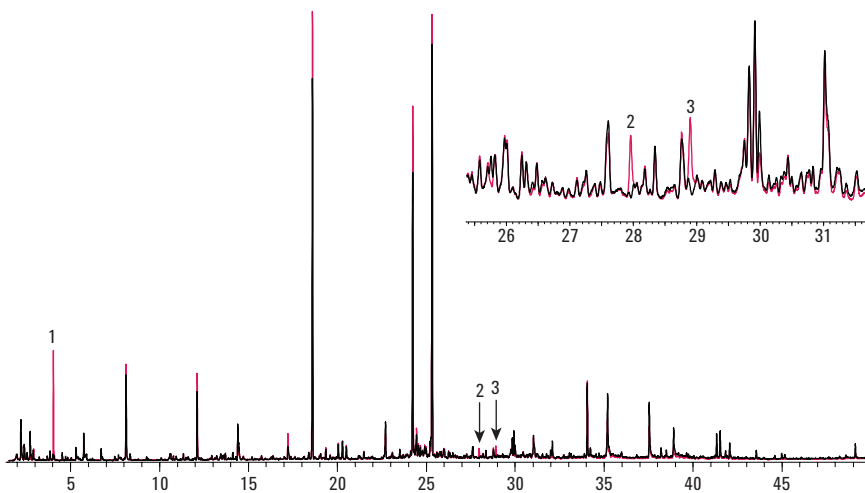


Figure 3. Overlaid chromatograms of thermal extraction of 15.1 mg IV bag material (black trace) and 15.4 mg of IV bag material with imprint (red trace) at 200 °C, split 1:30.

Table 3. Additional Compounds Identified from Bag Sample with Printed Area

No.	Compound	Possible origin
1	Methyl methacrylate	Intermediate (from imprint)
2	<i>o</i> -Toluenesulfonamide	Plasticizer, additive (from imprint)
3	<i>p</i> -Toluenesulfonamide	Plasticizer, additive (from imprint)

The additional peaks were identified as methyl methacrylate, a chemical used for the production of paints and lacquers, as well as *o*- and *p*-toluenesulfonamide. The latter chemicals are commonly used as plasticizers in coatings, paints, and printing inks. In addition, they promote adhesion, and have excellent thermal stability. These compounds have the potential to cause damage to DNA (genotoxic impurity), and thus have heightened concerns, and must be detected at ultra-low (ppb) levels.

The chromatographic fingerprint of the tubing and valve were very similar, indicating that they originate from the same polymer, most likely PVC. Due to the high content of DEHP in the IV tubing, the thermal extraction experiment was carried out at only 140 °C. Figure 4 shows the resulting chromatogram.

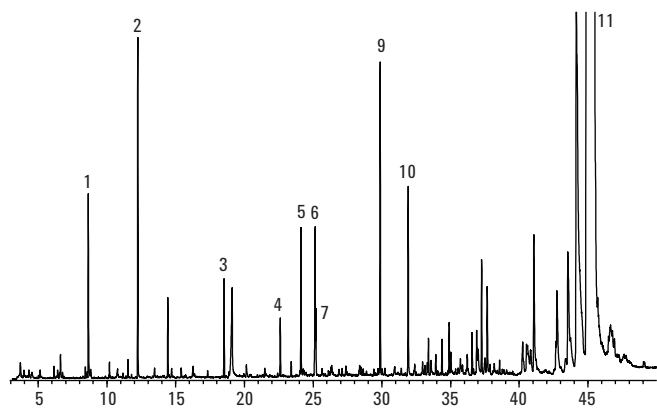


Figure 4. Thermal extraction of 3.7 mg IV tubing (PVC) at 140 °C, split 1:30.

Table 4. Compounds Identified in IV Bag and Valve

No.	Compound	Valve	Bag	Possible origin
1	Cyclohexanone	Yes	Yes	Residual solvent
2	2-Ethyl hexanol	yes	yes	DEHP breakdown product, intermediate
3	1,3-di- <i>tert</i> -Butyl benzene	Yes	Yes	Antioxidant degradation product
4	Diphenyl ether	Yes	Yes	Intermediate in the production of surface active agents and high-temperature lubricants
5	2,6-di- <i>tert</i> -Butyl- <i>p</i> -benzoquinone	Yes	Yes	BHT breakdown product
6	Butylated hydroxytoluene BHT	Yes	Lower conc. than the valve	Antioxidant
7	2,4-di- <i>tert</i> -Butyl phenol	Yes	Yes	Antioxidant degradation product
8	Diethyl phthalate (DEP)	Yes	No	Plasticizer
9	2-Ethylhexyl benzoate	yes	No	Plasticizer
10	2-Ethylhexyl salicylate	Yes	No	UV stabilizer
11	DEHP (Diethylhexyl phthalate)	yes	No	Plasticizer

The presence of cyclohexanone and 2-ethylhexanol in the chromatogram seems very plausible. The IV tubing is made of PVC containing high amounts of DEHP plasticizer. Residual cyclohexanone solvent is often found in PVC products and 2-ethyl hexanol is an intermediate in the production of DEHP.

Comparing these results with those of the IV bag material, we arrived at the conclusion that compounds from the tubing or plastic valve must have migrated into the bag material and contaminated it.

### System integrity is maintained even after samples with high concentrations of extractable are encountered

The chromatogram in Figure 5 demonstrates how sample fidelity is maintained, even when very high concentrations are encountered, such as the high DEHP content of the PVC components (valve and tubing) at 200 °C extraction temperature.

Although the sample size from the plastic valve was reduced to only 2.3 mg, and the extracted volatiles were introduced to the GC column with a split ratio of 1:30, the column was still overloaded with DEHP, and the peak stretched out over 10 minutes, starting at ~45 minutes. This shows that an essential precondition for successful direct extraction experiments is an inert sample flow path that is regenerated at the end of the analysis in preparation for the next sample. This ensures that sample-to-sample carryover will not occur, and will not compromise the analytical results, even if very high concentration levels are encountered. Figure 5 shows an overlay of the overloaded chromatogram (extraction at 200 °C) followed immediately by a blank run using an empty sample tube and identical instrument conditions.

The TDU GC/MS system is exceptionally reliable, exhibiting virtually no carryover even after very high concentrations were measured during the previous run.

### GC/MS analysis - stir bar sorptive extraction (SBSE) of aqueous simulants

SBSE with the Twister was applied to a 10-mL aliquot of the water sample from the leachables simulation experiment described in the sample preparation section. In parallel, a Twister extraction of a 10-mL blank water sample was performed, followed by thermal desorption-GC/MS analysis. The resulting chromatogram of the blank showed a couple of siloxanes from the PDMS coating of the Twister stir bar, but no significant traces of other organic compounds. The siloxanes are marked with an asterisk (\*) in all following chromatograms.

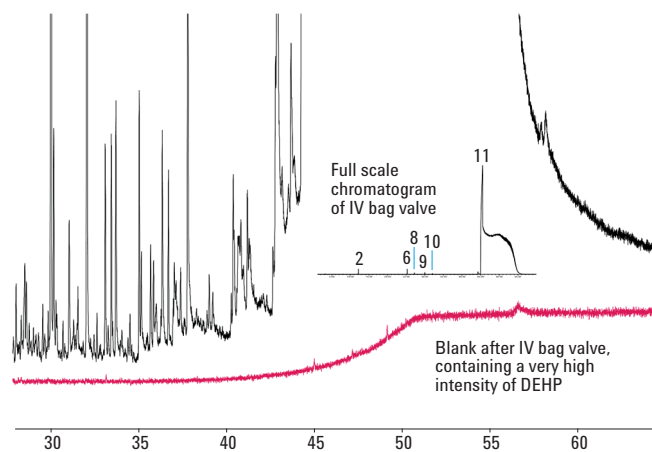


Figure 5. Overlay chromatograms of thermal extraction of 2.3 mg IV plastic valve (PVC) at 200 °C, split 1:30 (black trace) and a subsequent blank run (red trace) under same conditions.

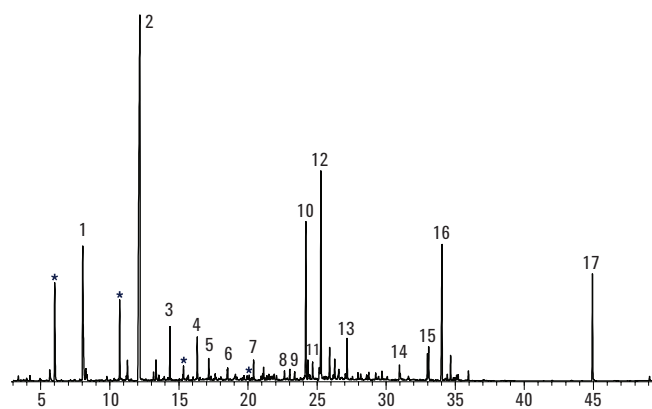


Figure 6. Stir bar sorptive extraction of a 10-mL aliquot of a 250 mL deionized water sample stored for 48 hours at 40 °C in an IV bag, splitless sample introduction.

No.	Compound
1	Cyclohexanone
2	2-Ethyl hexanol
3	Nonanal
4	Nonanol
5	2- <i>tert</i> -Butyl-1,4-benzoquinone
6	1,3-di- <i>tert</i> -Butyl benzene
7	Acetyl methylthiophene (?)
8	Diphenyl ether
9	1,1-Dimethylethyl-4-methoxyphenol (BHA)
10	2,6-di- <i>tert</i> -Butyl- <i>p</i> -benzoquinone
11	BHT
12	2,4-di- <i>tert</i> -Butyl phenol
13	Diethyl phthalate
14	3,5-di- <i>tert</i> -butyl-4-hydroxybenzaldehyde
15	Isobutyl phthalate
16	7,9-di- <i>tert</i> -butyl-1-oxaspiro-[4.5]deca-6,9-diene-2,8-dione
17	DEHP

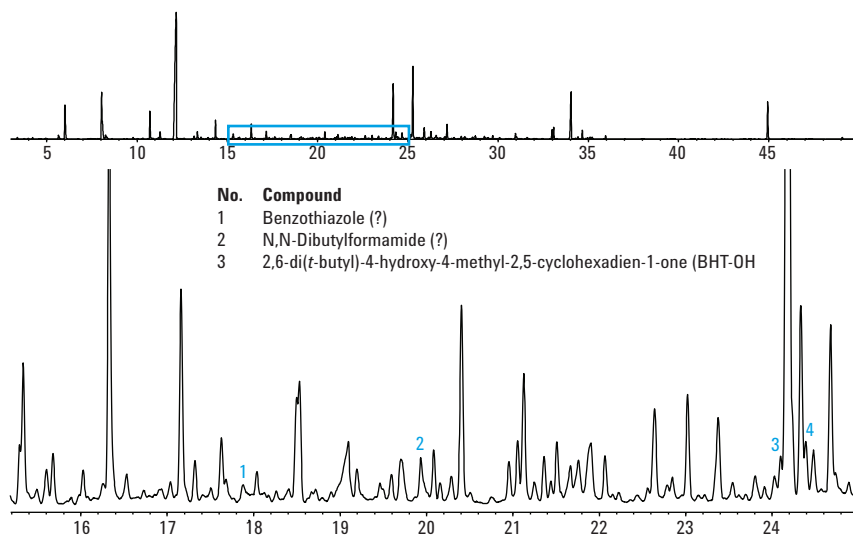


Figure 7. Stir bar sorptive extraction of an 10-mL aliquot of a 250 mL deionized water sample stored for 48 hours at 40 °C in an IV bag, splitless sample introduction (zoom 15–25 minutes).

Using SBSE, a couple of compounds could be identified that were also found in the previously mentioned thermal extraction experiments on the packaging material. Obviously, some of these compounds were leached into the aqueous simulant. Additional compounds were detected that had not been detected as extractables, possibly due to their presence at very low concentrations.

The Agilent 7200 Q-TOF mass spectrometer was used to further study some of the trace compounds (benzothiazole and

N,N-dibutylformamide), which were only tentatively identified using the MSD, and a group of compounds that all had  $m/z$  125 and 140 as major masses. Both Wiley 6 and NIST 14 implied they are sulfur containing analytes.

Figure 8 shows the confirmatory Q-TOF analysis of benzothiazole (RT 17.2 minutes), providing the proper formula for the compound. The accurate mass spectrum did not confirm the presence of N,N-dibutylformamide.

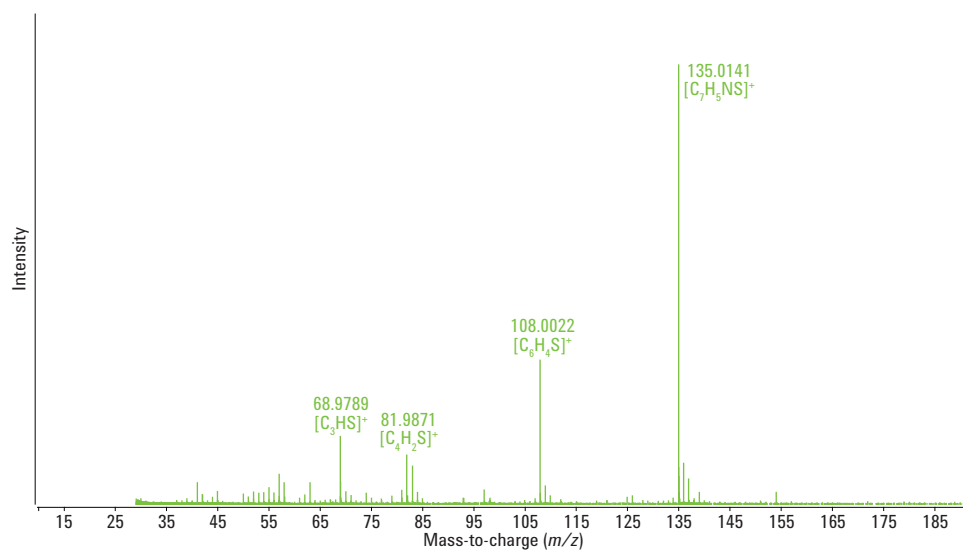


Figure 8. Stir bar sorptive extraction of an 10-mL aliquot of a 250-mL deionized water sample stored for 48 hours at 40 °C in an IV bag, splitless sample introduction. Presence of benzothiazol confirmed with the Q-TOF system (mass error:  $-0.4$  mDa = 2.8 ppm).



The single quad library results (Wiley 6 and NIST 14) did not show satisfactory results especially for the peak group with  $m/z$  125 and 140. Both libraries suggested that these compounds contain sulfur atoms, for example, acetyl methylthiophene. After the Q-TOF accurate mass measurements, the presence of sulfur in the molecules was

excluded, and the implication of the analytes containing sulfur was refuted by accurate mass analysis. Further analysis using chemical ionization and MS/MS measurements would be needed to elucidate the identity of the unknown analogs.

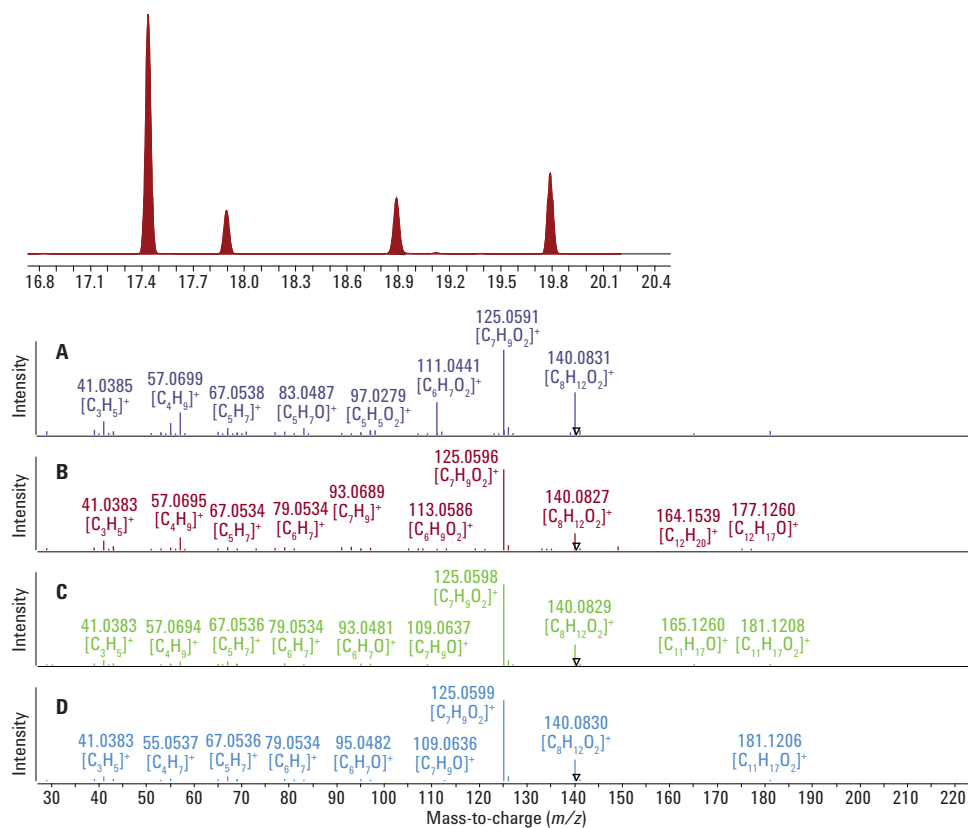


Figure 9. Stir bar sorptive extraction of a 10-mL aliquot of a 250-mL deionized water sample stored for 48 hours at 40 °C in an IV bag, splitless sample introduction. Presence of sulfur in compounds with masses  $m/z$  125 and 140 excluded through use of Q-TOF results.

Table 5 lists the compounds determined based on stir bar sorptive extraction and their likely origin from the IV bag components.

Table 5. Compound Identification of Stir Bar Sorptive Extraction of IV Bag Water Sample, Related to Their Origin from IV Bag Components

No.	Compound	Main source	Possible origin
1	Cyclohexanone	IV tubing	Residual solvent
2	2-Ethyl hexanol	Plastic valve	DEHP breakdown product, intermediate
3	Acetophenon	IV bag	Residual solvent
4	Nonanal		
5	Nonanol		
6	2- <i>tert</i> -Butyl-1,4-benzoquinone	IV bag	BHT breakdown product
7	Benzothiazole		Vulcanization agent
8	1,3-di- <i>tert</i> -Butyl benzene	IV bag	Antioxidant degradation product
9	Diphenyl ether		Intermediate in the production of surface active agents and high temperature lubricants
10	1,1 –Dimethylethyl-4-methoxyphenol (Butylated Hydroxyanisole BHA)	IV bag	Antioxidant
11	2,6-di( <i>tert</i> -butyl)-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one (BHT-OH)	IV bag	BHT breakdown product
11	2,6-di- <i>tert</i> -Butyl- <i>p</i> -benzoquinone	IV bag	BHT breakdown product
13	2,5-di- <i>tert</i> -Butyl-1,4-benzoquinone (BHT-quinone)	IV bag	BHT breakdown product
14	Butylated Hydroxytoluene BHT	Plastic valve	Antioxidant
15	2,4-di- <i>tert</i> -Butyl phenol	IV bag	Antioxidant degradation product
16	<i>tert</i> -Butylhydroquinone	IV bag	Antioxidant
17	Diethyl phthalate	Plastic valve	Plasticizer
18	Benzophenone		UV stabilizer
19	2-Ethylhexyl benzoate	Plastic valve, IV tubing	Plasticizer
20	1,4-di- <i>tert</i> -Butylhydroquinone	IV bag	Antioxidant
21	3,5-di- <i>tert</i> -butyl-4-hydroxybenzaldehyde	IV bag	BHT breakdown product
22	3,5-di- <i>tert</i> -Butyl-4-hydroxyacetophenone	IV bag	BHT breakdown product
23	Isobutyl phthalate	IV bag	
24	7,9-di- <i>tert</i> -butyl-1-oxaspiro-[4.5]deca-6,9-diene-2,8-dione	IV bag	Degradation product of 2,4-di- <i>tert</i> Butyl phenol
25	DEHP	Plastic valve, IV tubing	Plasticizer

## Conclusions

Thermal desorption of packaging components followed by Twister analysis of aqueous simulants provides a simple and efficient means of creating a comprehensive target list for future leachable experiments. Thermal desorption, when performed without an in-line valve or transfer line, can successfully transport heavy SVOCs to the GC/MS with very low carryover, even between severely overloaded samples. This was shown to be very useful in finding the origin of an extractable compound found in a package.

Also demonstrated was the need for the high resolving power and accurate mass of the GC/Q-TOF MS in some cases, both for confirmation and exclusion of target extractables. The use of Twister produced chromatograms rich with trace level species; only a few were discussed here. The Q-TOF is a powerful tool to deliver unambiguous confirmation of trace analytes, or highlight if further investigation is needed for positive identification. Coupling simple, rugged, and efficient thermal desorption sample introduction to the Q-TOF gives the instrument an opportunity to rise to its potential.

Finally, the data presented here were for the demonstration of concepts, and is necessarily incomplete; state-of-the-art practitioners would perform more rigorous work than what is shown in these examples. Many more replicates would have been performed, and quantitative or semiquantitative estimates of the extractables would have been determined, as required by FDA guidelines.

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