AppNote 2/2015

Extractables and Leachables Analysis of IV Bag Systems using 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

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

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

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

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Abstract
IV bag components were analyzed for extractables using direct thermal desorption/thermal extraction combined with a unit mass resolution GC/MSD system. The results were compared to those obtained for leachables by stir bar sorptive extraction of an aqueous simulant stored in the exact same type of IV bag, again combined with GC/MS determination of the leached compounds. In addition, the high resolution GC/Time of Flight (TOF) mass spectrometer was used to verify or disprove some of the MSD findings.

INTRODUCTION

Packaging used for pharmaceutical products may contain unwanted chemical compounds that may come in contact with the product resulting in changes to the product. To evaluate the packaging system, it may be filled with a simulant that approximates the chemistry of the drug product. Higher temperatures and/or more aggressive simulant conditions may be used in an attempt to accelerate the extraction and transfer of these chemical compounds to the simulant. Chemical compounds introduced from the packaging under these conditions are referred to as extractables.

If the drug product itself is analyzed for chemical compounds originating from the packaging after storage under normal conditions, the compounds found are referred to as leachables. Because both tests are normally carried out on the complete packaging system, understanding which part of the system contributed the extractables or leachables found requires additional chemical forensic work.

Table 1. Modified FDA/CDER/CBER Risk-Based Approach to Consideration of Leachables[a].

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

[a] 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 (e.g., oral tablets) by that definition carry no risk for leachables issues.

In a 1999 Guidance for Industry publication, the US FDA classified extractable/leachable concerns in packaging for common classes of drug products [1]. This classification would later be codified with minor modification in USP 1664 [2]. In Table 1., the likelihood of packaging component-dosage interaction is listed along with the degree of concern associated with the route of administration. Regulatory concern is greatest where highest degree of concern with the administration route occurs simultaneously with the highest likelihood of packaging interaction.

According to USP 1664, this situation occurs with a number of drug types and their packaging: Inhalation aerosols and sprays, injections and injectable suspensions, inhalation solutions, and transdermal ointments and patches. For these drug types, rigorous qualification of extractables and leachables is matched with the need for low levels of quantification.

Aqueous solutions are often used in the above-mentioned drug types (with the exception of transdermal ointments and patches). Solutions in IV bags are passed directly into the veins of the patient in significant amounts making extractables and leachables studies of IV Bags containing aqueous media especially critical. These bags may also be filled with a variety of drug products at the hospital pharmacy, making a traditional leachables experiment (a test on just one drug product) less relevant and harder to perform. Consequently, the results of the extractables experiments are even more important.

For those extractables which are non-polar or modestly polar, GC/MS analysis will be more successful than LCMS. However, GCMS of aqueous solutions is difficult because:

- Water is not compatible with traditional gas chromatography
- The detection limits needed (sometimes sub-ppb) are difficult to attain with even the most sensitive instruments, and
- Low concentrations or the introduction of novel compounds make the identification using unit mass-based mass spectral libraries challenging.

The first two issues can be addressed using Stir Bar Sorptive Extraction (SBSE), a technique commonly used in pharmaceutical and other applications where concentration of analytes and extraction of analytes from the aqueous matrix is necessary [3, 4]. Analytes are absorbed and concentrated on the Stir Bar ("Twister") and are subsequently desorbed using a thermal desorption system, re-concentrated in a Programmed Temperature Vaporizer (PTV) type GC inlet, and are then injected onto the GC column.

The concentration factor achieved by using SBSE-TD-GCMS often resolves some of the third issue, but sometimes does not. Where the use of unit mass spectrometry is insufficient, highly sensitive quadrupole time-of-flight mass spectrometers (QTOF-MS) can be used instead.

In this work we were confronted with the task of trying to determine the extractables from an IV bag system while at the same time understanding which part of the system they were introduced from (the leachables would be specific to a drug product to be tested at a future time).

Experimental

To solve this issue, the approach we took was:

1. Direct thermal desorption (extraction) of bag components at elevated temperatures
2. SBSE-GC/MS of an aqueous simulant stored in the bag at slightly elevated temperatures
3. Use of SBSE-GC-QTOF-MS where needed to resolve any qualification issues not solvable in step two.

Step 1 is extremely important: direct desorption at high (200°C) temperatures of the individual bag components provides a 'menu' of extractables candidates for the leachables analysis/simulation in step 2. More importantly, direct thermal desorption of individual IV system components makes it easier to assign a detected compound to the bag component from which it could be leached.

Materials and instrumentation. Empty and sterile, 250 mL capacity IV bags were provided by a customer. The bags were made from polypropylene, but, as indicated on the outer packing, "some product components contain DEHP-plasticized PVC".

Analysis of IV bag components were performed on a 7890B GC coupled with a 5977A MSD (Agilent Technologies), equipped with a PTV Inlet (CIS 4), Thermal Desorption Unit (TDU), and MultiPurpose Sampler (MPS) (all from GERSTEL).

For the SBSE experiments Twister stir bars (GERSTEL) coated with 24 µL PDMS were applied. For desorption of the Twister the above-mentioned instrumental setup was used.

The confirmatory analyses were done on a 7890B GC coupled with a 7200 QTOF (Agilent Technologies), also equipped with a PTV Inlet (CIS 4), Thermal Desorption Unit (TDU), and MPS robotic sampler (GERSTEL).

Direct thermal desorption (extraction) of IV bag components

Sample preparation. Small sample pieces (between 3 and 15 mg) were taken from the IV bag at the positions displayed in figure 1. These materials were then placed in empty, pre-conditioned TDU tubes for subsequent thermal extraction.

Figure 1. IV bag sampling spots.

GC/MS analysis. IV bag component samples placed in empty, pre-conditioned TDU tubes, were heated for direct thermal extraction at temperatures of 80, 140, and 200°C. During this process volatilized analytes are purged with the carrier gas into the pre-cooled CIS, concentrating the extracted compounds in the inlet for subsequent GC-MS analysis.

Thermal Desorption	*TDU (GERSTEL)*
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)
Transferzone Temperature	280°C

PTV inlet	*CIS 4 (GERSTEL)*
Liquid Nitrogen Cooling	
Liner Type	packed with deactivated glasswool
Carrier Gas	Helium
Pneumatics Mode	solvent venting
Vent Flow	50 mL/min
Vent Pressure	49 kPa until 0.1 min
Splitflow	30 mL/min @ 0.01 min
Temperature	-150°C (0.1 minutes), at 16°C/sec to 150°C, at 12°C/sec to 280°C (3 minutes)

GC	*Agilent 7890B*
Column	HP-5ms (Agilent), 30 m x 0.25 mm x 0.25 µm
Mode	constant flow, 1.0 mL/min
Temperature	40°C (1 minute), at 10°C/min to 200°C, at 20°C/min to 280°C (5 minutes)

MSD	*Agilent 5977A*
MS source	230°C
MS Quad	150°C
Scan	19 to 350 amu, 1.14 scans/sec
Threshold	40

Stir Bar Sorptive Extraction (SBSE) of an aqueous simulant

Sample preparation. A 250 mL volume of deionized water was filled into an empty IV bag and stored for 48 hours at a slightly elevated temperature of 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 was added and the vial was capped. The sample was extracted for 60 minutes through 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.

GC/MS analysis conditions. The Twister was desorbed at 240°C. Only those parameters that differ from the thermal extraction experiments are displayed.

Thermal Desorption	*TDU (GERSTEL)*
Tube Type	empty (Twister)
Temperature	30°C, at 60°C/min to 240°C (5 minutes)

PTV inlet	*CIS 4 (GERSTEL)*
Splitflow	30 mL/min @ 1.1 min

Q-TOF	*Agilent 7200*
MS source	230°C
Electron energy	70eV
Scan	29 to 350 amu
Acq rate	10 spectra/sec
Tune mode	4 Ghz (high resolution)

Results and Discussion

Please note: the evaluation of the data below is for demonstration purposes only, and is not in any way a thorough evaluation of all the analytes observed. A complete account would require more time and resources than was available for this project.

Direct thermal desorption (extraction) of IV bag components.

Thermal extraction of solid materials at high temperatures allows analysis of volatile and semi-volatile 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 [5]. This procedure minimizes sample preparation and eliminates sample contamination from solvents.

Figure 2 shows the resulting chromatogram following thermal extraction of 16.3 mg of IV bag material, split 1:30.

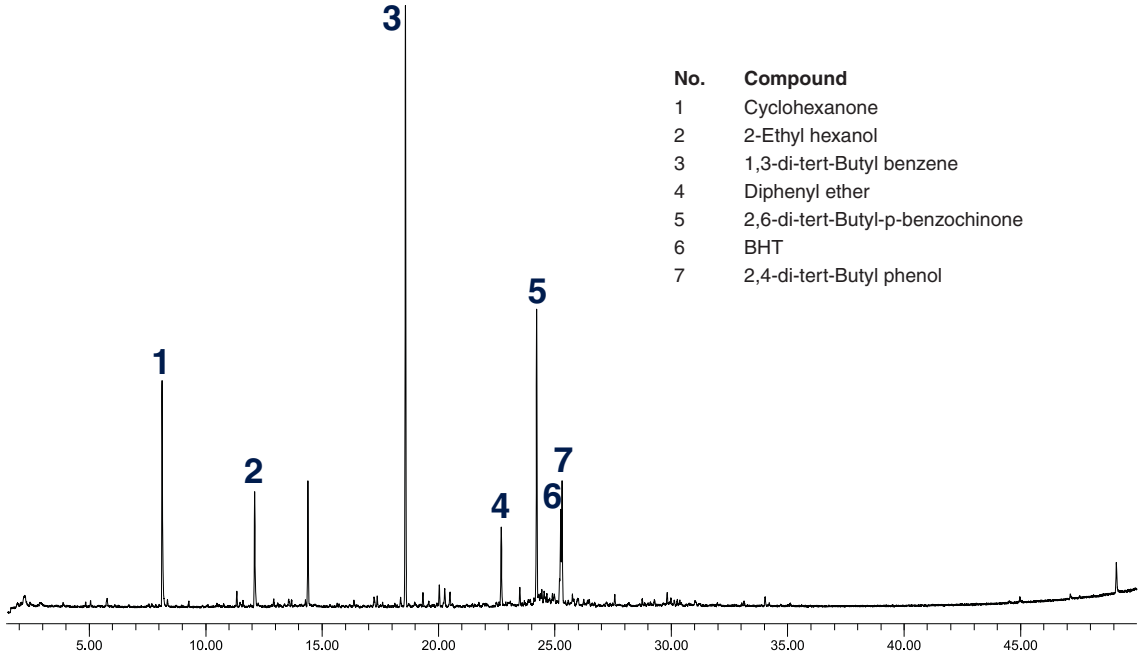

Figure 2. Thermal extraction of 13.6 mg IV bag material (polypropylene) at 80°C, split 1:30.

Cyclohexanone 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 [6]. 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.

The experiment was repeated, this time using an extraction temperature of 200°C. Figure 3 shows an overlay of the extraction at 80°C (black trace) and 200°C (red trace).

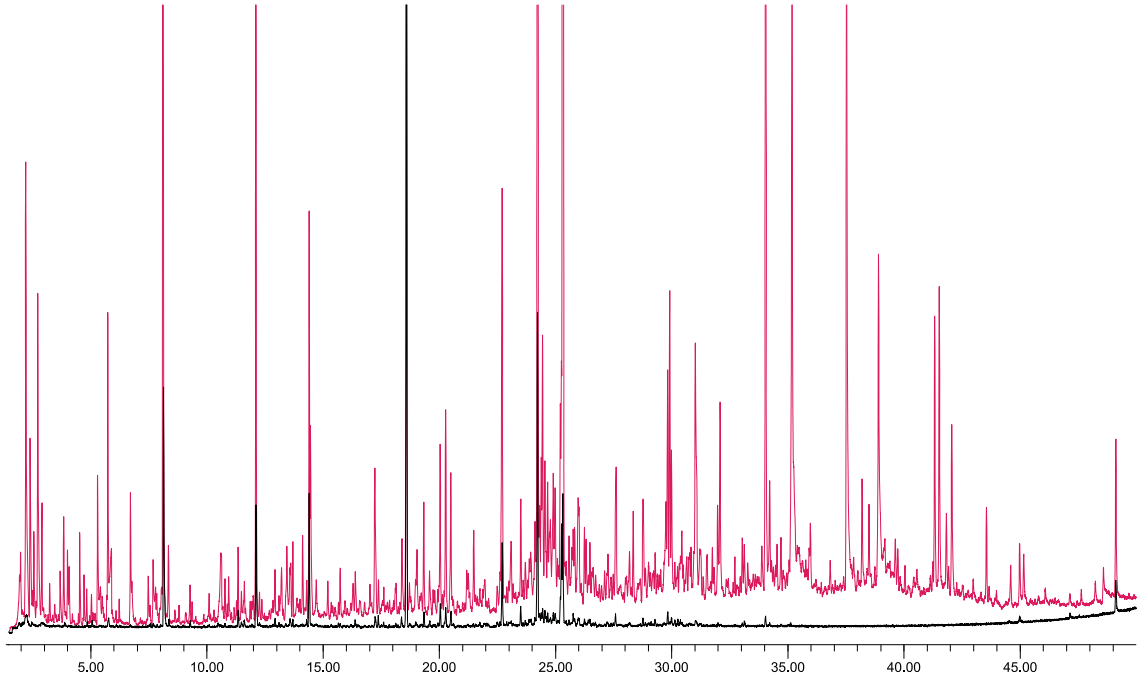

Figure 3. Overlay of 80°C extraction (black trace) and 200°C extraction (red trace).

The resulting chromatographic trace shows an increase, not only in recovery of semi-volatile compounds, which was to be expected, but also in recovery of volatile compounds (compounds eluting before cyclohexanone, 0-8 mins). Apparently these compounds (mainly residual solvents) are only released from the material by applying high extraction temperatures. Figure 4 shows this section in detail.

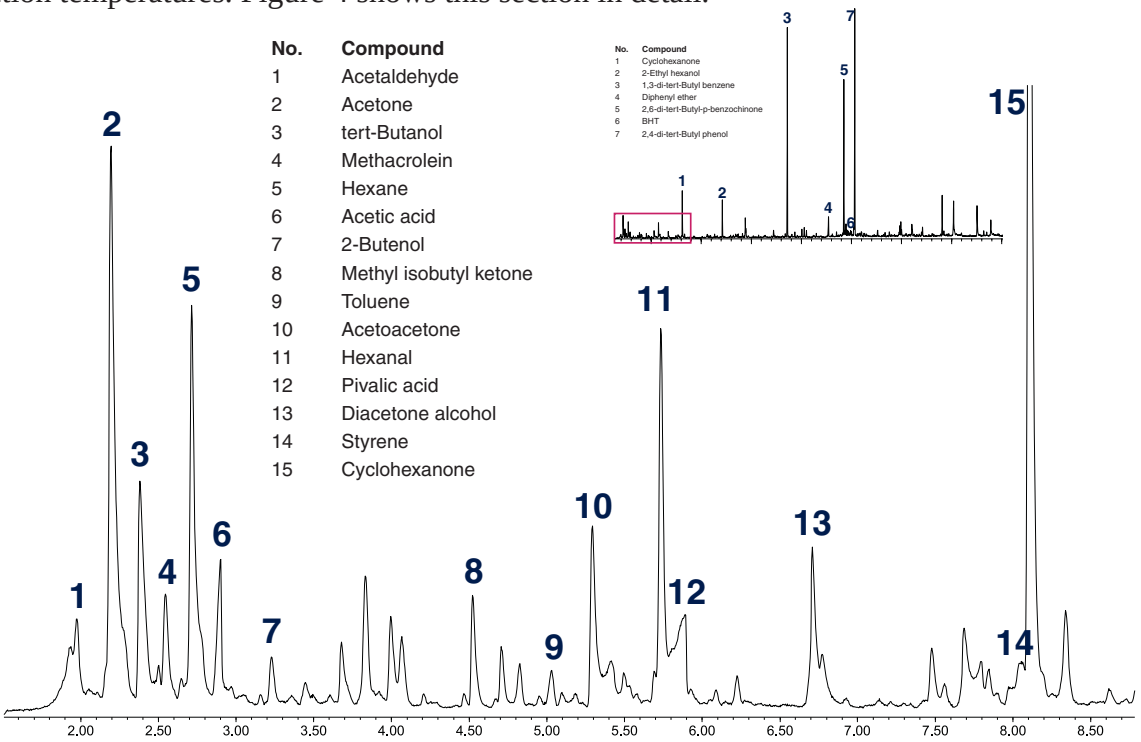

Figure 4. Thermal extraction of 15.1 mg IV bag material (polypropylene) at 200°C, split 1:30, early eluting compounds.

The next IV bag component analyzed was made of the same material, but the sample was taken from a part of the bag onto which text had been printed (see figure 1). When we compared this result with the one from sample without printed information by overlaying the chromatograms, three additional peaks were found (figure 5).

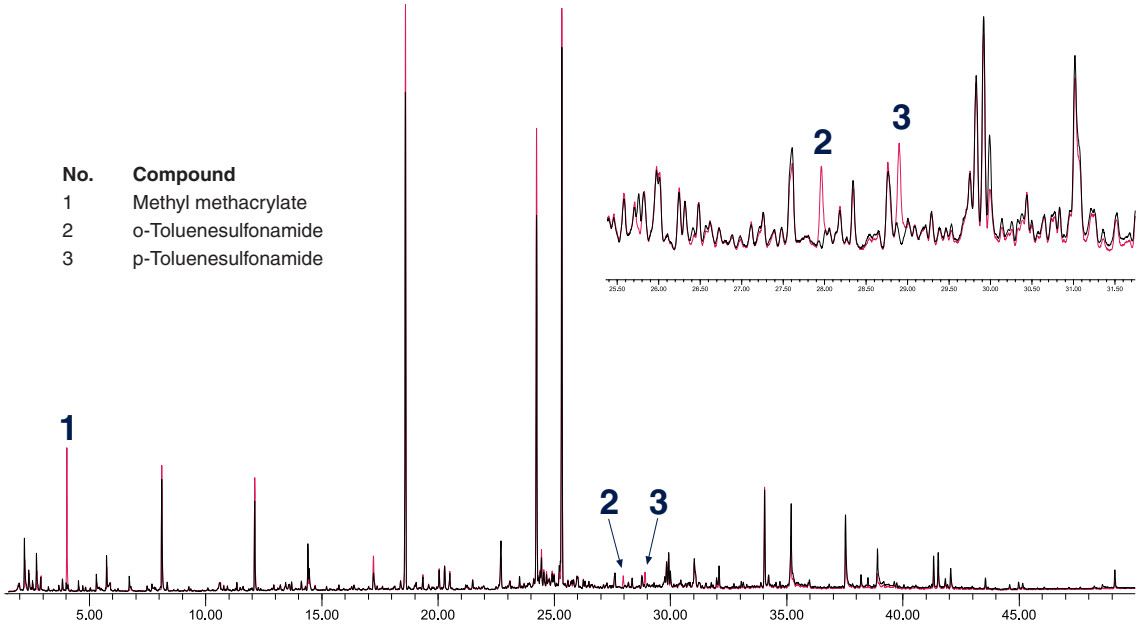

Figure 5. Overlaid chromatograms of thermal extraction of 15.1 mg IV bag material (black trace) and 15.4 mg of IV bag material with imprint (red trace) at 200°C, split 1:30.

The additional peaks were identified as methyl methacrylate, a chemical that is used among other things for the production of paints and lacquers, as well as o- and p-toluenesulfonamide. The latter ones 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 (as genotoxic impurities). They are of highlighted concern and ultra-low level detection is highly desirable.

Due to the high content of DEHP in the IV tubing material (most probably PVC) the thermal extraction experiment was carried out at only 140°C. The resulting chromatogram is shown in figure 6.

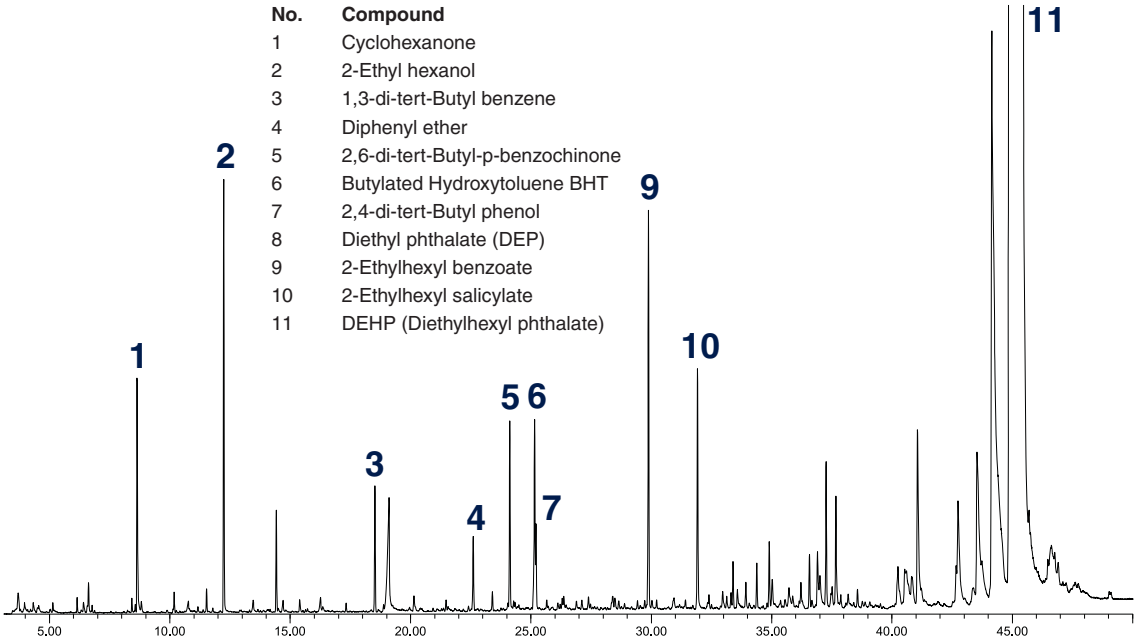

Figure 6. Thermal extraction of 3.7 mg IV tubing (PVC) at 140°C, split 1:30.

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. Cyclohexanone is a solvent that is often used during PVC production and 2-ethyl hexanol is an intermediate product in DEHP production. The analysis of the plastic valve, also performed at 140°C, showed a similar result (figure 7). This suggests that the valve and IV tubing are made of similar materials.

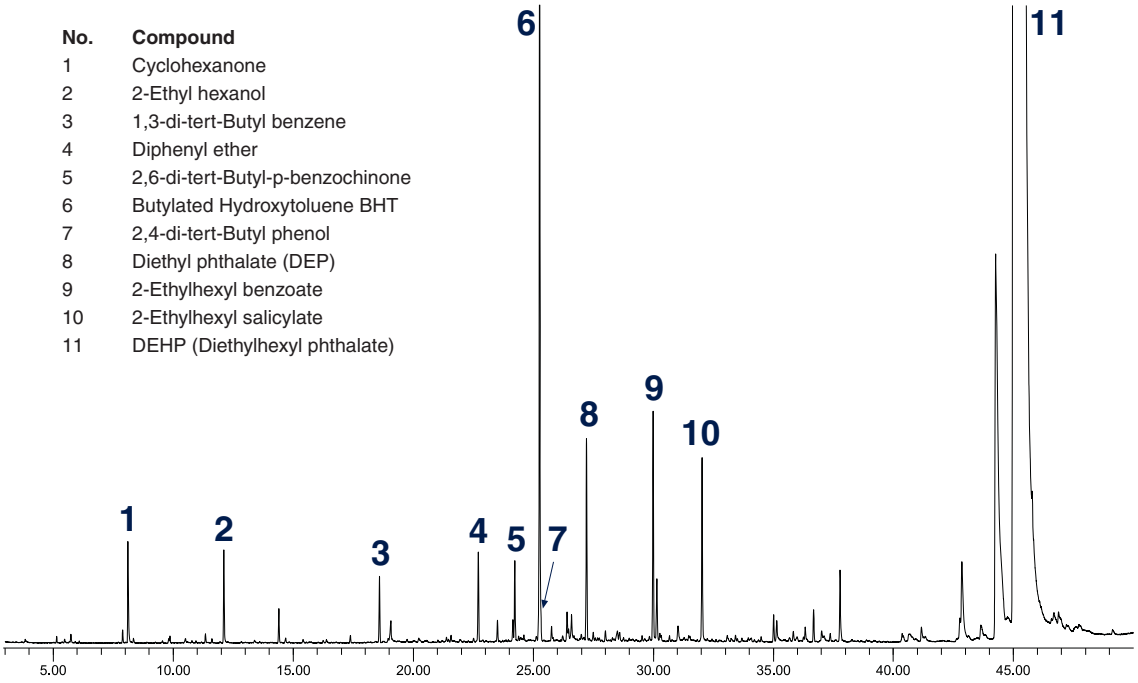

Figure 7. Thermal extraction of 3.5 mg IV plastic valve (PVC) at 140°C, split 1:30.

The major difference in the plastic valve is a higher BHT concentration plus the presence of diethyl phthalate (DEP), a commonly used plasticizer. Comparing these results with those of the IV bag material we arrived at the conclusion that compounds from the tubing and/or the plastic valve must have migrated into the bag material and contaminated it.

The following chromatogram demonstrates how high the DEHP content of the PVC components is compared to the other volatiles of this sample. 2.3 mg of the plastic valve material were thermally extracted at 200°C and introduced to the GC column with a split ratio of 1:30 (figure 8).

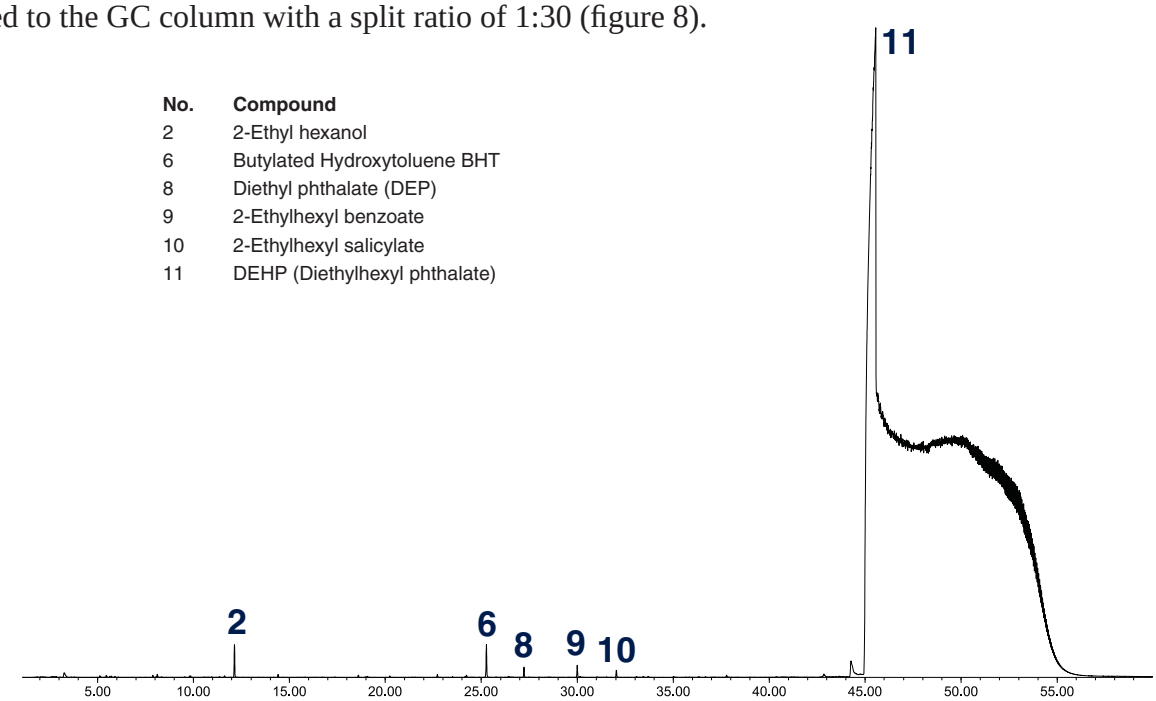

Figure 8. Thermal extraction of 2.3 mg IV plastic valve (PVC) at 200°C, split 1:30.

Although the sample size was reduced significantly to only 2.3 mg and the extracted volatiles were introduced to the GC column with a split ratio of 1: 30, the column is overloaded with DEHP and the peak is stretched out over 10 minutes. This shows that an absolute precondition for successful direct extraction experiments is an inert sample flow path. This is the only way to ensure that sample to sample carry over will not be experienced and will not compromise the analytical results even for compounds present at very high concentration levels .

Figure 9 shows an overlay of the overloaded chromatogram with a blank run with an empty sample tube performed immediately after the analysis using exactly the same instrument conditions. As can be seen, there is virtually no sample to sample carry-over; therefore, even samples with high concentrations of SVOC's can be analyzed without impacting the accuracy of subsequent analyses.

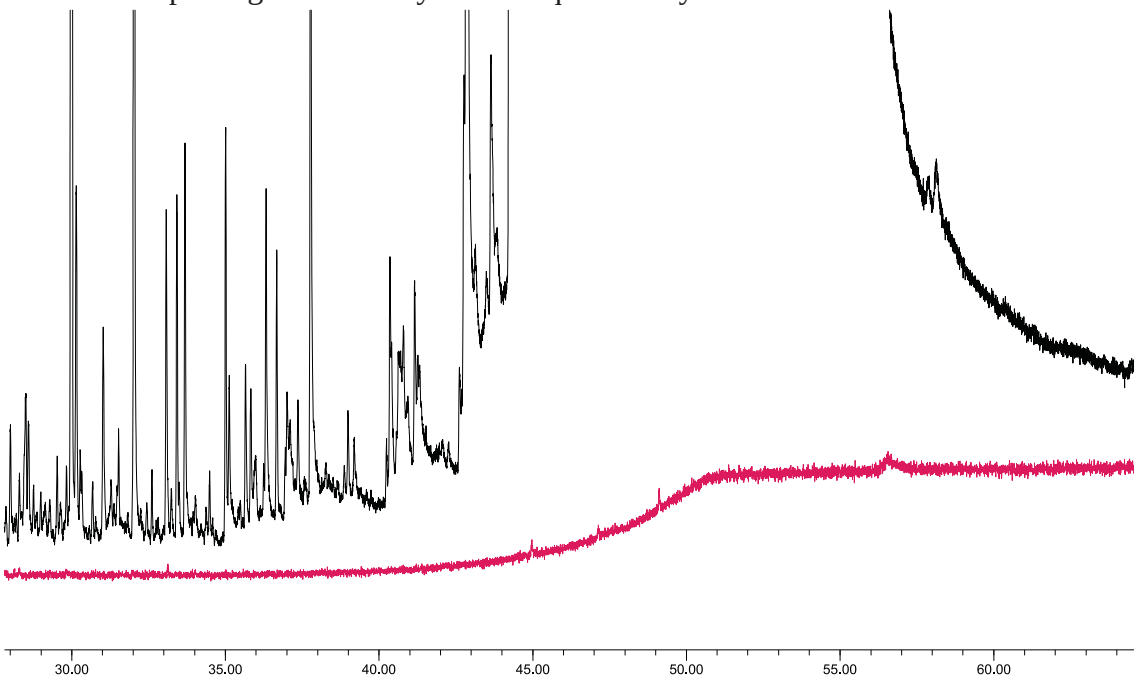

Figure 9. Overlay chromatograms resulting from thermal extraction of 2.3 mg IV plastic valve material (PVC) at 200°C, split 1:30 (black trace) and a subsequent blank run (red trace) performed immediately after using the same conditions. The blank run demonstrates that there is virtually no sample-to-sample carryover.

Stir Bar Sorptive Extraction (SBSE) of an aqueous simulant.

Stir bar sorptive extraction (SBSE) is a solvent-less sample extraction technique for enrichment of solutes from aqueous samples, it was first introduced by Baltussen et al. in 1999 [7]. SBSE minimizes sample preparation and avoids sample contamination from organic solvents that are usually required to extract analytes from water based samples. 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.

Stir bar sorptive extraction 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 (figure 10). In parallel, a Twister extraction of a 10 mL blank water sample was performed, and the analytes determined by thermal desorption-GC/MS. 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.

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

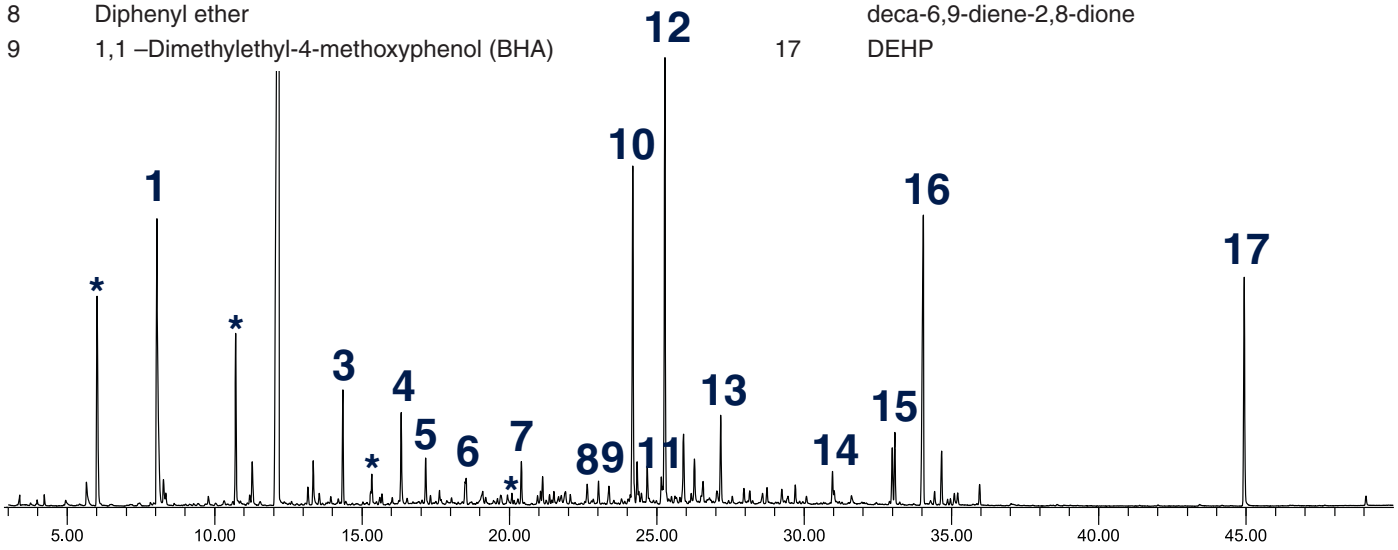

Figure 10. Stir bar sorptive extraction of a 10 mL aliquot of a 250 mL deionized water sample stored for 48 hours at 40°C in an IV bag, splitless sample introduction.

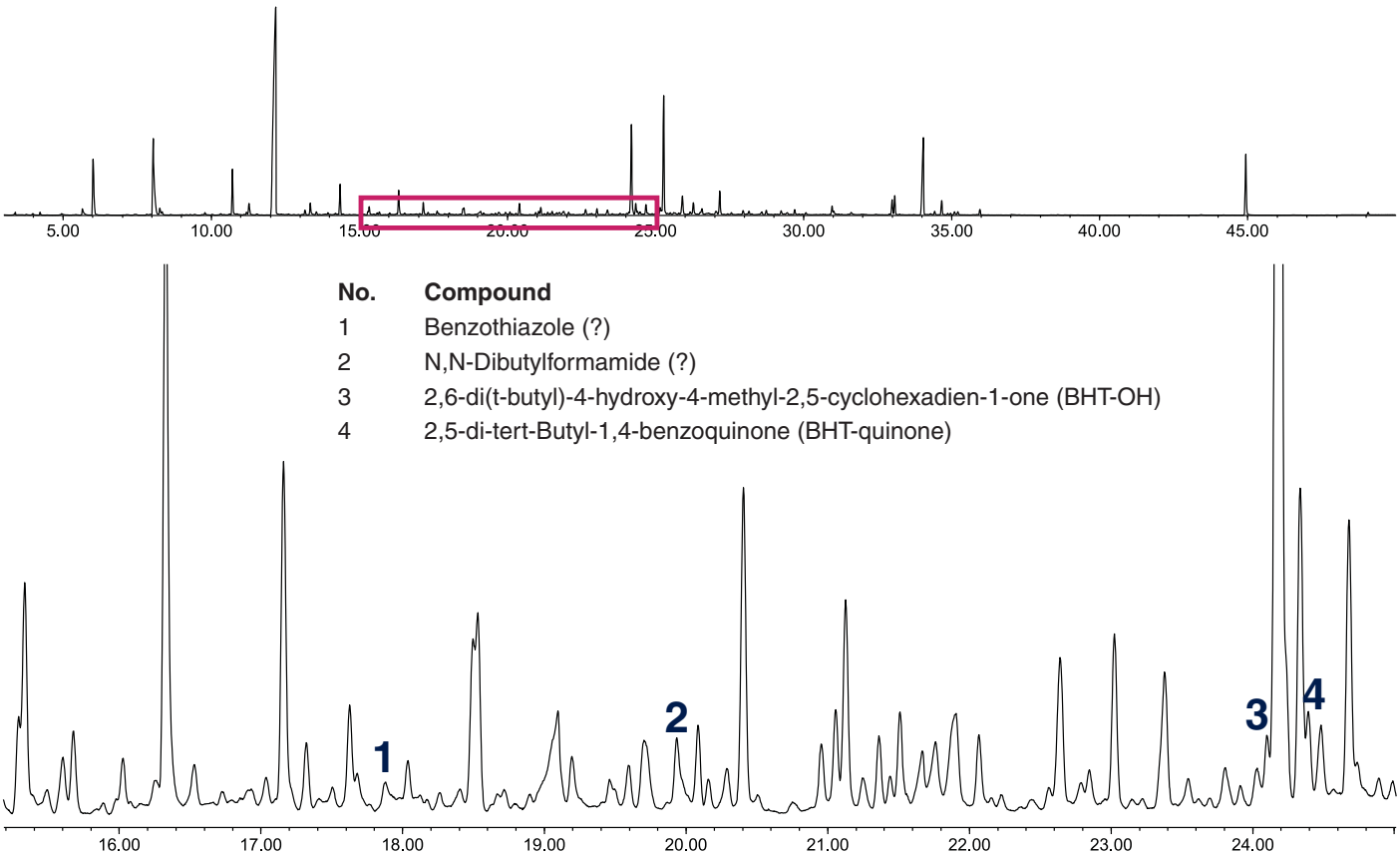

Figure 11. Stir bar sorptive extraction of a 10 mL aliquot of a 250 mL deionized water sample stored for 48 hours at 40°C in an IV bag, splitless sample introduction (zoom 15-25 minutes).

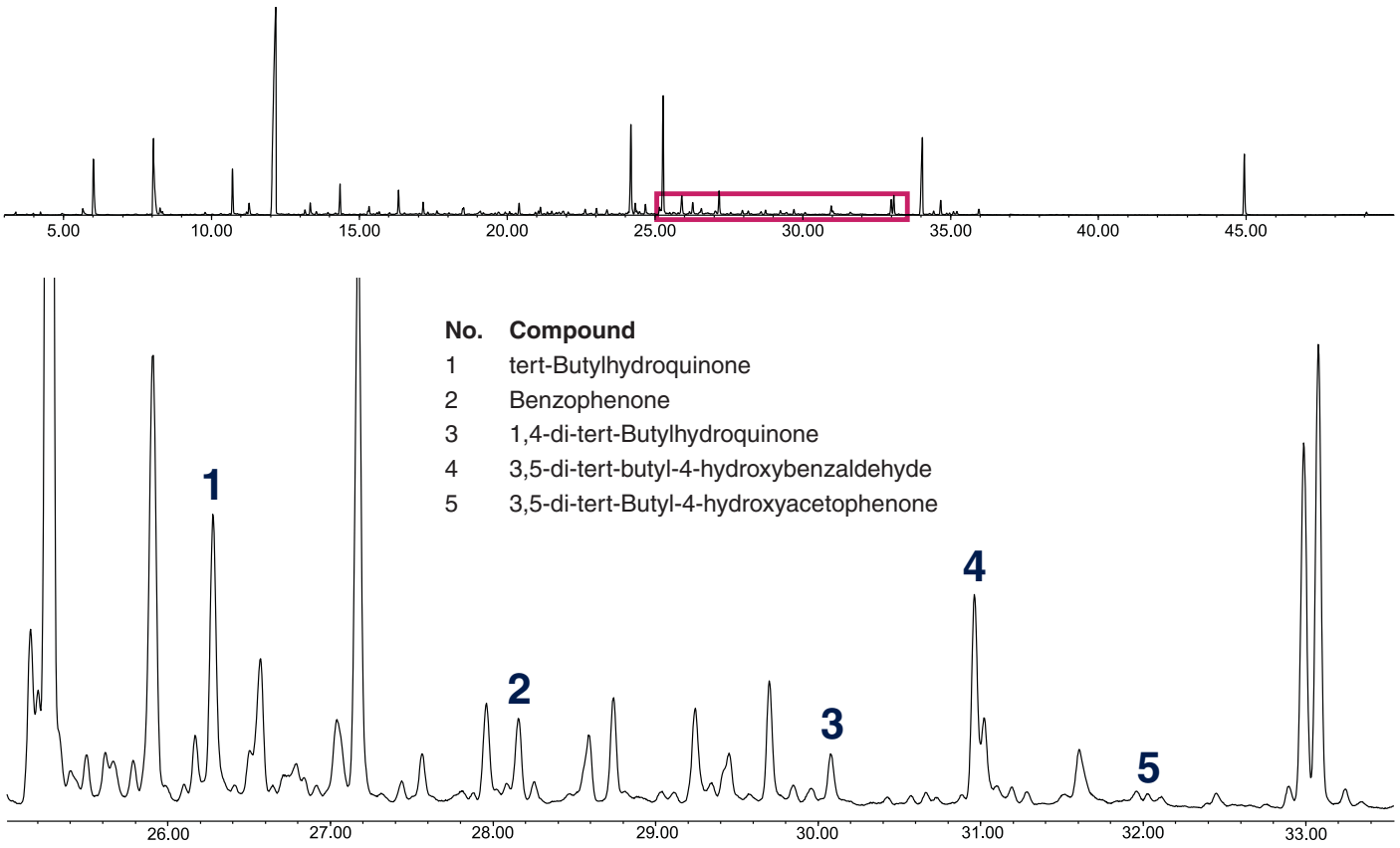

Figure 12. Stir bar sorptive extraction of a 10 mL aliquot of a 250 mL deionized water sample stored for 48 hours at 40°C in an IV bag, splitless sample introduction (zoom 25-33.5 minutes).

Using SBSE, a couple of compounds could be identified that were also found in the previously mentioned thermal extraction experiments performed 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. Some compounds, among them Benzothiazole, N,N-Dibutyl formamide, and a group of compounds that had m/z 125 and 140 as major masses were additionally checked by means of time-of-flight mass spectrometry.

Figure 13 shows the confirmatory TOF-run for Benzothiazole. The presence of N,N-Dibutylformamide could not be confirmed.

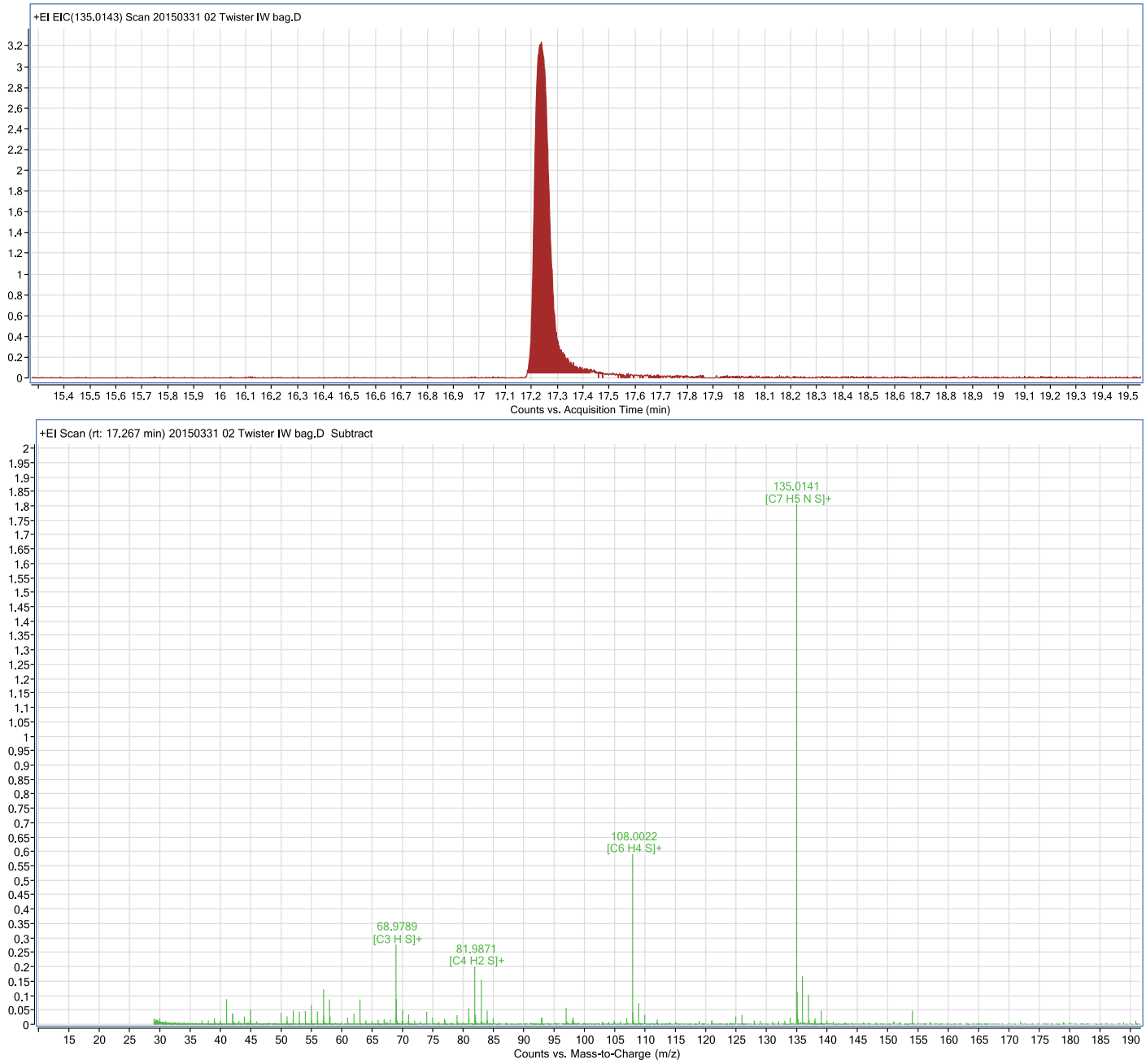

Figure 13. Stir bar sorptive extraction of a 10 mL aliquot of a 250 mL deionized water sample stored for 48 hours at 40°C in an IV bag, splitless sample introduction. Presence of Benzothiazol confirmed with Time-of-Flight mass spectrometry (mass error: -0.17 mDa = -1.26 ppm).

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 molecules, e.g. Acetyl methylthiophene. Only after the TOF was used for verification could the presence of sulfur in the molecules be excluded. The findings of the single quad could not be confirmed (figure 14).

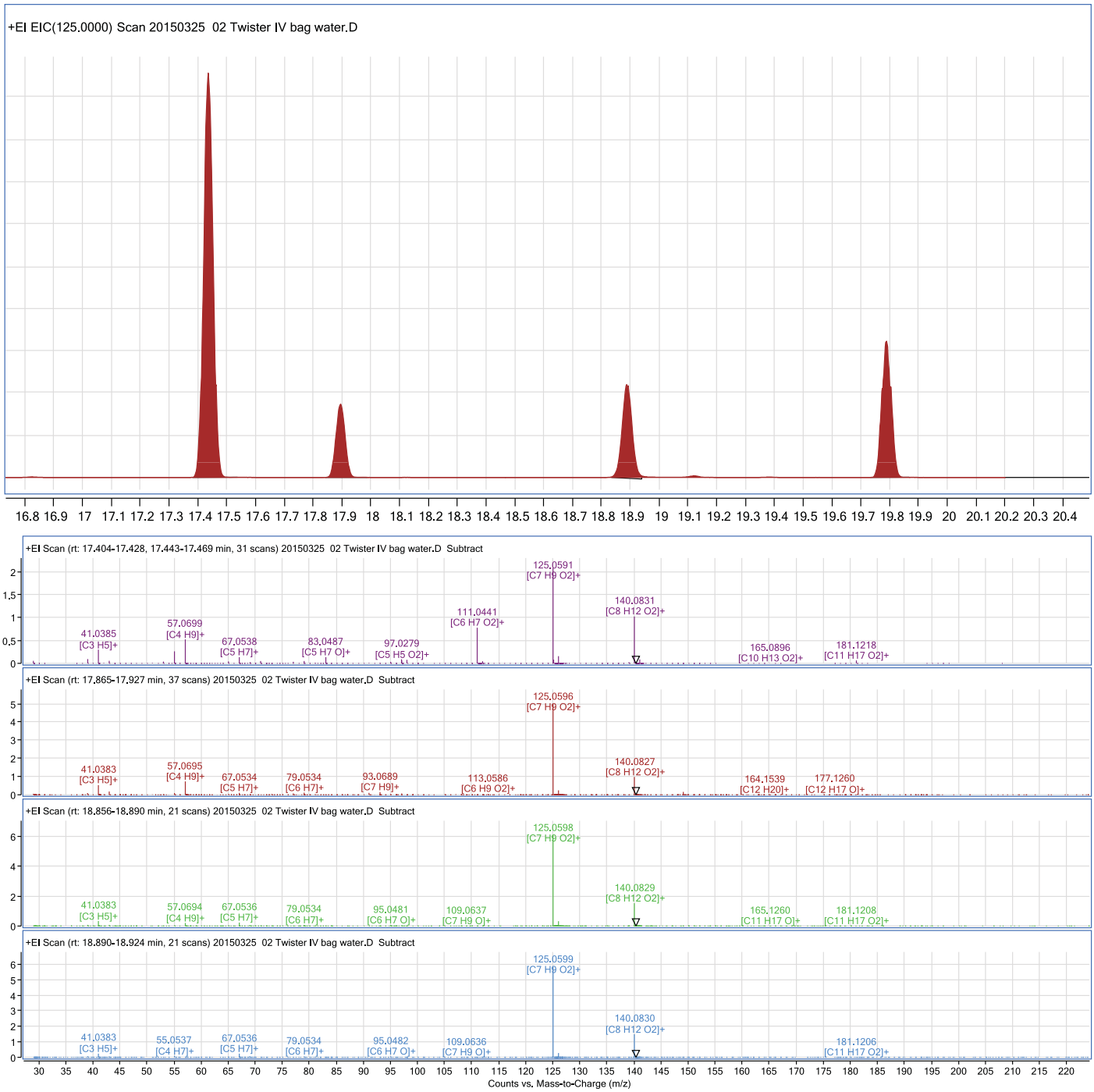

Figure 14. Stir bar sorptive extraction of a 10 mL aliquot of a 250 mL deionized water sample stored for 48 hours at 40°C in an IV bag, splitless sample introduction. The presence of sulfur-containing compounds with masses m/z 125 and 140 was refuted through use of Time-of-Flight mass spectrometry.

Table 2 lists compounds determined based on stir bar sorptive extraction along with their related source among the IV bag components and their possible origin.

Table 2. Compounds identified following stir bar sorptive extraction of an aqueous simulant placed in an IV bag listed along with the IV bag component source and possible origin.

No.	Compound	Main Source	Possible origin
1	Cyclohexanone	IV tubing	Residual solvent
2	2-Ethyl hexanol	plastic valve	DEHP metabolite, intermediate
3	Acetophenon	IV bag	Residual solvent
4	Nonanal		
5	Nonanol		
6	2-tert-Butyl-1,4-benzoquinone	IV bag	BHT metabolite
7	Benzothiazole		Vulcanization agent
8	1,3-di-tert-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(tert-butyl)-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one (BHT-OH)	IV bag	BHT metabolite
11	2,6-di-tert-Butyl-p-benzoquinone	IV bag	BHT metabolite
13	2,5-di-tert-Butyl-1,4-benzoquinone (BHT-quinone)	IV bag	BHT metabolite
14	Butylated Hydroxytoluene BHT	plastic valve	Antioxidant
15	2,4-di-tert-Butyl phenol	IV bag	Antioxidant degradation product
16	tert-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-tert-Butylhydroquinone	IV bag	Antioxidant
21	3,5-di-tert-butyl-4-hydroxybenzaldehyde	IV bag	BHT metabolite
22	3,5-di-tert-Butyl-4-hydroxyacetophenone	IV bag	BHT metabolite
23	Isobutyl phthalate	IV bag	
24	7,9-di-tert-butyl-1-oxaspiro-[4.5]deca-6,9-diene-2,8-dione	IV bag	degradation product of 2,4-di-tert 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 leachables experiments. Thermal desorption, when performed without an in-line valve or transfer line, can successfully transport heavy SVOC's to the GCMS with very low carry-over, even between severely overloaded samples, and was shown to be very useful in determining the package component source of any extractable compound.

Also demonstrated was the need for the high resolving power and accurate mass of the GC-QTOF-MS in some cases, both for confirmation and for exclusion of compounds in extractables data (and in leachables data as well). The use of Twister produced chromatograms rich with trace species, and only a few were discussed here. In general the QTOF is a powerful tool for examining all of these species if the sample introduction technique used can introduce them. Coupling simple, rugged, and efficient thermal desorption sample introduction to the QTOF gives the instrument an opportunity to rise to its potential.

The data presented here was generated for demonstration of concepts. In order to comply with FDA guidelines, additional replicate measurements need to be performed as well as quantitative or semi-quantitative estimates of the extractables.

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GERSTEL GmbH & Co. KG
Eberhard-Gerstel-Platz 1
45473 Mülheim an der Ruhr
Germany
+49 (0) 208 - 7 65 03-0
+49 (0) 208 - 7 65 03 33
gerstel@gerstel.com
www.gerstel.com

GERSTEL Worldwide

GERSTEL, Inc.
701 Digital Drive, Suite J
Linthicum, MD 21090
USA
+1 (410) 247 5885
+1 (410) 247 5887
sales@gerstelus.com
www.gerstelus.com

GERSTEL AG
Wassergrabe 27
CH-6210 Sursee
Switzerland
+41 (41) 9 21 97 23
+41 (41) 9 21 97 25
swiss@ch.gerstel.com
www.gerstel.ch

GERSTEL K.K.
1-3-1 Nakane, Meguro-ku
Tokyo 152-0031
SMBC Toritsudai Ekimae Bldg 4F
Japan
+81 3 5731 5321
+81 3 5731 5322
info@gerstel.co.jp
www.gerstel.co.jp

GERSTEL LLP
10 Science Park Road
#02-18 The Alpha
Singapore 117684
+65 6779 0933
+65 6779 0938
SEA@gerstel.com
www.gerstel.com

GERSTEL (Shanghai) Co. Ltd
Room 206, 2F, Bldg.56
No.1000, Jinhai Road,
Pudong District
Shanghai 201206
+86 21 50 93 30 57
china@gerstel.com
www.gerstel.cn

GERSTEL Brasil
Av. Pascoal da Rocha Falcão, 367
04785-000 São Paulo - SP Brasil
+55 (11)5665-8931
+55 (11)5666-9084
gerstel-brasil@gerstel.com
www.gerstel.com.br

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