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

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Introduction

Materials used in the production of medical devices contain substances that have the potential to leach from the devices. Extractables and leachables (E&L) 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 a comprehensive chemical characterization. Application-specific accurate mass libraries combined with an efficient screening workflow, helps to increase confidence in compound identification that saves time on reviewing data while focused on E/L relevant compounds. In this study, we analyzed catheters extracts using high-resolution MS and performed data analysis using accurate mass libraries.

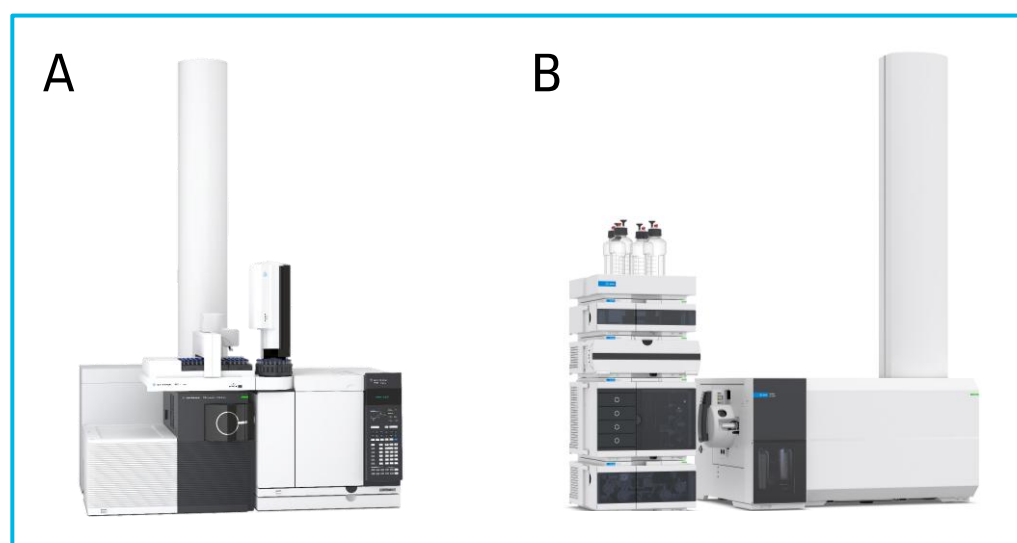


Figure 1. A) 7250 GC/Q-TOF and B) Revident LC/Q-TOF

Experimental

Catheters from three suppliers were used in this study. Catheter A was made from PVC, and did not include DEHP, DINP, 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 was a silicone-coated latex catheter made with natural rubber latex base and no DEHP or BPA. E&L standards were obtained from AChemTek. Catheters were extracted with ethanol:water 1:1 solvent at 37 °C for 24 and 48 hours as well as 7 days and analyzed using GC/Q-TOF and LC/Q-TOF systems. The GC/MS analysis was performed using the 8890 GC coupled to the 7250 Q-TOF and the new Agilent low bleed DB-5Q column.

Experimental

Detailed instrumental parameters are shown in Tables 1 and 2.

Table 1. GC/Q-TOF method parameters

Parameter	Value
MS	Agilent 7250 GC/Q-TOF
GC	Agilent 8890 GC
Column	Agilent DB-5Q, 30 m, 0.25 mm, 0.25 μ m
Inlet	MMI, 4 mm Ultra Inert liner, single taper with wool
Injection volume	1 μ L
Injection mode	Splitless
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
Source temperature	200 °C
Electron energy	70 eV
Emission current	5 μ A
Spectral acquisition rate	5 Hz
Mass range	50 to 1000 m/z

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 x 100 mm Column
Column temperature	40 °C
Injection volume	1 μ L
Flow rate	0.35 mL/min
Mobile Phase A	Water w/2.5mM 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
Collision energy	20; 40
MS range	40-1700 m/z
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	3500 V

The GC/MS data were processed using MassHunter Quantitative Analysis software (version 12.1). Compound identification was performed using both targeted and non-targeted data analysis approaches using the new GC/MS accurate mass E&L library as well as NIST23 EI Library respectively. The LC/MS data were processed using MassHunter Explorer 2.0 with integrated compound identification. Statistical analysis was performed using Mass Profiler Professional (MPP) software (version 15.1). The software was configured for stringent data integrity.

E&L Combined Workflows for LC/Q-TOF and GC/Q-TOF

Overview of LC/Q-TOF and GC/Q-TOF workflows for E&L analysis is shown in Figure 2. The LC/Q-TOF workflow consisted of untargeted analysis and identification of the unknowns. The GC/Q-TOF workflow additionally included suspect screening based on the new GC/MS E&L accurate mass Personal Compound Database and Library (PCDL).

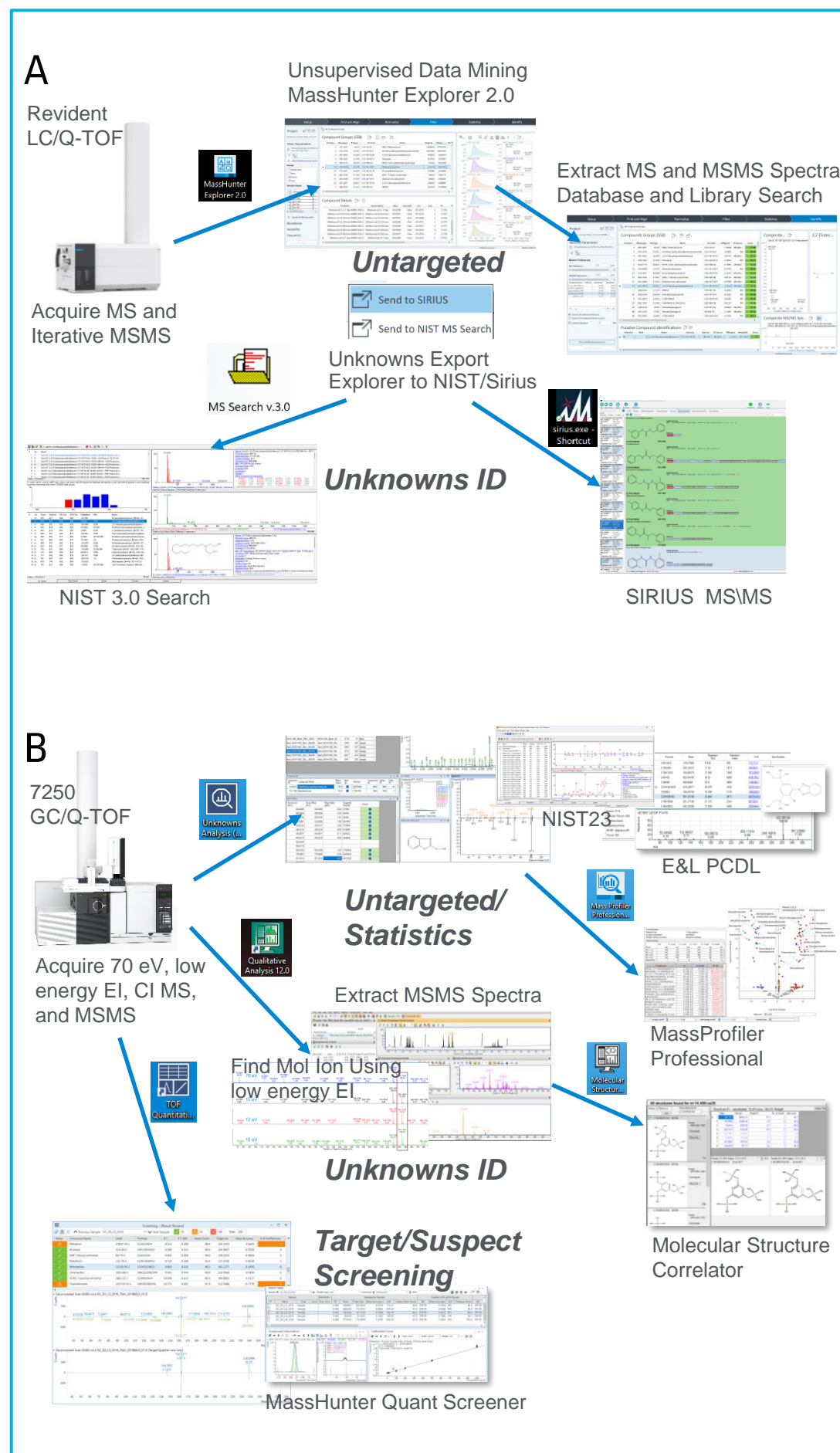


Figure 2. Outline of the E&L workflow for LC/Q-TOF (A) and GC/Q-TOF (B).

Accurate Mass E&L Library for GC/Q-TOF

To create a new Agilent accurate mass E&L Personal Compound Database Library (PCDL) for GC/Q-TOF, over 400 spectra have been collected for E&L compounds. All accurate mass fragment ions in each spectrum have been annotated with formulas based on accurate mass information and isotope ratios (Figure 3). The fragment formula annotations were then verified and converted to the theoretical m/z.

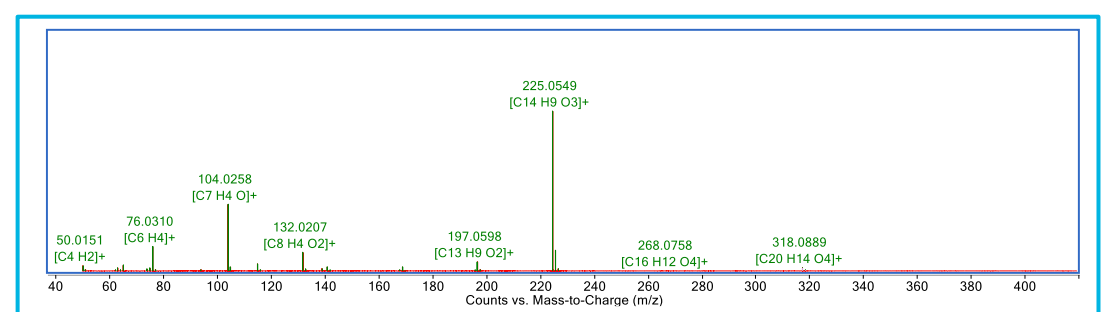


Figure 3. Fragment formula annotation of spectrum for one of the E&L compounds (diphenyl terephthalate) in MassHunter Qualitative Analysis software.

Examples of a few PCDL EI spectra, representative of typical E&L compound classes are shown in Figure 4.

New E&L PCDL for GC/Q-TOF: > 400 spectra

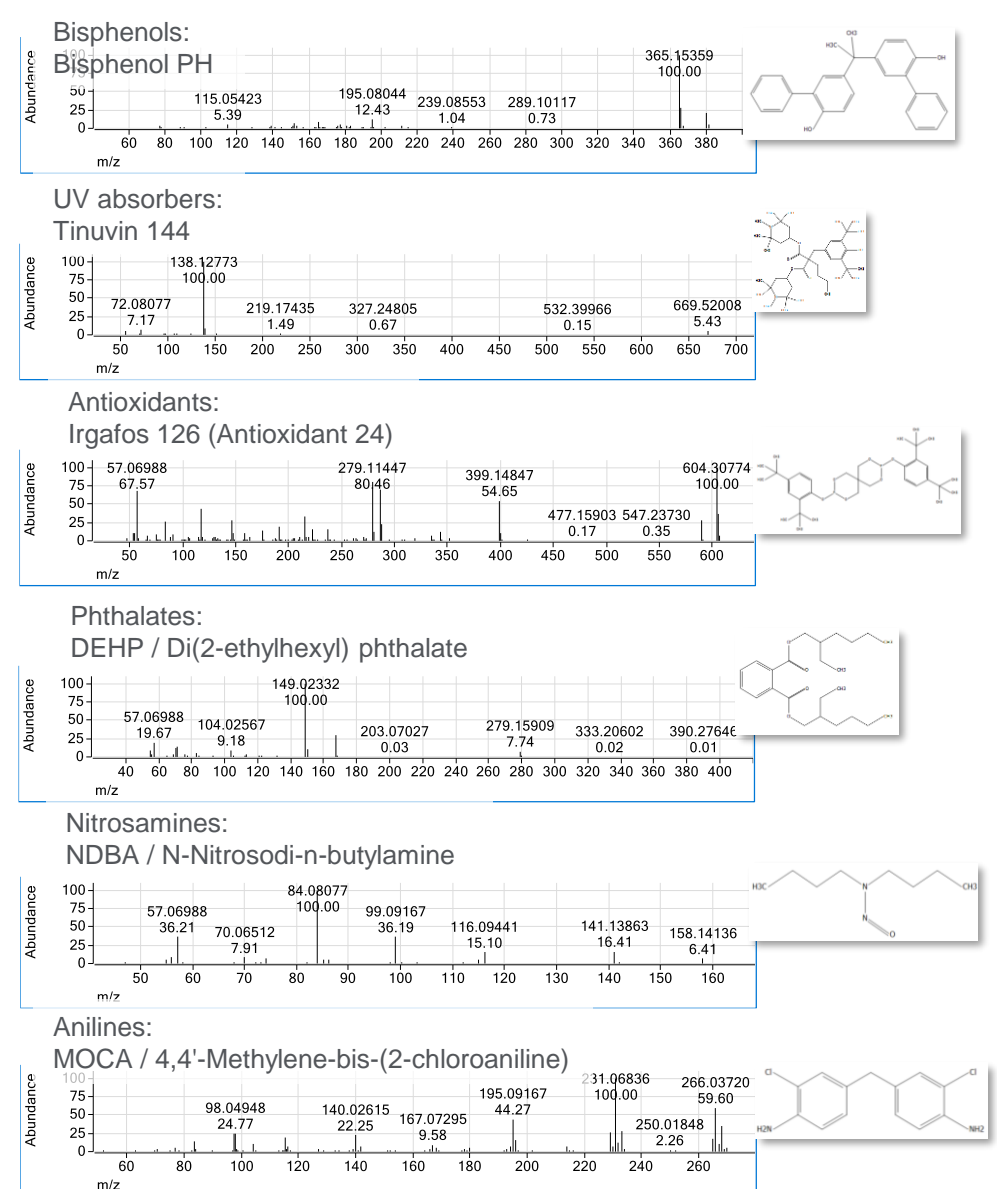


Figure 4. Examples of accurate mass spectra in E&L GC/Q-TOF PCDL.

Using Suspect Screening to Identify Extractables in Catheter Samples

GC Screener tool (shown in Figure 5) was used to identify E&L compounds in catheter extracts using targeted approach that takes advantage of the new accurate mass E&L PCDL.

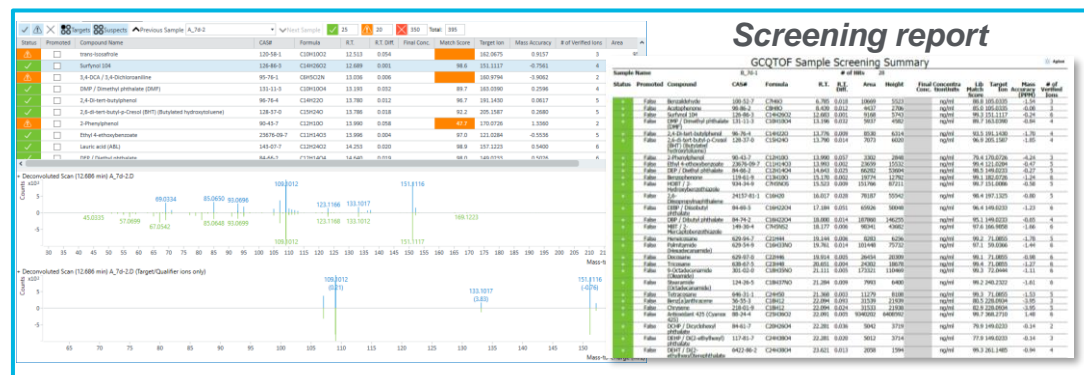


Figure 5. Screener results.

The suspect screening results are summarized in Table 3. Table 3. Screener results summary.

Compound Name	CAS#	Formula	RT	Match Diff.	Score	Target Ion	Mass Error, ppm	# of Verified Ions	A-7d Area	A-7d Area	B-7d Area	B-7d Area	C-7d Area	C-7d Area
Benzaldehyde	100-52-7	C7H6O	6.79	0.018	88.8	105.0335	-1.54	3	-	9042	-	10669	-	-
Acetophenone	98-86-2	C8H8O	8.44	0.012	85.0	105.0335	-0.08	3	-	-	-	4437	-	-
Caprolactam**	105-60-2	C6H11NO	11.04	0.092	99.4	113.0835	-0.25	6	-	-	-	4917	16395	
N,N-Dibutylformamide*	761-65-9	C9H19NO	11.51	0.026	99.6	114.0913	0.64	6	307783	403140	-	-	3149	6652
Surfynol 104	126-86-3	C14H26O2	12.68	0.001	99.3	151.1117	-0.24	6	2702	7288	-	9168	-	-
DMP / Dimethyl phthalate	131-11-3	C10H10O4	13.20	0.032	89.7	163.039	-0.84	4	-	11057	-	5937	2413	6308
2,4-Di-tert-butylphenol	96-76-4	C14H22O	13.78	0.009	93.5	191.143	-1.70	4	36178	48380	716	8530	50538	115291
2,6-di-tert-butyl-p-Cresol (BHT)	128-37-0	C15H24O	13.79	0.014	96.9	205.1587	-1.85	4	13688	15579	-	7073	-	-
Phenanthrene*	85-01-8	C14H10	16.71	0.024	81.7	178.0777	-2.34	2	-	2604	-	-	-	-
Ethyl 4-ethoxybenzoate	23676-09-7	C11H14O3	13.99	0.002	99.4	121.0284	-0.47	5	4701	5669	-	23659	1456	4781
DEP / Diethyl phthalate	84-66-2	C12H14O4	14.64	0.025	98.5	149.0233	-0.27	5	25793	55550	-	66282	25288	53080
Benzophenone	119-61-9	C13H10O	15.17	0.002	99.1	182.0726	-1.24	6	8865	10718	-	19774	4209	8734
HOBt / 2-Hydroxybenzothiazole	934-34-9	C7H5NOS	15.52	0.009	99.7	151.0086	-0.58	5	-	-	-	151766	-	-
2,6-Diisopropynaphthalene	24157-81-1	C16H20	16.02	0.028	98.4	197.1325	-0.80	5	7259	202515	2563	78187	2287	16989
DIBP / Diisobutyl phthalate	84-69-5	C16H22O4	17.18	0.051	96.4	149.0233	-1.23	6	51893	86876	-	65926	20546	21903
DBP / Dibutyl phthalate	84-74-2	C16H22O4	18.00	0.014	95.1	149.0233	-0.65	4	73081	151248	-	187860	40377	34261
MBT / 2-Mercaptobenzothiazole	149-30-4	C7H5NS2	18.18	0.006	97.6	166.9858	-1.66	6	-	-	-	98341	-	-
Heneicosane	629-94-7	C21H44	19.14	0.006	99.2	71.08553	-1.78	5	-	-	-	5681	8283	-
Palmitamide (Hexadecanamide)	629-54-9	C16H33NO	19.76	0.014	97.1	59.03656	-1.44	6	32712	95805	-	101448	-	-
BPA / Bisphenol A	80-05-7	C15H16O2	19.80	0.003	73.3	213.091	-0.88	2	-	-	-	2824	-	-
Docosane	629-97-0	C22H46	19.91	0.005	99.1	71.08553	-0.98	6	36539	9968	13088	26454	3769	20675
Tricosane	638-67-5	C23H48	20.65	0.004	99.4	71.08553	-1.27	6	10280	6030	1030	24302	-	13350
9-Octadecenamide (Oleamide)	301-02-0	C18H35NO	21.11	0.005	99.3	72.04439	-1.11	6	81819	545775	-	173321	-	-
DEHA / Di(2-ethylhexyl) adipate*	103-23-1	C28H54O4	21.28	0.016	97.1	129.0546	-0.04	6	25216	359143	-	122805127	180654466	-
Stearamide (Octadecanamide)	124-26-5	C18H37NO	21.28	0.009	99.2	240.2322	-1.61	6	5496	12529	-	7993	-	-
Tetracosane	646-31-1	C24H50	21.37	0.003	99.3	71.08553	-1.53	5	-	-	-	11279	-	-
BKF (Cyanox 2246)*	119-47-1	C23H32O2	21.47	0.010	90.5	340.2397	-1.28	2	242	402	-	-	-	-
Antioxidant 425 (Cyanox 425)	88-24-4	C25H36O2	22.09	0.005	99.7	368.271	1.48	6	-	-	-	9340202	15853	22187
DEHP / Di(2-ethylhexyl) phthalate	117-81-7	C24H38O4	22.28	0.020	77.9	149.0233	-0.14	3	-	8035	-	5012	-	-
DEHT / Di(2-ethylhexyl)terephthalate	6422-86-2	C24H38O4	23.62	0.013	99.3	261.1485	-0.94	4	-	1734	-	2058	-	-

RT Difference, Match Score, Mass Error and number of verified ions reported for the B-7d except *A-7d and **C-7d. The red shade reflects relative amount for a given compound across the samples

Extractable Profiles of the Different Types of Catheters Using Non-Targeted Analysis

The GC/Q-TOF data were processed in Unknowns Analysis using SureMass deconvolution followed by E&L PCDL and NIST23 library match (Figure 6).

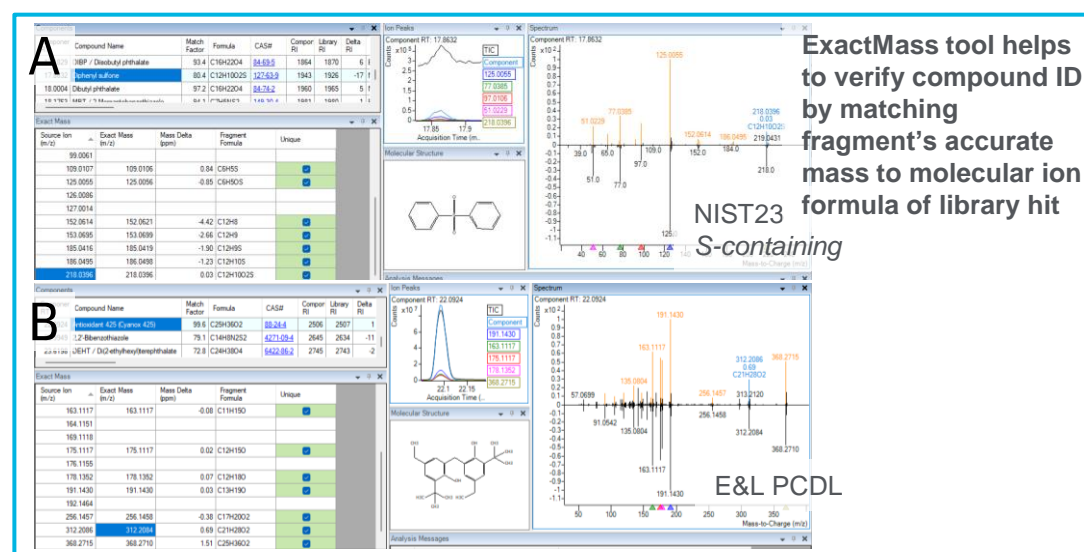


Figure 6. Examples non-targeted analysis hits from catheter B using NIST23 library (A) and E&L PCDL (B).

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Compound information and ID were imported to MPP for further statistical analysis. Principal component analysis (PCA) plot showed a distinct clustering between the three catheter types (Figure 7A). An example showing variation in extractables profiles between two catheter types (A and B) is displayed in Figure 7B.

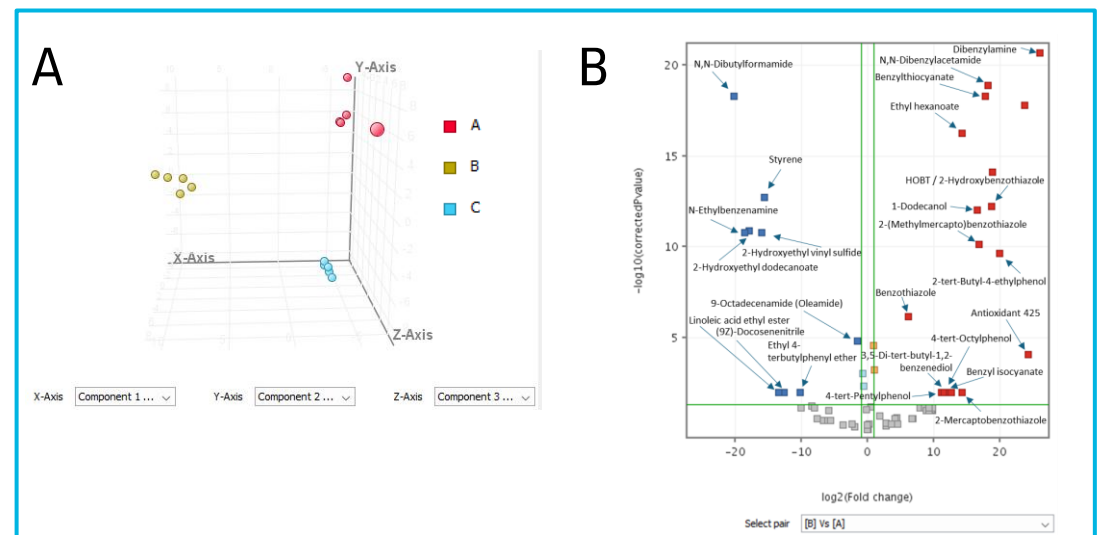


Figure 7. PCA clustering of extracts from three catheters (A) and Volcano plot comparing extractables profiles of catheters A and B detected by the GC/Q-TOF.

Compounds coverage by LC/Q-TOF non-targeted analysis was complimentary to the results obtained by GC/Q-TOF. LC/Q-TOF analysis of catheter extracts (Figure 8) confirmed presence of sulfur compounds, some of which were also detected by GC/Q-TOF.

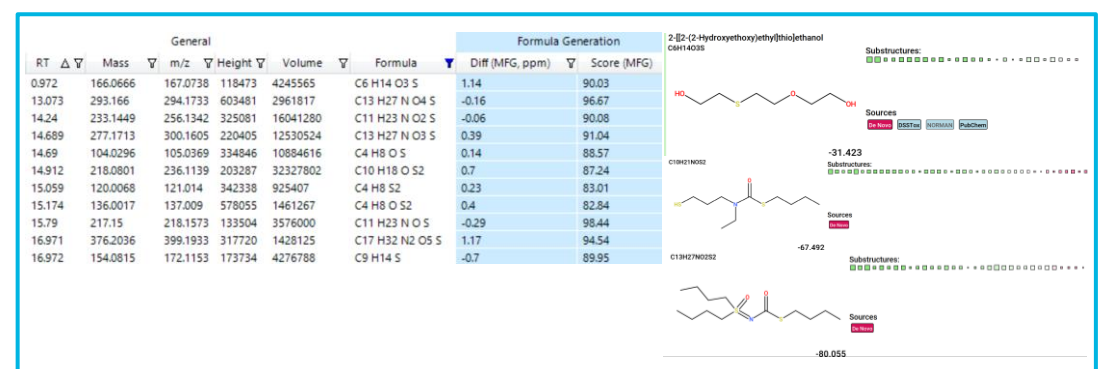


Figure 8. LC/Q-TOF non-targeted analysis results indicating the presence of S-containing compounds in catheter B extract.

Conclusions

- A combined workflow for the analysis of extractables and leachables by high-resolution GC/MS and LC/MS was developed using catheter extracts.
- 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.