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Targeting Efficiency: A Database and Optimized Method for Sensitive and Reliable Targeted LC/MS Analysis of Extractables and Leachables

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Introduction

Targeted Analysis for Extractables and Leachables

Targeted extractable and leachable (E&L) analysis for evaluation of medical devices, drug delivery systems, consumer products, and food contact materials all require sensitive and robust methods for routine analysis.

Developing a method for these applications is challenged by the wide range of chemical classes covered, often large numbers of target analytes, and frequent presence of isobaric compounds. In this study we compare common reverse phase columns, mobile phase additives, and ionization parameters to achieve a robust, sensitive, and highly reproducible dynamic multiple reaction monitoring (dMRM) method and MRM database with corresponding retention times for an easy-to-implement solution for routine targeted LC/MS E&L analysis.

Experimental

Broad Range of E&L Standards for Representative Monitoring of Method Performance

A specially developed E&L kit containing 350 LCMS-amenable standards (AChemTek) was utilized to optimize chromatographic, MS source and MRM conditions. Column stationary chemistry, column dimensions, mobile phase and mobile phase buffers compositions (formic acid, ammonium formate, and ammonium fluoride) were compared to determine optimum conditions for separations and MS response (ionization efficiency) for the E&L analysis.

MS parameters were optimized using automated MRM and source optimization features in MassHunter Acquisition software.

Figure 1. The Agilent1290 Infinity III LC system paired with the Agilent 6475 LC/TQ provide a robust platform with sensitive and robust performance for E&L analysis.

Experimental

Optimized Method for LC/TQ Yields Efficient Targeted Analysis of Extractables and Leachables

Table 1. Optimized LC Conditions

1290 LC Conditions	
Analytical column	Agilent Poroshell 120 Aq-C18, 2.1 x 150 mm, 2.7 µm PN: 693775-742
Delay column	Agilent Poroshell 120 EC-C18 4.6 x 50 mm, 2.7 µm PN: 699975-902
Column temperature	40 °C
Autosampler temperature	5 °C
Needle wash	10 s; 50% isopropanol, 25% methanol, 25% acetonitrile
Mobile phase	A: 2.5 mM ammonium formate, 0.05% formic acid, 100 µM ammonium fluoride in water B: 2.5 mM ammonium formate, 0.05% formic acid, 100 µM ammonium fluoride in methanol
Flow rate	0.35 mL/min
Gradient program	Time %B 0.0 2 1.0 2 16.0 100 26.0 100 26.1 2
Total run time	29.1 min

Table 2. 6475 LC/TQ AJS Source Conditions

Dual AJS ESI Source Conditions	
Gas Temperature, Flow	250 °C, 12 L/min
Nebulizer Pressure	35 psi
Sheath Gas Temperature, Flow	300 °C, 11 L/min
Nozzle Voltage	0 V (+), 2000 V (-)
Capillary Voltage	4000 V

Extractions from Food Contact Materials

3 types of vacuum sealer bags commonly used for food storage and sous vide cooking were extracted with ethanol at 70 °C for 10, 20, and 60 minutes. Samples from each extract and timepoint were analyzed by LC/TQ to evaluate the extracted levels of common food contact material E&L compounds.

Results and Discussion

Mobile Phase Selection Impacts Sensitivity, Adduct Formation, and Chromatographic Resolution

The addition of low levels of formic acid and ammonium formate to the mobile phases showed marked improvements in sensitivity, particularly for positive ions.

Adding 100 µM ammonium fluoride to the mobile phases also reduced the formation of sodium adducts, (Figure 2) promoting the formation of meaningful fragment ions, and further boosting sensitivity.

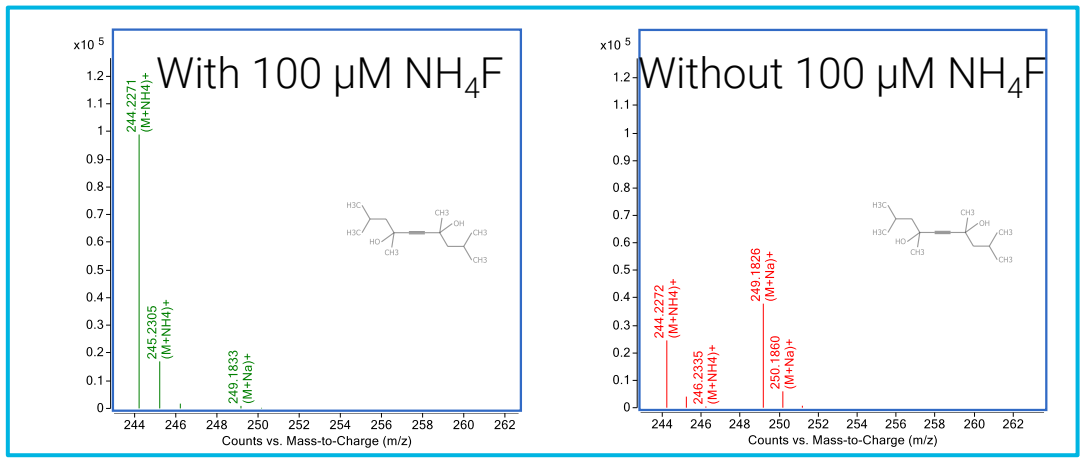

Figure 2. Reduction of sodium adduct formation for 2,4,7,9-Tetramethyl-5-decyne-4,7-diol with addition of NH_4F to the mobile phases (left) versus without (right).

Column and Gradient Selection are Key for Achieving Isobar Separation.

Optimum separation for the majority of common isomer and isobar pairs (Figure 3) was achieved with a 26-minute gradient on a 150 mm Aq-C18 column.

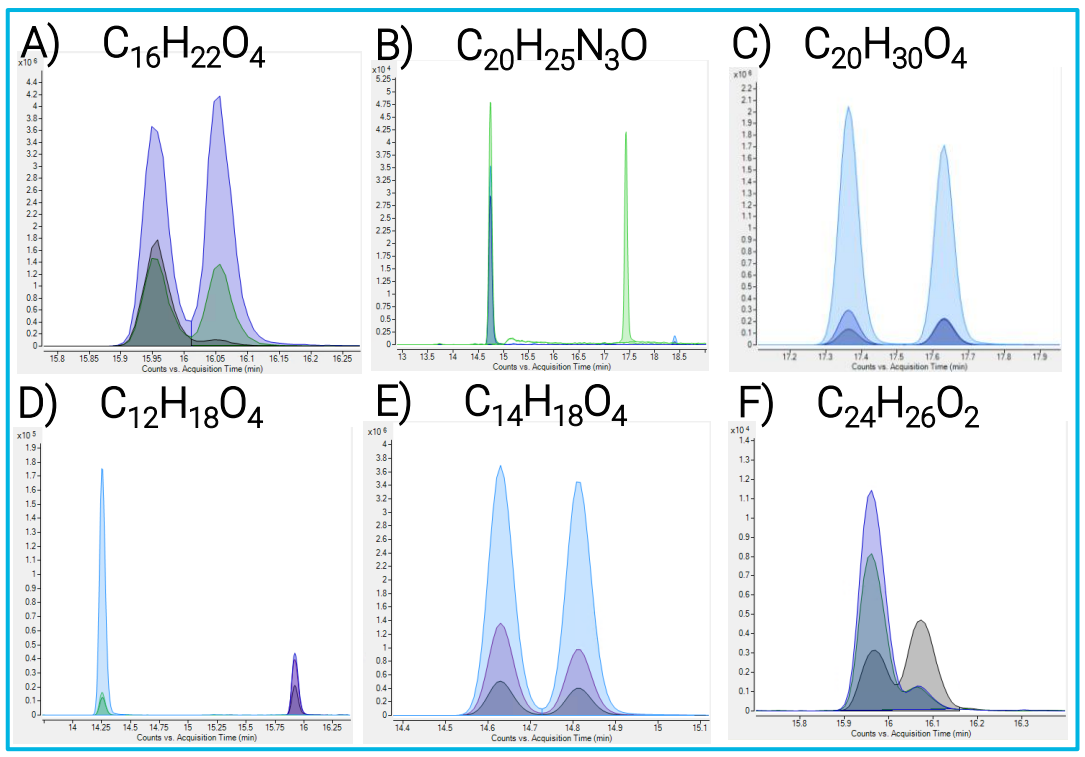

Figure 3. Separation of common E&L isomer pairs with optimized chromatography: A) dibutyl phthalate & diisobutyl phthalate, B) 2-benzotriazolyl-4-t-octylphenol & Tinuvin 320, C) di-n-hexyl phthalate & diisohexyl phthalate, D) 1,6-bis(acryloxyloxy)hexane & 1,6-diaminohexane, E) dipropyl phthalate & diisopropyl phthalate, F) bisphenol M & bisphenol P.

MassHunter Optimizer Streamlines Optimization of MRM and Source Parameters for Easy Method Updates.

350 E&L standards were used to build an MRM database. All MRM transitions, collision energies, and fragmentor voltages were automatically optimized using Optimizer in MassHunter Acquisition using the process and parameter ranges shown in Figure 4.

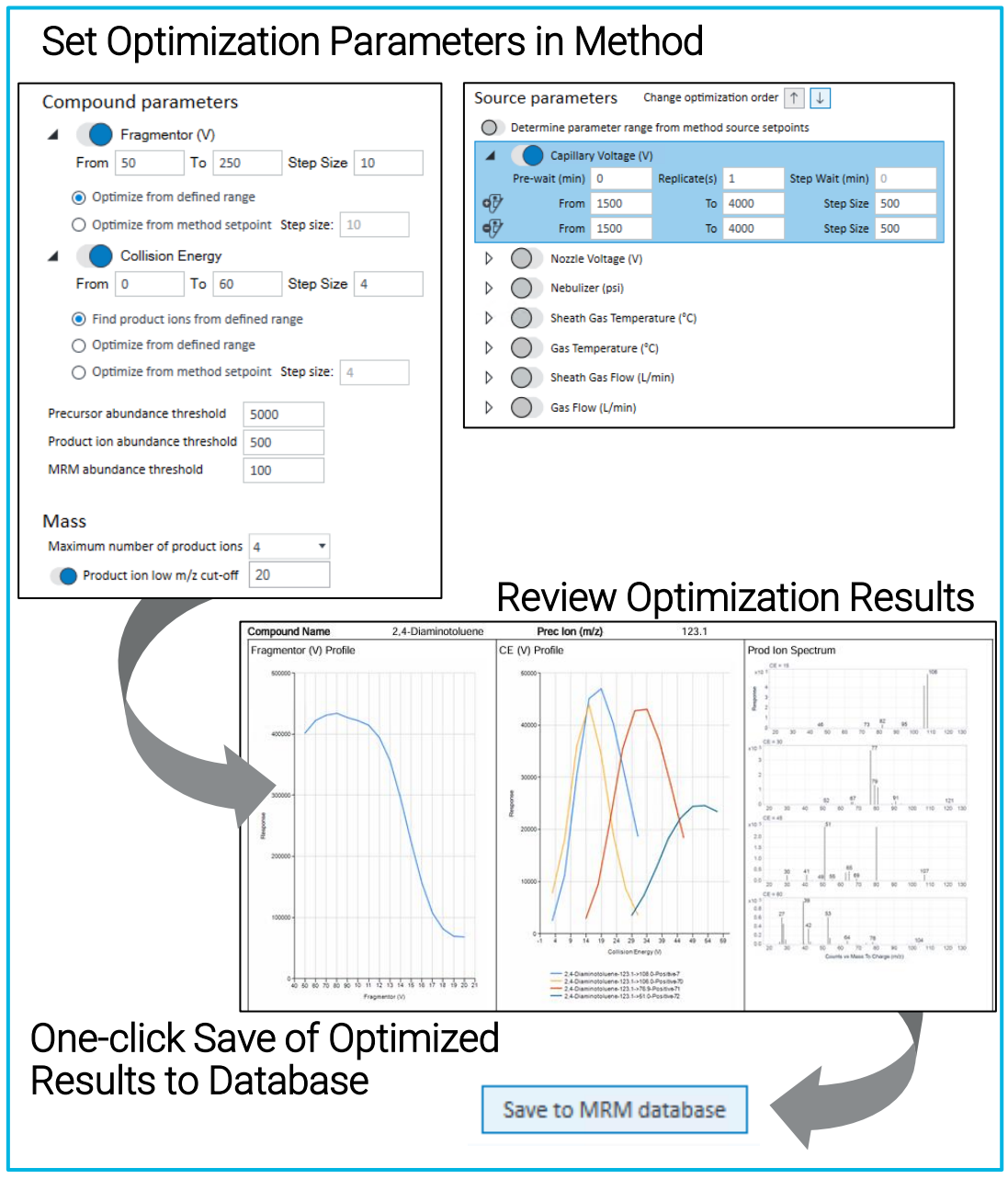

Figure 4. User-specified ranges for MRM parameters are used for automated compound optimization using Optimizer in MassHunter Acquisition. Optimized results are easy-to-review and can be directly saved to an MRM database or method.

Database of 1000+ Transitions for 303 E&L Compounds built Using MassHunter Optimizer.

At least 2 MRM transitions each for 303 E&L compounds were optimized. The top transitions for each compound were included in a new MRM database. Transitions for both positive and negative polarities were included, when applicable.

The remaining 47 compounds from the standard mixes required either APCI ionization or volatile analysis by GC/MS and were therefore not included in this ESI-LC-MS database. The MRM database was paired with the optimized chromatography to build a new dMRM method for easy-to-implement targeted E&L analysis.

Results and Discussion

Optimized Method Yields Reproducible Chromatograms across E&L Compound Classes.

The optimized dMRM method showed reproducible performance when applied to food contact material extracts, including reproducible retention times, peak areas, and quantifier : qualifier ion ratios (Figure 5).

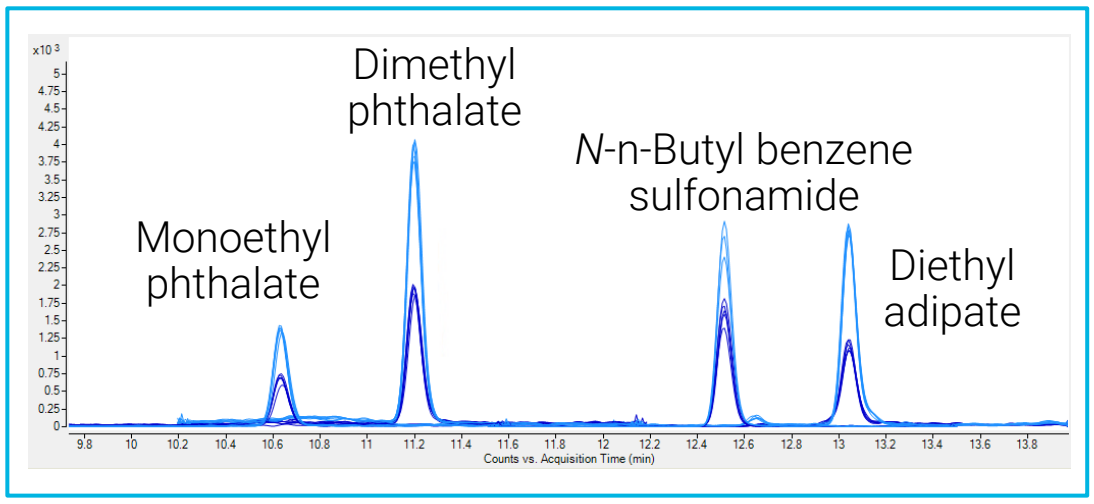

Figure 5. MRM chromatogram overlays (n = 6) Food contact material samples – ethanol extract – with quantifier ions (light blue) and qualifier ions (dark blue).

Wide Linear Dynamic Ranges Facilitate Quantification of E&L Compounds at Real-World Extract Concentrations.

E&L standards were prepared across a range of concentrations from 0.5 to 200 ppb and analyzed using the optimized dMRM method. Calibration curves with wide linear ranges across a variety of E&L compound classes (Figure 6) facilitate quantification of both high- and low-abundance analytes.

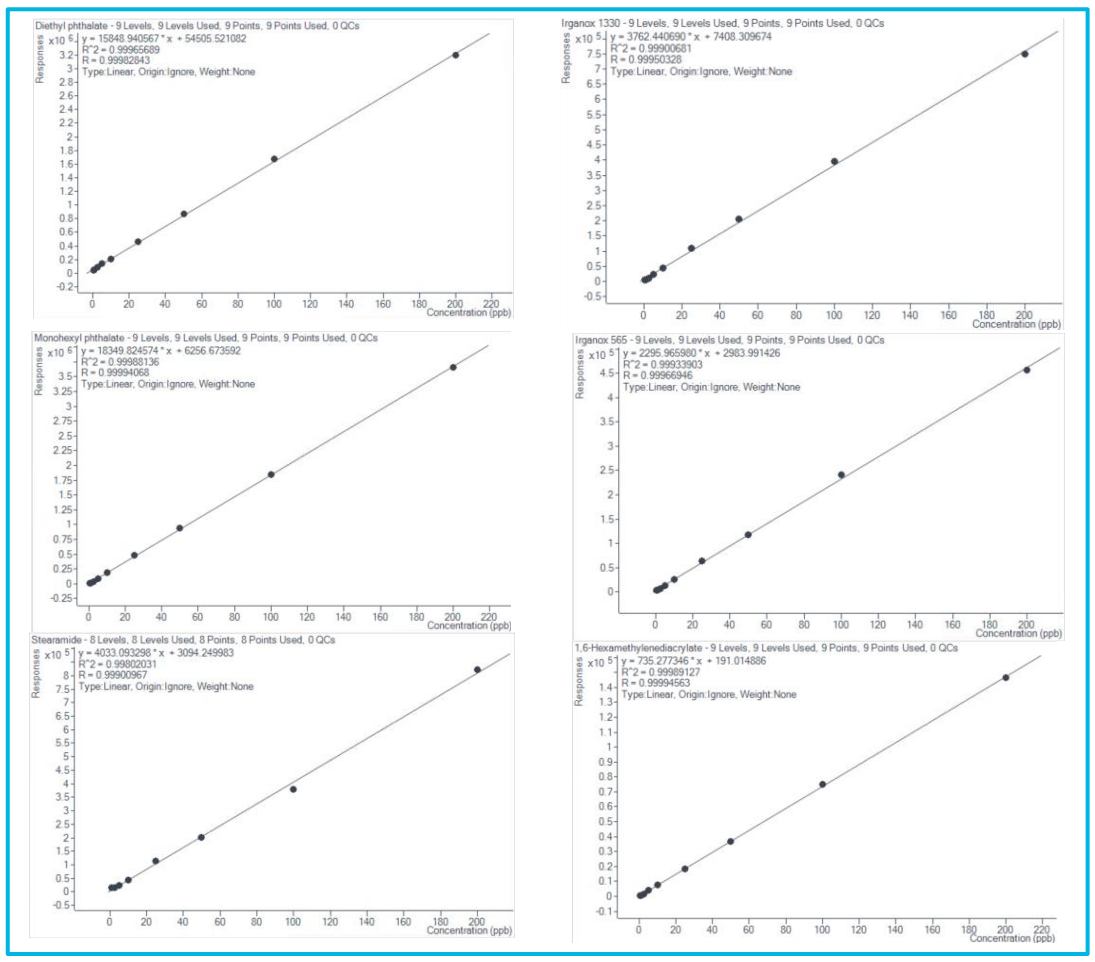

Figure 6. Linear calibration curves for example analytes across E&L compound classes with $R^2 > 0.998$.

New E&L LC/TQ Database Applied for Quantification of Food Contact Material Extracts.

Extracted compound concentrations from vacuum sealer bags heated with ethanol for 10, 20, and 60 minutes were monitored using the optimized dMRM method. Fatty acid amides, phthalates, antioxidants, diethylene glycol, and tris(2,4-di-t-butylphenyl)phosphate featured prominently in the extracts, with concentrations increasing with longer extraction periods. Figure 7 shows the change in analyte concentrations over time.

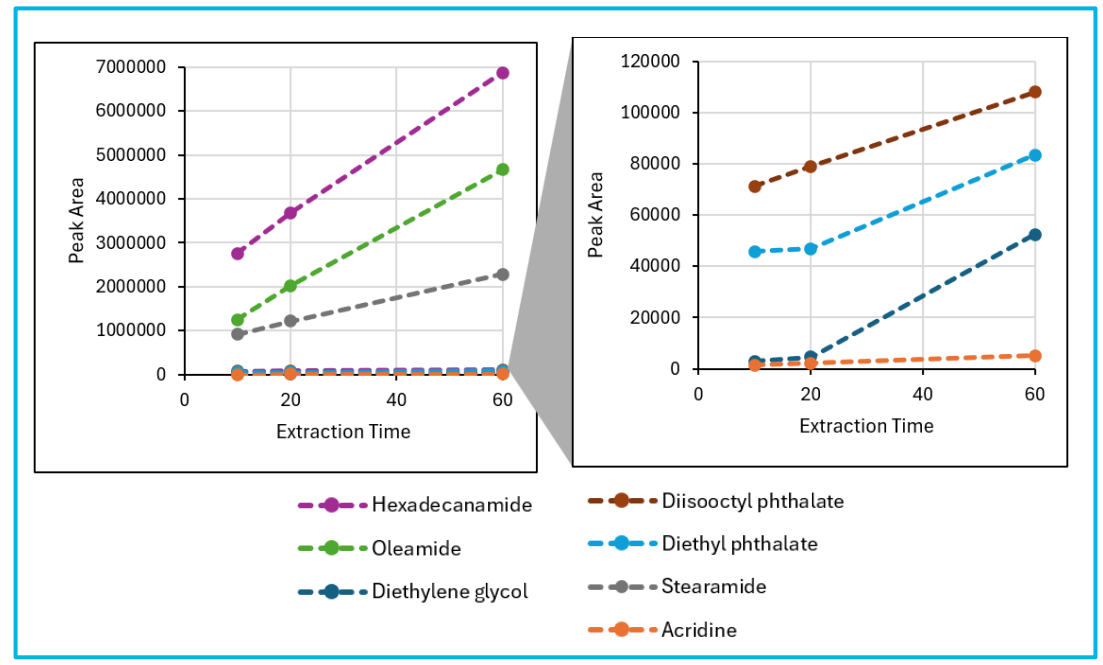

Figure 7. Changes in compound concentrations in vacuum sealer bag extracts over time.

Conclusions

New Extractables and Leachables LC/TQ Database and Optimized Chromatography Facilitate Sensitive and Reproducible Targeted E&L Analysis.

- MassHunter Optimizer facilitates automated compound and source parameter optimization to streamline database building or adding new compounds to existing methods.
- Use of methanol-based mobile phase containing ammonium formate and ammonium fluoride substantially increased signal response for target MRM transitions across E&L compound classes.
- The 6475 LC/TQ with optimized dMRM method facilitates targeted analysis of 303 common E&L compounds at real-world extract concentrations with reproducible retention times and peak areas.

For more food contact material analysis, check out WP307 for LC/Q-TOF and WP311 for GC/MS!

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