Application Note

Extractables and Leachables

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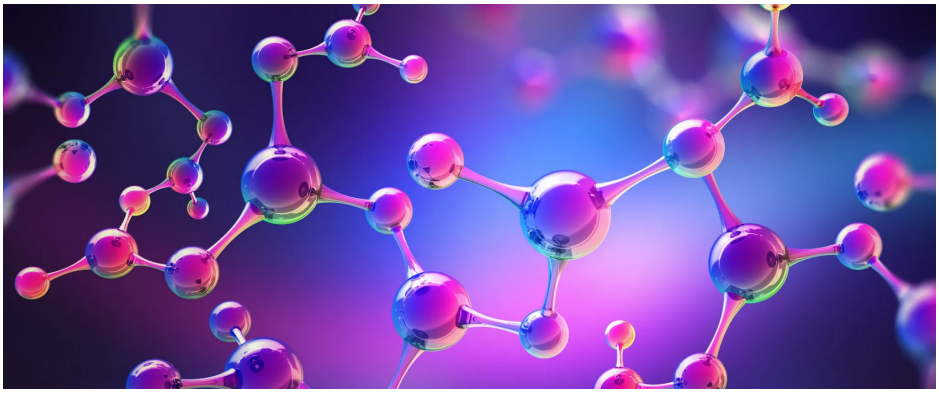
Analysis of Extractables and Leachables in Catheters Using Accurate Mass Libraries and High-Resolution GC/MS and LC/MS



Authors

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Abstract

Materials used in the production of medical devices contain substances with the potential to leach into body fluids and tissues and potentially cause adverse biological reactions. Characterization of leachables from these materials is therefore important to assert biocompatibility and compliance.

In this study, to achieve comprehensive coverage of extractable and leachable (E&L) compounds, catheter extracts were analyzed using high-resolution GC/Q-TOF and LC/Q-TOF. Dedicated E&L accurate mass libraries specific to each technique were developed and used in conjunction with both targeted and nontargeted data processing workflows to help focus on E&L-relevant substances.

Introduction

Extractables and leachables represent a range of structurally diverse compounds including antioxidants, UV absorbers, dyes, catalysts, plasticizers, and polymer degradation products. Therefore, both liquid and gas chromatography techniques coupled with mass spectrometry detectors (LC/MS and GC/MS) are utilized to achieve comprehensive chemical characterization. LC/MS covers more polar, higher molecular weight and thermally unstable chemicals, while GC/MS is more suitable for the detection of nonpolar volatile and semivolatile E&L compounds.

Chemical characterization of medical devices can benefit from both targeted and nontargeted analyses. Nontargeted workflows help to identify a broad range of chemicals by leveraging comprehensive libraries (such as NIST). They can also serve as an entry point for statistical analysis, e.g., when comparing the E&L profiles of different groups of samples, as well as for structural elucidation of unknowns. Suspect screening workflows, in turn, can be beneficial in reliably identifying application-specific compounds, even when present at trace levels. Dedicated E&L accurate mass libraries combined with an efficient suspect screening workflow can increase confidence in compound identification and save time on reviewing the data while staying focused on E&L-relevant compounds.

To support data integrity and facilitate compliance with electronic record regulations such as US FDA 21 CFR Part 11 and EU Annex 11, this analysis utilized OpenLab Electronic Content Management (ECM) XT. The system provides centralized scientific data management along with built-in technical controls such as versioning, activity logs, and eSignatures, as well as automated data organization, reporting, and archiving capabilities to ensure consistent and reliable data handling.

The goal of this study was to evaluate the benefits of using a combined high-resolution GC/MS and LC/MS workflow with application-specific (E&L-focused) accurate mass libraries for the E&L analysis of extracts from commercial catheters.

Experimental

Samples and sample preparation

Catheters from three suppliers were used in this study. Per manufacturer specifications catheter A was made from polyvinyl chloride (PVC) and did not include di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), bisphenol A (BPA), or natural rubber latex. Catheter B was made with natural rubber latex base and silicone elastomer coating, and there was no claim to be phthalate or BPA free. Catheter C is a silicone-coated latex catheter made with a natural rubber latex base and no DEHP or BPA.

The standards for building the E&L accurate mass personal compound and database library (PCDL) were from the CLAP kit and the Agilent Food Contact E/L Standards Kits obtained from AChemTek.

Catheters were extracted with 1:1 ethanol:water solvent at 37 ˚C for 24 hours, 48 hours, and 7 days. Extractions using 100% ethanol or hexane could also be completed in the future to avoid potential solvent partitioning that might take place using the 1:1 ethanol:water extracts.

Data acquisition

The catheter extracts were analyzed using GC/Q-TOF and LC/Q-TOF systems. GC/MS analysis was performed using the 8890 GC coupled to the 7250 Q-TOF and the Agilent Ultra-low bleed DB-5Q column. LC/MS analysis was performed using the 1290 Infinity II LC coupled to the Revident LC/Q-TOF.

All data were acquired using Acquisition 13.0. Detailed instrument parameters are shown in Tables 1 (GC/Q-TOF) and 2 (LC/Q-TOF).

Table 1. GC/Q-TOF method parameters.

Parameter	Value
MS	Agilent 7250 GC/Q-TOF
GC	Agilent 8890 GC
Column	Agilent J&W DB-5Q, 30 m × 0.25 mm, 0.25 µm (p/n 122-5532Q)
Inlet	Multimode inlet, 4 mm Ultra Inert liner, single taper with wool (p/n 5190-3163)
Injection Volume	1 µL
Injection Mode	Pulsed splitless (1 min purge, pulse at 40 psi for 1.1 min)
Inlet Temperature Program	65 °C for 0.01 min, 300 °C/min to 280 °C
Oven Temperature Program	45 °C for 2 min; 12 °C/min to 325 °C, 11 min hold
Carrier Gas	Helium
Column Flow	1 mL/min constant flow
Transfer Line Temperature	325 °C
Quadrupole Temperature	150 °C
Ion Source Temperature	200 °C (Q-TOF)
Electron Energy	70 eV
Emission Current	5 µA
Spectral Acquisition Rate	5 Hz
Mass Range	*m/z* 50–1,000

Table 2. LC/Q-TOF method parameters.

Parameter	Value
LC	Agilent 1290 Infinity II
MS	Agilent Revident LC/Q-TOF
Column	Agilent PS AQ-C18 2.1 × 100 mm Column (p/n 695775-742)
Column Temperature	40 °C
Injection Volume	1 µL
Flow Rate	0.35 mL/min
Mobile Phase A	Water w/2.5 mM NH_4 formate 0.05% FA
Mobile Phase B	Methanol w/2.5 mM NH_4 formate 0.05% FA
LC Gradient	2% B for 1.0 min; to 100% B at 16.0; hold 100% B to 28.0 min; to 2% at 28.1 min post time 5 min
MS Source	Dual AJS ESI
MS Mode	Auto MS/MS
Polarity	Positive
Collison Energy	20; 40
Mass Range	*m/z* 40–1,700
Acquisition Rate	4 spectra/sec for MS; 6 spectra/sec for MS/MS
Drying Gas Temperature	250 °C
Drying Gas	11 L/min
Nebulizer Pressure	35 psi
Sheath Gas Temperature	300 °C
Capillary Voltage	3,500 V

Data processing

The GC/MS data were processed using MassHunter Quantitative Analysis software (version 12.1). Compound identification was performed using both suspect screening and nontargeted data analysis workflows utilizing the new GC/MS accurate mass E&L PCDL as well as NIST23 EI Library, respectively. For more information regarding the E&L PCDL contact your local sales representative. Retention indices (RI) were calculated and used to ensure reliable library matching. Statistical analysis was performed using Mass Profiler Professional (MPP) software (version 15.1).

The LC/MS data were processed using Agilent MassHunter Explorer 2.0 software, providing a means to process both MS and MS/MS data in an unsupervised, nontargeted data analysis workflow that allowed for retention time corrections, compound and feature alignment across samples, background subtraction using fold change, principal component analysis, and hierarchical clustering to show grouping of compounds in extracts and between catheters. When possible, the compound identification was completed based on exact mass match to compounds in an E&L focused database and also compared with MS/MS spectral library matching. For compounds not present in a database, the software provides a means to do MS/MS library searching using NIST 2023 and/or SIRIUS software. The nontargeted analysis part of the E&L workflow is described in more detail in an accompanying application note (5994-8904EN).

Results and discussion

E&L workflows for LC/Q-TOF and GC/Q-TOF

The workflows for E&L studies are usually complex and include multiple steps, where a large number of compounds with diverse chemical structures and a wide range of concentrations need to be detected, identified, and quantified. The E&L workflows often involve differential analysis for comparison of sample groups or different lots.[1,2] Typical LC/Q-TOF and GC/Q-TOF workflows and software used for E&L analysis are summarized in Table 3.

Suspect screening and target quantitation workflow for E&L can be performed using both GC/Q-TOF and LC/Q-TOF data in MassHunter Quantitative Analysis based on the methods automatically created from accurate mass E&L accurate mass personal compound database and library (PCDL). Nontargeted analysis takes advantage of a variety of databases including NIST and E&L PCDL, among others. It is performed in the MassHunter Unknowns Analysis software for GC/Q-TOF, and in MassHunter Explorer for LC/Q-TOF. Explorer also provides streamlined differential analysis and direct access to SIRIUS for structure elucidation. In the case of GC/Q-TOF, data alignment, filtering, statistical analysis, and unknowns structure elucidation are performed in MassProfiler Professional and Molecular Structure Correlator.

Catheter extracts were analyzed using a nontargeted analysis and suspect screening and taking advantage of the new GC/MS E&L accurate mass PCDL.

Table 3. Overview of the E&L workflow and software for LC/Q-TOF and GC/Q-TOF.

Instrument	Suspect Screening/ Target Quantitation	Nontargeted: Peak Picking/Library/ Database Search	Unknowns ID	Differential Analysis
GC/Q-TOF	MassHunter Quantitative Analysis/E&L PCDL	MassHunter Unknowns Analysis/ NIST/E&L PCDL	Molecular Structure Correlator	MassProfiler Professional
LC/Q-TOF		MassHunter Explorer/NIST and other databases	NIST/Sirius	MassHunter Explorer

Development of new E&L accurate mass library for GC/Q-TOF

To create a new Agilent accurate mass E&L PCDL for GC/Q-TOF, over 400 spectra have been collected for E&L compounds. All fragment ions in each spectrum have been annotated with formulas based on accurate mass information and isotope ratios (Figure 1). The fragment formula annotations were then verified and converted to the theoretical *m/z*.

To reduce baseline and provide cleaner spectra for GC-amenable E&L compounds with high boiling points, the Agilent low bleed DB-5Q column was used to acquire the data. The retention times and retention indices from compounds of a variety of chemical structures and boiling points were consistent with the DB-5MS UI column, as has been previously demonstrated.[3]

The RI from the E&L PCDL and NIST (when a compound was present in NIST) were compared, and the results are shown in Figure 2.

For most compounds, the RI delta was within 20 RI units. 24% of compounds fell in the RI delta range between 21 and 40. Only a few compounds had RI delta over 100 RI units. Typically, these compounds either did not have experimental RI in NIST23 library, in which case, an AI-predicted RI was used for comparison, or the experimental RI from NIST23 only had one or two replicates. These results suggest that in an E&L experiment, when using NIST library with RI and selecting a narrow RI delta, one can expect to miss true hits due to lacking experimental RI data or an insufficient number of replicates. In contrast, E&L PCDL provides experimental RI values for all compounds, thus improving confidence in compound identification.[4]

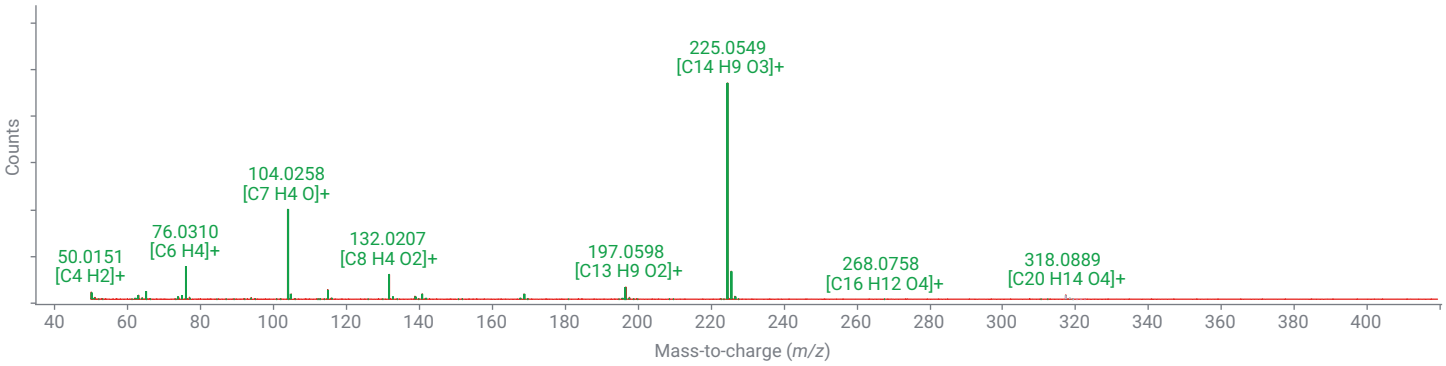


Figure 1. Fragment formula annotation of spectrum for one of the E&L compounds (diphenyl terephthalate) in Agilent MassHunter Qualitative Analysis software.

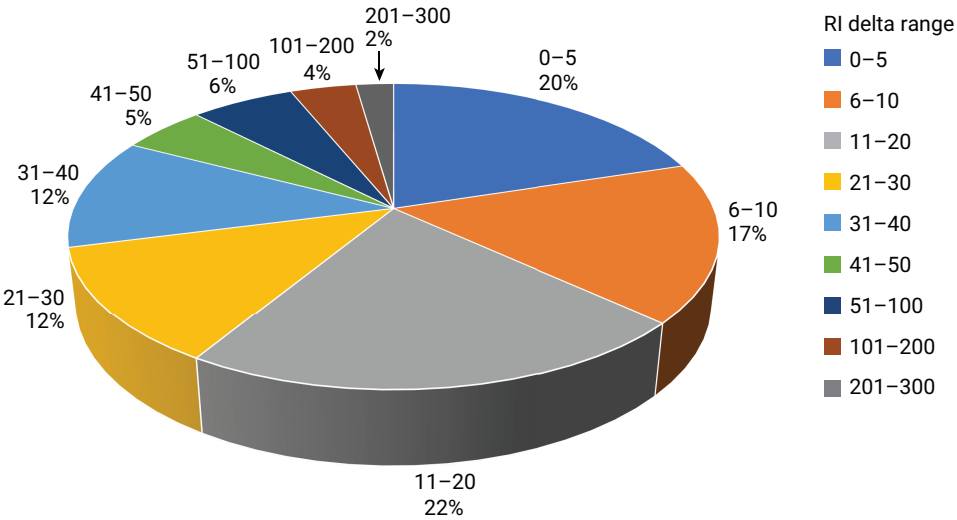


Figure 2. RI delta between E&L PCDL compounds and NIST.

Currently, the E&L PCDL for GC/Q-TOF contains over 400 accurate mass EI spectra. These include a range of chemical and functional compound classes such as bisphenols, antioxidants, UV-absorbers, phthalates, glycol ethers, organophosphates, fatty amides, fatty acids, and fatty acid esters, among others. Examples of a few PCDL EI spectra, representative of typical E&L compound classes, are shown in Figure 3.

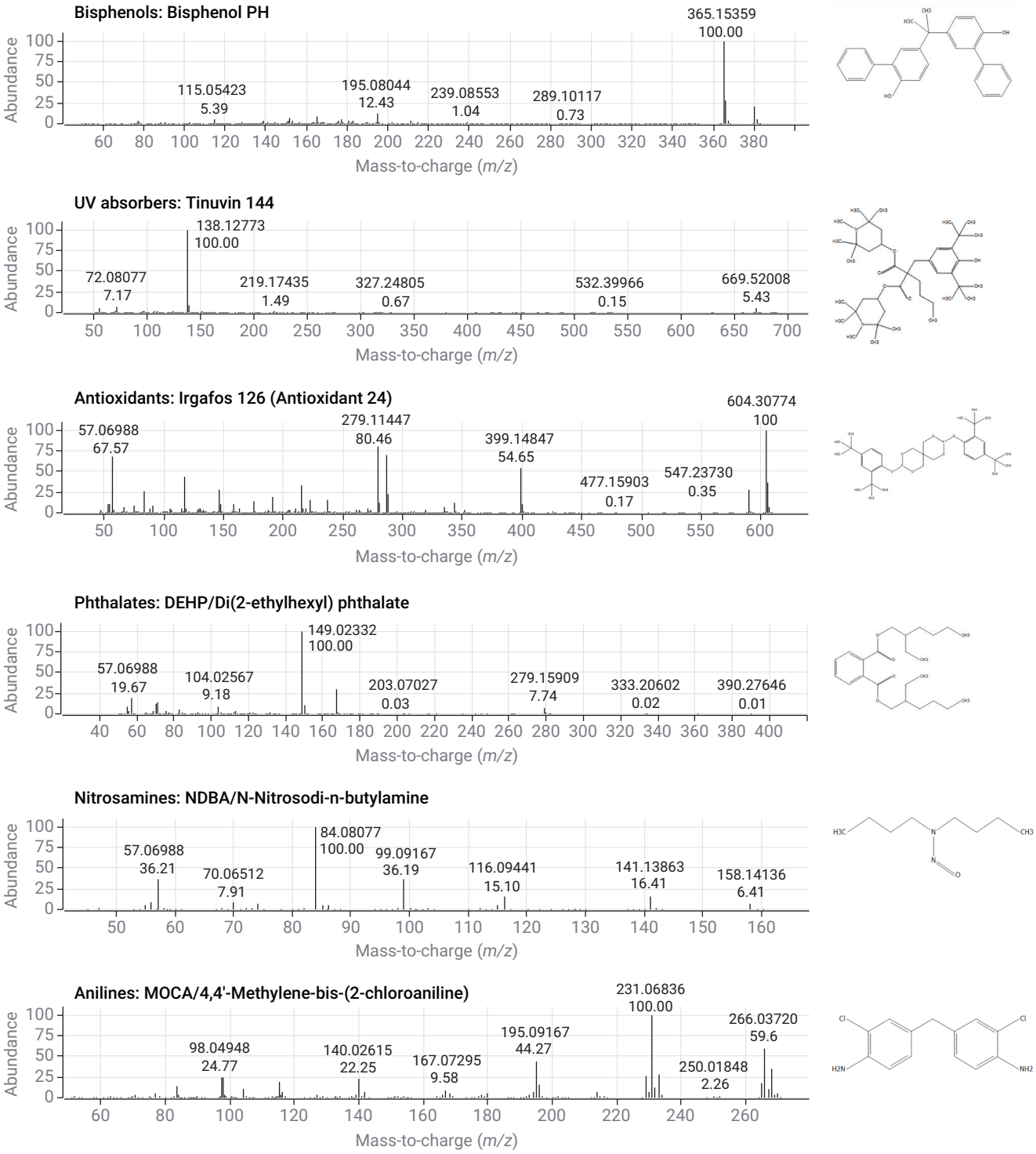


Figure 3. Examples of accurate mass spectra in E&L GC/Q-TOF PCDL. Note that spectra for several of these compounds are not present in NIST23.

Identification of extractables in catheter samples by GC/Q-TOF using suspect screening

To perform suspect screening, a screener method was first automatically created from the new accurate mass EI E&L PCDL in MassHunter Quantitative Analysis software and further optimized to minimize false negatives while also keeping false positives under control. This was achieved by lowering the coelution score (which plays a minor role in GC/MS data analysis) while keeping a narrow RT window. The main parameters of the screening method are shown in Table 4. The same parameters were applied to all compounds, although they can be customized for each compound individually, if desired.

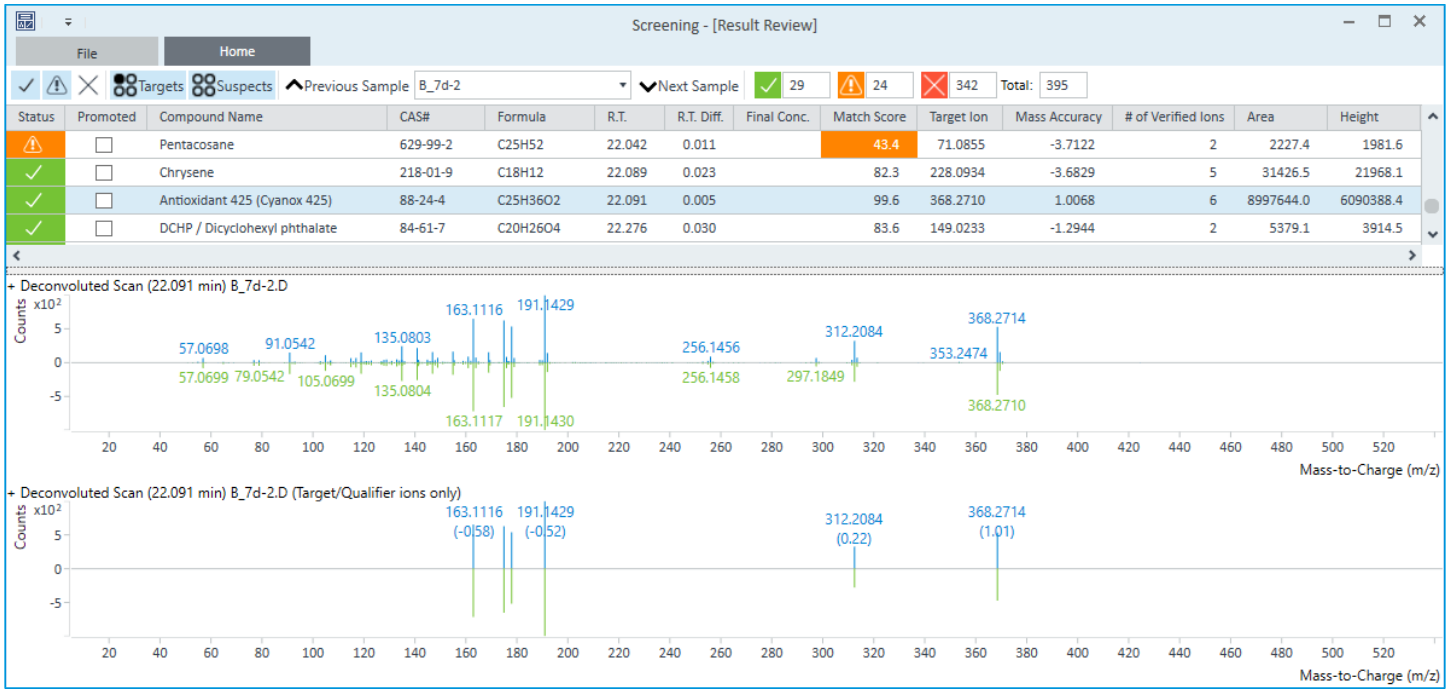
Table 4. GC/Q-TOF screener method parameters.

Screener Method Parameter	Value
Retention Time Window	0.1 min
Min. S/N	3
Coelution Score	10
Mass Accuracy	5 ppm
Library Match Score	70
Number of Verified Ions	2
Data Format Used	SureMass

One of the primary advantages of the screener tool when setup optimally is the capability to provide a concise summary, where the user needs to review only a small portion of the results, since most hits are automatically classified as either confirmed or rejected. This approach is a significant time saver, especially when processing large data sets.

The screener results summary window, displayed in Figure 4A, shows only the key parameters in the table for the user to review, e.g., RT and RT difference, library match score, mass accuracy of the quantifier ion, and number of verified ions. It also includes mirror plots for visual reference. This view is specifically designed to help a user accurately and instantly classify dubious hits in cases where algorithm cannot provide an unambiguous answer. The summary table is linked to the Quant batch table where the rest of the parameters, such as qualifier signal-to-noise ratio, mass error and coelution score for every qualifier ion, can be found and examined if necessary (Figure 4B).

A



B

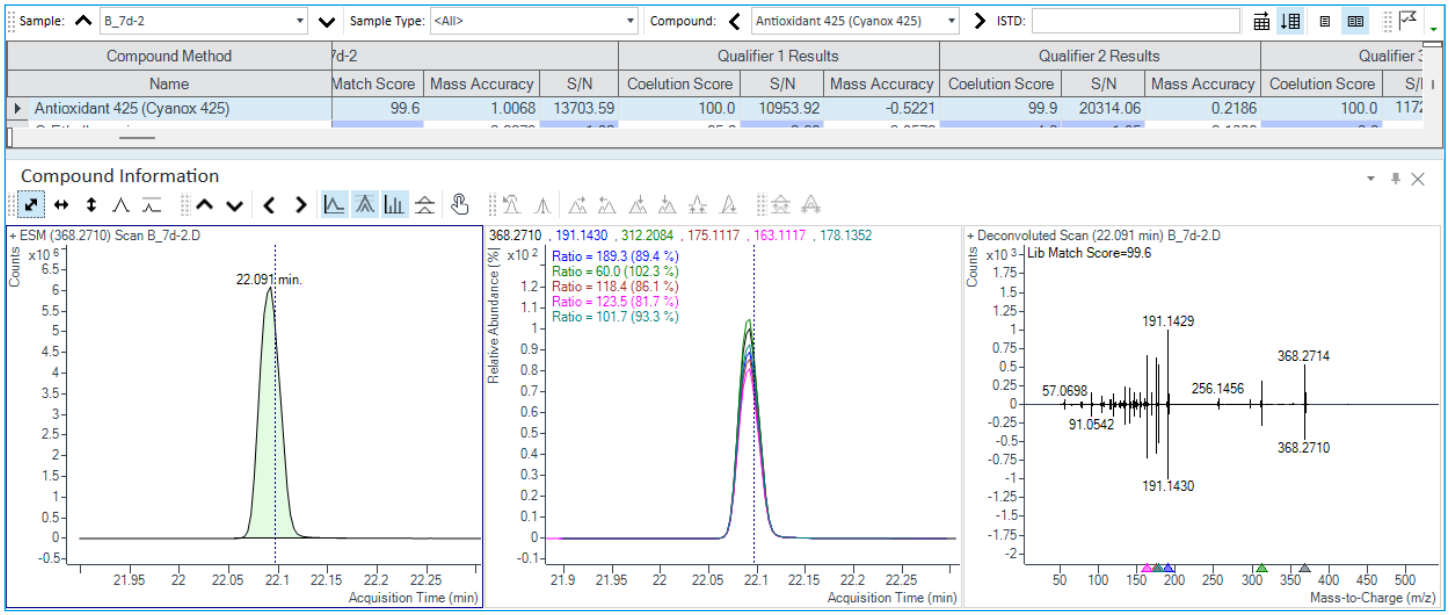


Figure 4. Review of the GC/Q-TOF screener results: (A) Results summary window; (B) Detailed quant batch table.

The suspect screening results of E&L analysis in catheter extracts are summarized in Table 5.

For most identified E&L compounds, their levels increased in catheter extracts with an increase in the extraction time from 2 days (2d) to 7 days (7d). Most prominent compounds identified in catheter extracts based on the screener and E&L PCDL were phthalates, phenolic antioxidants, and fatty amides. A and B catheter brands contained a higher number of compounds identified with the E&L PCDL.

Interestingly, BPA detection only in catheter B at 7 days of extraction was consistent with the claim that catheters A and C were BPA free, but there was no such claim for catheter B (Table 5). Another interesting observation based on the suspect screening results was the detection of plasticizer Di(2-ethylhexyl) adipate (DEHA) in catheters A and C. Its presence in catheter A is expected, since catheter A is made of PVC, and DEHA is known to leach from PVC products.[5]

Table 5. GC/Q-TOF suspect screening results summary for catheter extracts at 2 and 7 days. Different catheter brands are denoted as A, B, or C.

Compound Name	CAS No.	Formula	RT (min)	RT Diff. (min)	Match Score	Target Ion	Mass Error (ppm)	No. of Verified Ions	A-2d	A-7d	B-2d	B-7d	C-2d	C-7d
Benzaldehyde	100-52-7	C_7H_6O	6.79	0.018	88.8	105.0335	−1.54	3	–	9,042	–	10,669	–	–
Acetophenone	98-86-2	C_8H_8O	8.44	0.012	85.0	105.0335	−0.08	3	–	–	–	4,437	–	–
Caprolactam**	105-60-2	$C_6H_{11}NO$	11.04	0.092	99.4	113.0835	−0.25	6	–	–	–	–	4,917	16,395
N'N-Dibutylformamide*	761-65-9	$C_9H_{19}NO$	11.51	0.026	99.6	114.0913	0.64	6	307,783	403,140	–	–	3,149	6,652
Surfynol 104	126-86-3	$C_{14}H_{26}O_2$	12.68	0.001	99.3	151.1117	−0.24	6	2,702	7,288	–	9,168	–	–
DMP/Dimethyl phthalate (DMF)	131-11-3	$C_{10}H_{10}O_4$	13.20	0.032	89.7	163.039	−0.84	4	–	11,057	–	5,937	2,413	6,308
2,4-Di-tert-butylphenol	96-76-4	$C_{14}H_{22}O$	13.78	0.009	93.5	191.143	−1.70	4	36,178	48,380	716	8,530	50,538	115,291
2,6-di-tert-butyl-p-Cresol (BHT)	128-37-0	$C_{15}H_{24}O$	13.79	0.014	96.9	205.1587	−1.85	4	13,688	15,579	–	7,073	–	–
Ethyl 4-ethoxybenzoate	23676-09-7	$C_{11}H_{14}O_3$	13.99	0.002	99.4	121.0284	−0.47	5	4,701	5,669	–	23,659	1,456	4,781
DEP/Diethyl phthalate	84-66-2	$C_{12}H_{14}O_4$	14.64	0.025	98.5	149.0233	−0.27	5	25,793	55,550	–	66,282	25,288	53,080
Benzophenone	119-61-9	$C_{13}H_{10}O$	15.17	0.002	99.1	182.0726	−1.24	6	8,865	10,718	–	19,774	4,209	8,734
HOBT/2-Hydroxybenzothiazole	934-34-9	C_7H_5NOS	15.52	0.009	99.7	151.0086	−0.58	5	–	–	–	151,766	–	–
2,6-Diisopropylnaphthalene	24157-81-1	$C_{16}H_{20}$	16.02	0.028	98.4	197.1325	−0.80	5	7,259	202,515	2563	78,187	2,287	16,989
DIBP/Diisobutyl phthalate	84-69-5	$C_{16}H_{22}O_4$	17.18	0.051	96.4	149.0233	−1.23	6	51,893	86,876	–	65,926	20,546	21,903
DBP/Dibutyl phthalate	84-74-2	$C_{16}H_{22}O_4$	18.00	0.014	95.1	149.0233	−0.65	4	73,081	151,248	–	187,860	40,377	34,261
MBT/2-Mercaptobenzothiazole	149-30-4	$C_7H_5NS_2$	18.18	0.006	97.6	166.9858	−1.66	6	–	–	–	98,341	–	–
Heneicosane	629-94-7	$C_{21}H_{44}$	19.14	0.006	99.2	71.08553	−1.78	5	–	5,681	–	8,283	–	–
Palmitamide (Hexadecanamide)	629-54-9	$C_{16}H_{33}NO$	19.76	0.014	97.1	59.03656	−1.44	6	32,712	95,805	–	101,448	–	–
BPA/Bisphenol A	80-05-7	$C_{15}H_{16}O_2$	19.80	0.003	73.3	213.091	−0.88	2	–	–	–	2,824	–	–
9-Octadecenamide (Oleamide)	301-02-0	$C_{18}H_{35}NO$	21.11	0.005	99.3	72.04439	−1.11	6	81,819	545,775	–	173,321	–	–
DEHA/Di(2-ethylhexyl) adipate*	103-23-1	$C_{22}H_{42}O_4$	21.28	0.016	97.1	129.0546	−0.04	6	25,216	359,143	–	–	122,805,127	180,654,466
Stearamide (Octadecanamide)	124-26-5	$C_{18}H_{37}NO$	21.28	0.009	99.2	240.2322	−1.61	6	5,496	12,529	–	7,993	–	–
BKF (Cyanox 2246)*	119-47-1	$C_{23}H_{32}O_2$	21.47	0.010	90.5	340.2397	−1.28	2	242	402	–	–	–	–
Antioxidant 425 (Cyanox 425)	88-24-4	$C_{25}H_{36}O_2$	22.09	0.005	99.7	368.271	1.48	6	–	–	–	9,340,202	15,853	22,187
DEHP/Di(2-ethylhexyl) phthalate	117-81-7	$C_{24}H_{38}O_4$	22.28	0.020	77.9	149.0233	−0.14	3	–	8,035	–	5,012	–	–
DEHT/Di(2-ethylhexyl) terephthalate	6422-86-2	$C_{24}H_{38}O_4$	23.62	0.013	99.3	261.1485	−0.94	4	–	1,734	–	2,058	–	–

RT Difference, Match Score, Mass Error, and number of verified ions reported for the B-7d except *A-7d and **C-7d. The numbers in the last six columns of the table represent peak area for quantifier ions.

However, it was found at even higher levels in catheter C, which is made of silicone-coated latex. Though not typically detected in silicone, DEHA could be present in some silicone tubings.[6]

LC/Q-TOF suspect screening confirmation of LC-amenable compounds reported by GC/Q-TOF

Many of the semivolatile non-aliphatic compounds detected by GC/Q-TOF are LC amenable. Therefore, to confirm the presence of LC-amenable compounds detected by GC/Q-TOF in catheter extracts, LC/Q-TOF data analysis was focused on using the list of compounds reported by the GC/Q-TOF (Table 5) as a suspect/target compound list. This approach uses the find-by-formula (FBF) suspect screening workflow in MassHunter Qualitative Analysis. The algorithm utilizes the formulas of the target compounds and calculates the exact mass of potential ion adducts ($[M+H]^+$, $[M+NH_4]^+$, $[M+Na]^+$) to obtain the extracted ion chromatogram (EIC), the background subtracted average mass spectrum, and when possible, the corresponding MS/MS spectra (Figure 5).

The results of the LC/MS suspect screening analysis of 7 day extracts are shown in Table 6 for both positive and negative ion detection.

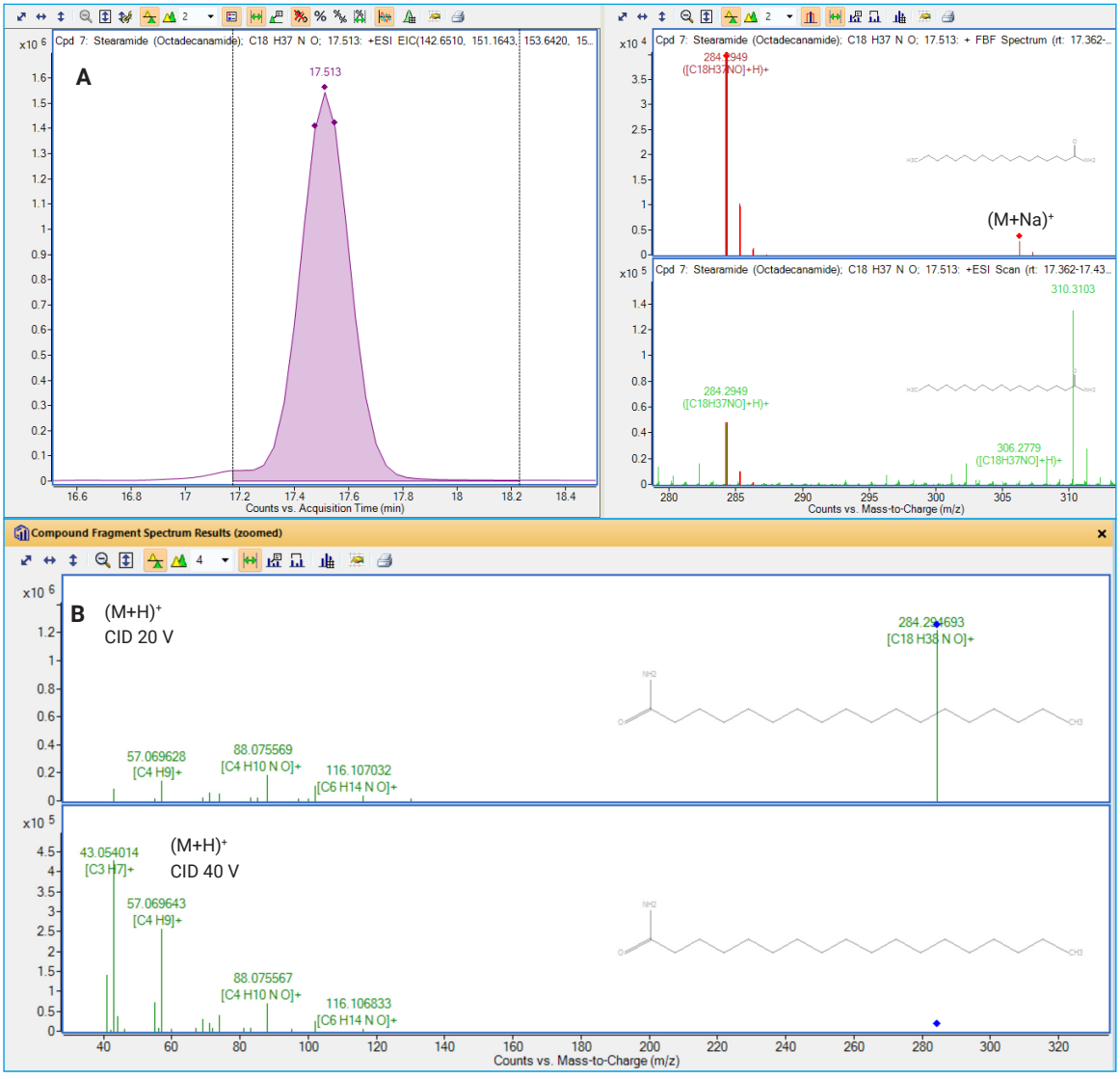


Figure 5. An example of LC/Q-TOF find-by-formula results for stearamide identified in extract A using mass accuracy, isotope abundance and MS/MS library search. (A) EIC (left) and annotated spectra, displaying either only formula-annotated molecular ion adducts (top) or the averaged spectrum (bottom). (B) MS/MS spectra of $(M+H)^+$ adducts of stearamide at different collision energies.

Table 6. LC/Q-TOF suspect screening results in positive and negative ion ESI.

Compound Name	Formula	Mode	RT* (min)	Mass	Mass Error (ppm)*	A-7d*	B-7d*	C-7d*
Benzaldehyde	C_7H_6O	Pos	1.5	106.0418	−0.6	5,431	36,391	ND
HOBT 2-Hydroxybenzothiazole	C_7H_5NOS	Pos/Neg	10.1	151.0093	0.15	ND	159,166	ND
MBT 2-Mercaptobenzothiazole	$C_7H_5NS_2$	Pos/Neg	10.46	166.9864	0.34	ND	1,281,918	ND
DEP Diethylphthalate	$C_{12}H_{14}O_4$	Pos	12.48	222.0891	0.37	44,654	ND	52,723
Palmitamide	$C_{16}H_{33}NO$	Pos	16.81	255.2562	0.02	14,683,063	12,262,859	79,596
Dibutyl Phthalate	$C_{16}H_{22}O_4$	Pos	15.2	278.1518	−0.14	438,053	262,843	91,980
Di-isobutyl Phthalate	$C_{16}H_{22}O_4$	Pos	15.27	278.1518	−0.16	966,113	843,834	110,586
Oleamide (9-Octadeceneamide)	$C_{18}H_{35}NO$	Pos/Neg	16.98	281.2722	−0.26	26,839,260	16,847,529	ND
Stearamide	$C_{18}H_{37}NO$	Pos	17.21	283.2874	0.71	23,383,790	19,998,077	42,878
Cyanox 425	$C_{25}H_{36}O_2$	Pos/Neg	17.22	368.2716	0.09	ND	1,604,748	ND
DEHA	$C_{22}H_{42}O_4$	Pos/Neg	17.52	370.3077	1.56	ND	ND	186,653,634
DEHP	$C_{24}H_{38}O_4$	Pos	19.37	390.277	0.05	1,497,261	2,640,467	1,025,392
Cyanox 2246	$C_{23}H_{32}O_2$	Neg	17.1	340.2397	−0.04	491,514	247,204	ND

*RT, mass error, and peak area (the last three columns) are shown for positive mode unless only detected in negative mode.
ND = Not detected

Nontargeted analysis of extractable profiles of various catheter types

A nontargeted workflow was used to expand the scope of compound annotation for GC/Q-TOF and include NIST23 in the library search in addition to the accurate mass E&L PCDL. The data were processed in MassHunter Unknowns Analysis using SureMass deconvolution followed by E&L PCDL and NIST23 library match. Both libraries can be searched simultaneously, and high-quality library hits were detected with both libraries (Figure 6).

Figure 6. Examples of GC/Q-TOF nontargeted analysis from catheter B using NIST23 library (A) and E&L PCDL (B).

To improve confidence in compound identification, the library search in both cases was performed with RI matching. The RI difference between an identified component and a respective library hit was smaller for E&L PCDL as compared to NIST23. The delta RIs for one of the catheter extracts (B7d) are displayed in Table 7.

The maximum RI difference observed for the PCDL was 6 RI units, with an average of approximately 2 RI units. For NIST23, the RI delta was significantly larger, with a maximum of 22.6 RI units and an average of approximately 8 RI units.

The ExactMass tool of MassHunter Unknowns Analysis helped to further verify compound ID by matching the fragment's accurate mass to molecular ion formula of library hit (Figure 6). The results of ExactMass validation are displayed in the ExactMass table and the mirror plot, where the evaluated ions are highlighted when their accurate *m/z* matches the library hit formula.

Table 7. Comparison of RI differences for the extractables detected by both NIST23 and E&L PCDL in catheter B.

Component RT (min)	Compound Name	Formula	CAS No.	Component RI	NIST23 Delta RI	PCDL Delta RI
6.79	Benzaldehyde	C_7H_6O	100-52-7	967.1	5.1	0.9
8.44	Acetophenone	C_8H_8O	98-86-2	1,071.1	5.1	0.9
12.69	Surfynol 104	$C_{14}H_{26}O_2$	126-86-3	1,407.2	0.2	0.2
13.20	DMP / Dimethyl phthalate	$C_{10}H_{10}O_4$	131-11-3	1,454.0	0.0	3.0
13.78	2,4-Di-tert-butylphenol	$C_{14}H_{22}O$	96-76-4	1,507.6	6.4	1.4
14.64	DEP / Diethyl phthalate	$C_{12}H_{14}O_4$	84-66-2	1,592.4	1.6	2.4
15.52	HOBT / 2-Hydroxybenzothiazole	C_7H_5NOS	934-34-9	1,682.8	6.8	0.8
16.02	2,6-Diisopropylnaphthalene	$C_{16}H_{20}$	24157-81-1	1,735.1	7.1	3.1
17.18	DIBP / Diisobutyl phthalate	$C_{16}H_{22}O_4$	84-69-5	1,864.0	5.0	6.0
18.18	MBT / 2-Mercaptobenzothiazole	$C_7H_5NS_2$	149-30-4	1,980.5	4.5	0.5
19.76	Palmitamide	$C_{16}H_{33}NO$	629-54-9	2,179.1	4.9	1.9
21.11	Oleamide	$C_{18}H_{35}NO$	301-02-0	2,364.8	21.2	0.8
21.28	Stearamide	$C_{18}H_{37}NO$	124-26-5	2,389.3	15.3	1.3
22.09	Antioxidant 425 (Cyanox 425)	$C_{25}H_{36}O_2$	88-24-4	2,506.4	22.6	0.6
23.62	Di(2-ethylhexyl)terephthalate	$C_{24}H_{38}O_4$	6422-86-2	2,745.1	8.9	2.1

In addition to the E&L compounds identified by the E&L PCDL, a nontargeted approach allowed identification of compounds that were not included in the E&L PCDL. As an example, linoleamide ((9Z,12Z)-9,12-octadecadienamide) was identified in the catheter A extract (Figure 7), adding to the fatty amide series often used as lubricants in PVC polymers.

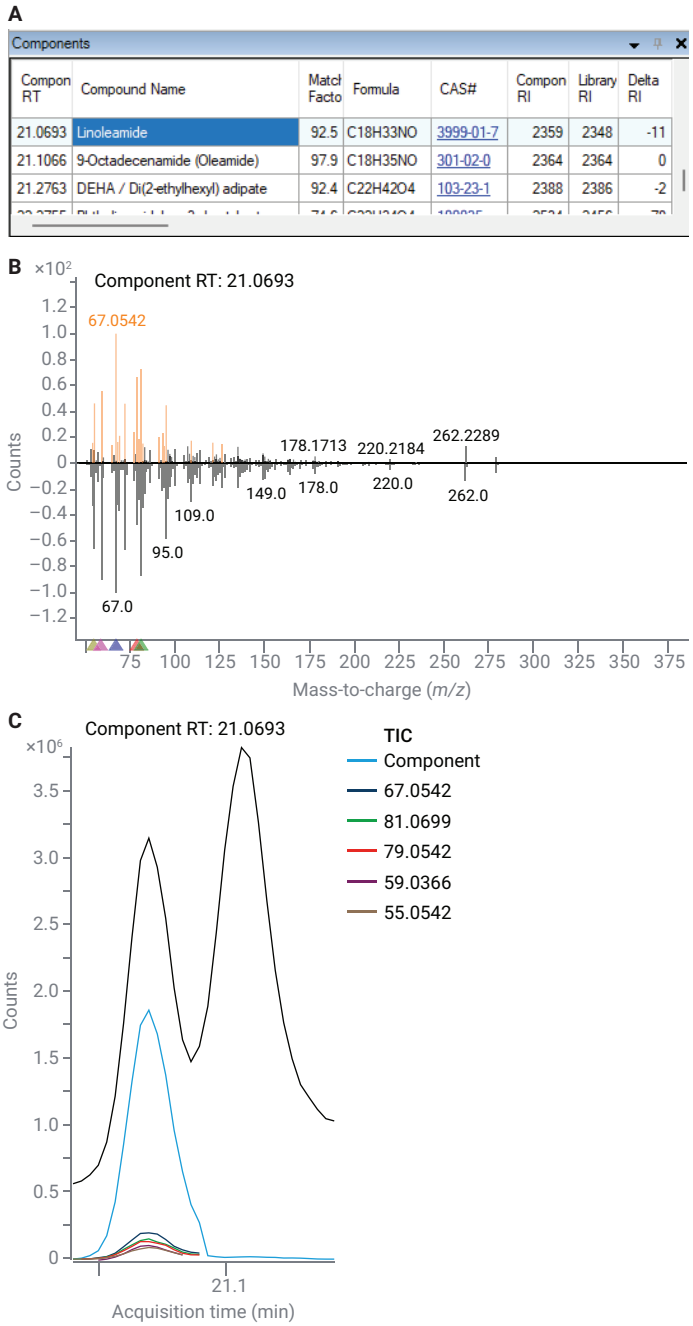


Figure 7. Example of fatty acid amide identified in catheter A extract using the NIST23 library. (A) Component table; (B) Mirror plot; (C) Component ion peaks.

Further data analysis was performed in Mass Profiler Professional (MPP) for GC/Q-TOF and Explorer for LC/Q-TOF. The principal component analysis (PCA) plot showed a distinct clustering between the three catheter types for both GC/Q-TOF (Figure 8A) and LC/Q-TOF (Figure 8B).

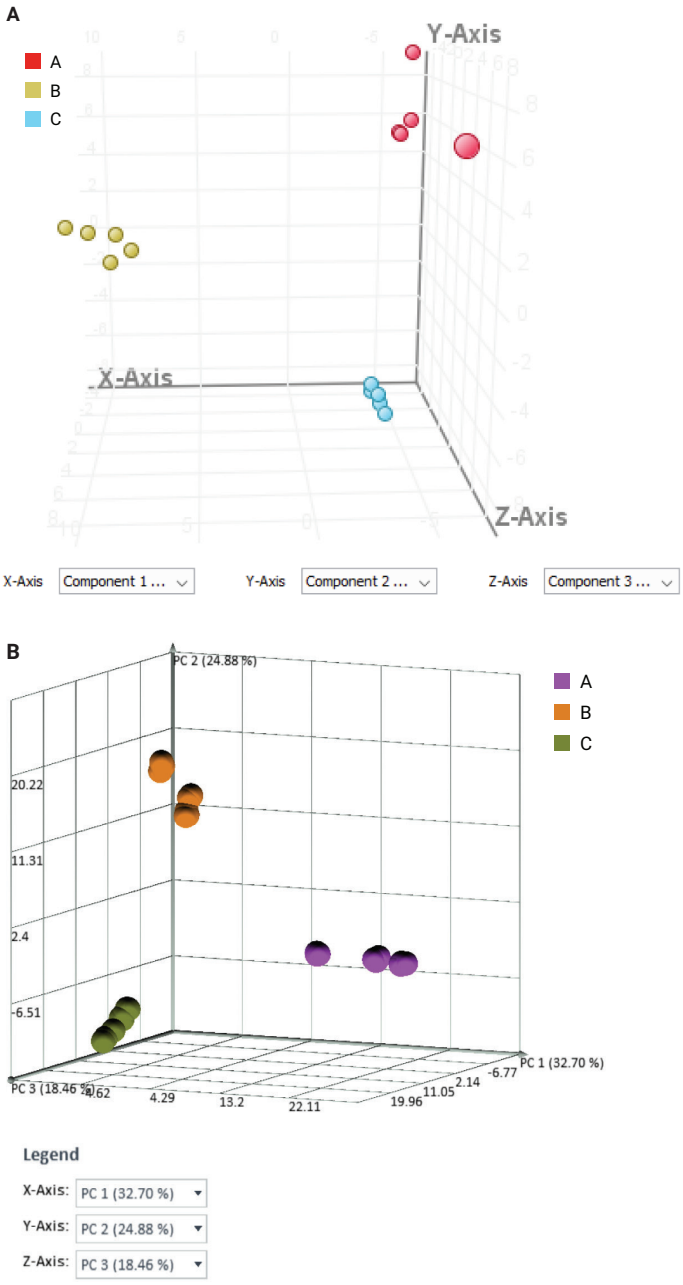


Figure 8. PCA clustering of extracts from three catheters based on GC/Q-TOF (A) and LC/Q-TOF (B) data.

An example showing variation in GC/Q-TOF extractables profiles between two catheter types (A and B) is displayed in Figure 9. Notably, thiazoles and phenolic antioxidants were detected at higher levels in catheter B, consisting of silicone-coated natural rubber latex; these compounds are used to increase vulcanization rate and resistance to degradation, respectively.

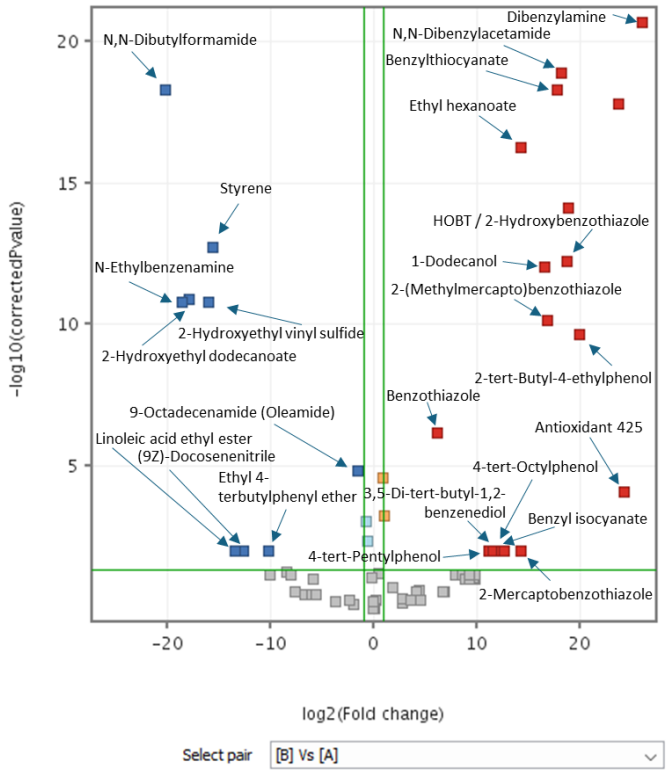


Figure 9. Volcano plot comparing extractables profiles of catheters A and B detected by GC/Q-TOF.

Using the nontargeted analysis approach, several sulfur-containing suspect compounds were detected in the ethanol:water extract from catheter B by LC/Q-TOF (Table 8).

The combination of accurate mass, isotope pattern matching, and MS/MS library searching provides a means to generate proposed formulas and possible structures. A more detailed description of diversity of the compounds in the catheter extracts detected by LC/Q-TOF is provided in 5994-8904EN.

Table 8. Tentative sulfur-containing compounds from catheter B extract.

RT	Mass	Formula	MFE Score	Height	Volume	Mass Error (ppm)
14.73	277.1712	$C_{13}H_{27}NO_3S$	98.17	1,561,393	11,001,443	0.28
14.274	233.1449	$C_{11}H_{23}NO_2S$	96.74	1,442,574	9,770,372	–0.38
1.031	166.0665	$C_6H_{14}O_3S$	93.36	1,448,416	4,446,752	0.73
13.1	293.1661	$C_{13}H_{27}NO_4S$	97.61	284,477	2,267,002	0.07
15.208	309.1433	$C_{13}H_{27}NO_3S_2$	96.42	159,343	824,899	0.34

Conclusion

This application note describes the analysis of extractables and leachables in catheter extracts in a combined workflow using high-resolution GC/MS and LC/MS. It also describes the construction, evaluation, and use of the new dedicated accurate mass E&L library for analysis of E&L compounds in suspect screening and nontargeted analyses.

Both GC/MS and LC/MS techniques were necessary to cover a comprehensive list of E&L compounds. Although several E&L compounds were detected by both GC/MS and LC/MS, in most cases hydrocarbons, most plasticizers, and some antioxidants were more amenable to GC/MS.

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