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Advanced High-Resolution LC/MS-Based Characterization of Extractables from Food Contact Materials Enabled by a Newly Developed Chemical Database

David A. Weil*, Sierra Durham, Matthew Curtis and Sofia Nieto.

Agilent Technologies, Santa Clara CA, 95051

Introduction

Food comes into contact with numerous materials and articles throughout production, processing, storage, preparation, transportation, and serving. These polymer-based food contact materials (FCMs) can transfer chemicals into food, potentially creating safety concerns. Because extractable and leachable (E&L) compounds span a wide range of physical and chemical properties, accurate detection requires both GC/MS and LC/MS analytical approaches. This study describes the use of high-resolution LC/MS, combined with a new FCM-specific database and MS/MS library, to support confident identification of extractable and leachable compounds obtained from ethanol extracts of various suppliers of food vacuum sealer bags.

Method

A Food Contact Materials (FCM) database was created using two standards kits from AChemTek (Woburn, MA) along with more than 50 commercially available industrial polymer additives. The standards were analyzed using an Infinity III 1290 LC interfaced to the Agilent Revident LC/Q-TOF (Figure 1). Both MS and MS/MS spectra were acquired using optimized system and source conditions to minimize in-source fragmentation (Table 1). MS/MS data were collected at 10, 20, and 40 eV and each extract was injected three times using iterative MS/MS to automatically generate an exclusion list and obtain MS/MS spectra for low abundance compounds. The reverse-phase (RP) HPLC method was developed to enhance separation of structural isomers and ensure elution of higher-molecular-weight hydrophobic compounds.

Figure 1. Infinity III 1290 LC and Revident LC/Q-TOF

Experimental

The instrumental parameters are shown in Table 1.

Table 1. LC/QTOF Instrument Parameters

Parameter	Value
LC	Agilent 1290 Infinity II
MS	Agilent Revident LC/Q-TOF
Column	**Analytical:** Agilent Poroshell Aq-C18 2.1 x 150 mm, 2.7 µm **Delay:** Agilent Poroshell EC-C18 4.6x50 mm, 2.7 µm
Column temperature	40 °C
Injection volume	5 µL
Flow Rate	0.35 mL/min
Mobile Phase A	Water w/ 2.5 mM NH_4Formate, 0.05% FA, 100 µM NH_4F
Mobile Phase B	Methanol w/ 2.5 mM NH_4Formate, 0.05% FA, 100 µM NH_4F
LC Gradient	2% B for 1.0 min; to 100% B at 16.0; hold 100% B to 26.0 min; to 2% at 26.1 min post time 3 min
MS Source	Dual AJS ESI
MS Mode	Auto MS/MS
Polarity	Positive
Collison Energy	10, 20, 40 eV
MS Range	40-1700 *m/z*
Acquisition Rate	4 spectra/sec for MS; 6 spectra/sec for MS/MS
Drying Gas	250 °C, 12 L/min
Sheath Gas	300 °C, 11 L/min
Nebulizer Pressure	35 psi
Nozzle Voltage	0 V
Capillary Voltage	4000 V

MassHunter Explorer 2.0 Non-Targeted Data Analysis

The LC/Q-TOF workflow for E&L analysis consists of iterative data dependent acquisition (DDA) followed by nontargeted data analysis (NTA) using the Agilent MassHunter Explorer 2.0 software to extract MS and corresponding MS/MS spectra. Compound identification is done by searching against multiple databases with optional export remaining unknowns to either NIST MS Search 3.0 or Sirius (6.3.3) (Figure 2).

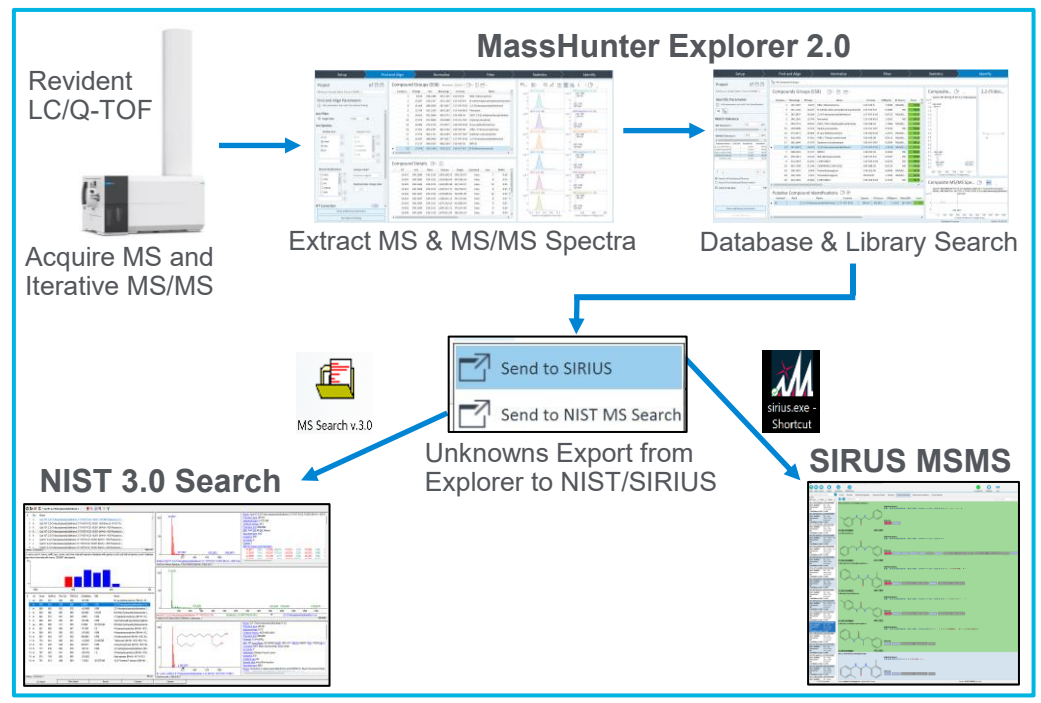

Figure 2. Data Analysis Workflow

ChemVista Software Leveraging Third Party Content

A major challenge in LC/MS E&L analysis is the confident identification of compounds present in an extract. Unlike GC/MS, where extensive commercial EI libraries such as Wiley/NIST 2023 contain more than 3 million spectra with retention index (RI) values, LC/MS libraries are smaller and typically focused on non-E&L related compounds. Ultra-large public databases such as PubChem™ and ChemSpider™, while containing more than 120 million structures, the databases lack application-specific annotations and searchable MS/MS spectra, limiting their utility for FCM studies. Agilent ChemVista database and library management software addresses this gap by enabling the creation of application-specific spectral libraries using online resources.

For this study, information from the Food Packaging Forum was used to download FCM-related compounds from the Food Contact Chemicals database FCCdb; 12,285 compounds, the Food Contact Priority List FCCprio; 1,222 high-risk compounds, and the Migrating and Extractable Food Contact Chemicals database FCCmigex; 5,300 compounds. This consolidated FCM list was paired with MS/MS spectra collected from reference standards and with MS/MS spectra downloaded from the MassBank of North America (MONA) and MassBank EU databases. Using ChemVista, an application-specific, downloadable FCM library containing more than 3,000 compounds with associated MS/MS spectra was created and exported as a *.SDF file a custom database for use with NIST MS Search 3.0. Exporting compounds with proposed smiles structures provides a means to have custom database for the Bright Giant Sirius MS/MS search software. Figure 3 shows example of ChemVista Software merging FCM content.

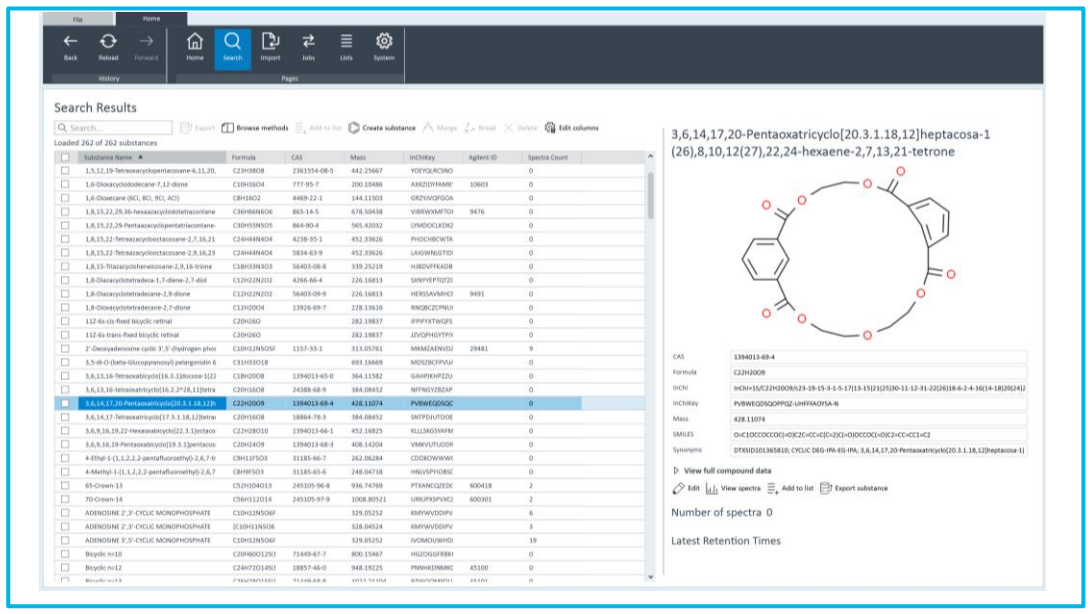

Figure 3. ChemVista Software Database Merged Content.

Explorer Processing MS and MS/MS Data

MassHunter Explorer 2.0 extracts both MS and MS/MS high-resolution mass spectra by RT, accurate mass and abundance. The gap filling option is turned off to better separate structural isomers. The MS/MS spectra are extracted by precursor mass (adducts), averaging of collision energies and with the deisotoping option on to simplify database searching. Results from the “Find and Align” step is shown below in Figure 4.

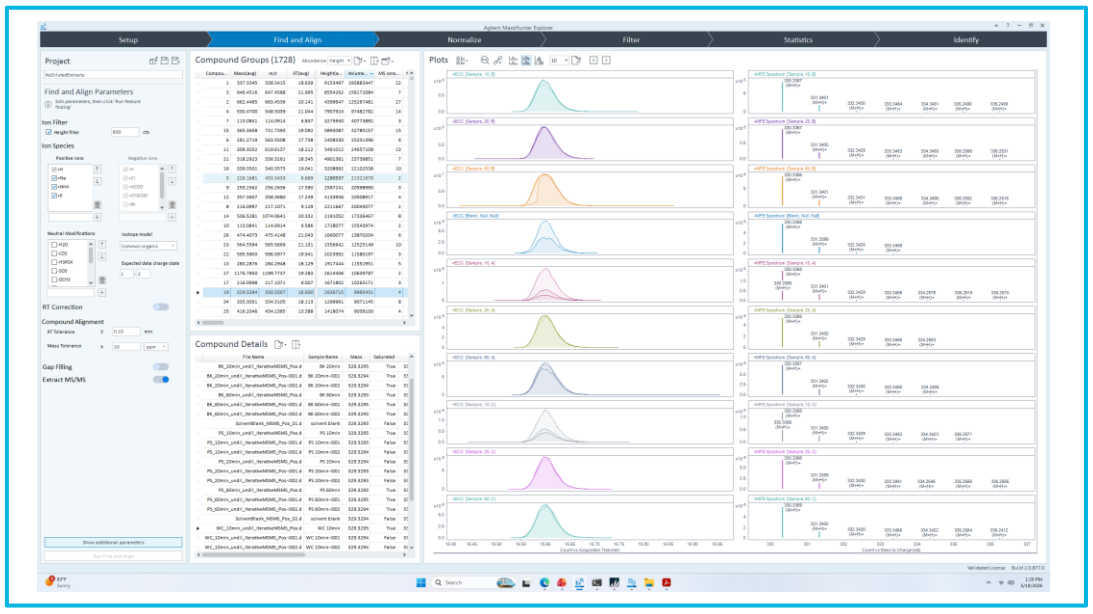

Figure 4. Results from “Find and Align” Explorer 2.0.

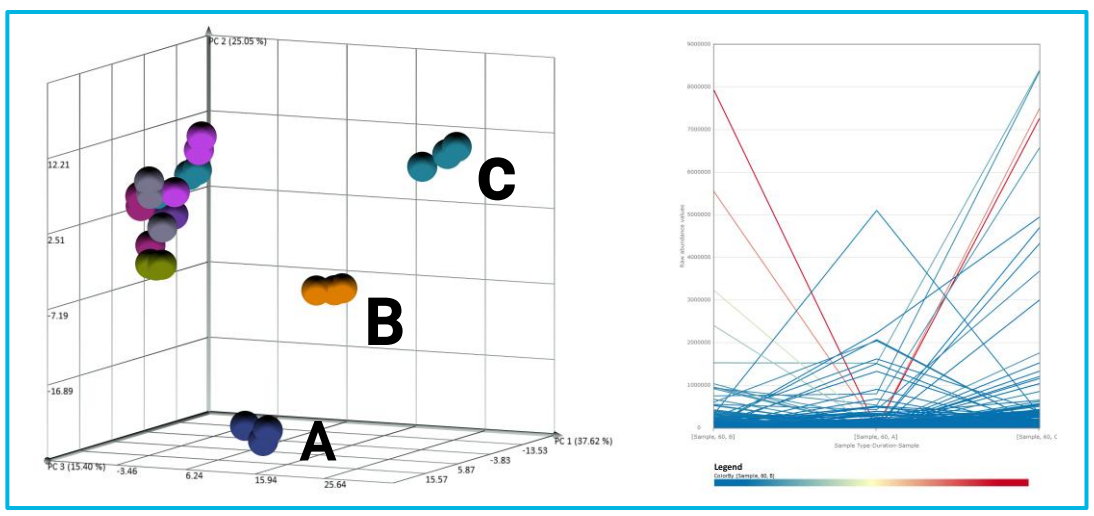

Figure 5. (Left) 3D PCA showing separation of extracts from samples A, B, C at 60 minutes but minor distinctions between samples at 10 and 20 minutes.
(Right) Fold change plot between samples A, B, and C.

Food Contact Material Extraction Conditions

Initial LC/MS analyses were performed from ethanol extracts of three vacuum-seal storage bags labeled as A, B and C that were heat at 70 °C for 10, 20 and 60 minutes. The initial extracts were diluted 10 and 100-fold to demonstrate the ability of the system to detect these food contact materials E&L compounds over wide concentration ranges. An ethanol sample handling blank was added to the samples to identify compounds from impurities in the mobile phases and the LC system.

Results and Discussion

Identify Unique Compounds in Extracts A, B and C

Explorer provides two means to identify E&L compounds that are unique to a specific vacuum seal bag. The first by using Volcano Plots comparing two samples at a time (Figure 6, left) comparing extracts A to B and comparing A to C. The second approach is the Unique Features function (Figure 6, right) showing 104 compounds are unique to Extract C, 17 Unique to Extract A and 11 are unique to Extract B.

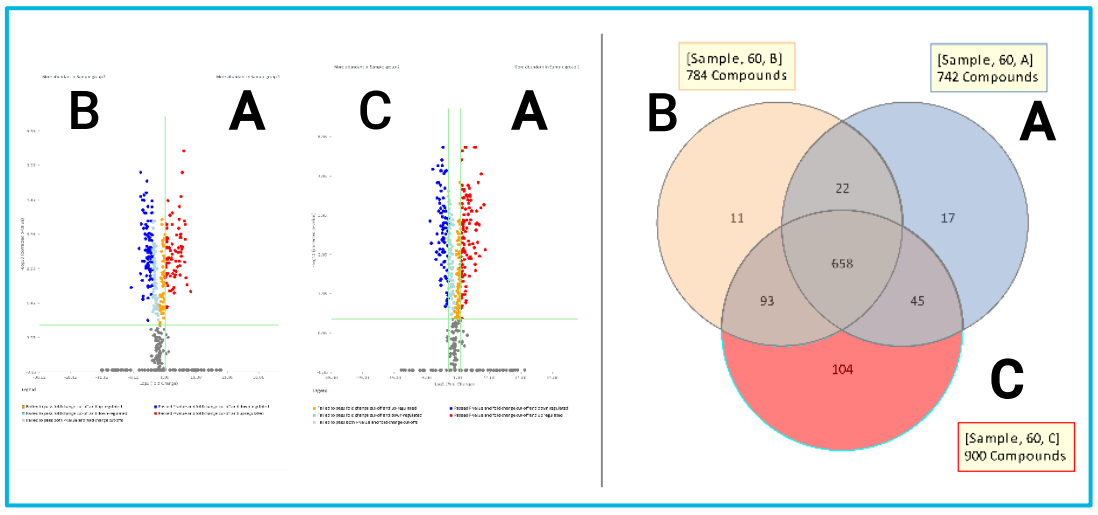

Figure 6. Volcano plots comparing extracts B to A and C to A (left) and unique features Venn diagram (right).

Cyclic Oligomers in Samples from Extract C

Sample C contains a series of cyclic oligomers $C_{19}H_{30}O_8$ to $C_{24}H_{24}O_{10}$ with retention times between 12.3 to 14.5 minutes with similar MS/MS spectra (Table 2). The Sirius software was used to confirm the formula of these compounds and predict the structures of these cyclic esters using the custom FCM database (Figure 7).

Table 2. Formulas for Cyclic Oligomers in Sample C.

Retention Time (min)	Neutral Mass	Formula
12.32	432.1996	$C_{20}H_{32}O_{10}$
12.32	416.2046	$C_{20}H_{32}O_9$
13.04	452.1683	$C_{22}H_{28}O_{10}$
13.30	452.1683	$C_{22}H_{28}O_{10}$
13.30	452.1683	$C_{22}H_{28}O_{10}$
13.40	416.2048	$C_{20}H_{32}O_9$
13.40	416.2046	$C_{20}H_{32}O_9$
13.80	422.1577	$C_{21}H_{26}O_9$
13.94	386.1941	$C_{19}H_{30}O_8$
14.05	422.1577	$C_{21}H_{26}O_9$
14.30	400.2097	$C_{20}H_{32}O_8$
14.30	436.1733	$C_{22}H_{28}O_9$
14.31	436.1733	$C_{22}H_{28}O_9$
14.32	472.1369	$C_{24}H_{24}O_{10}$

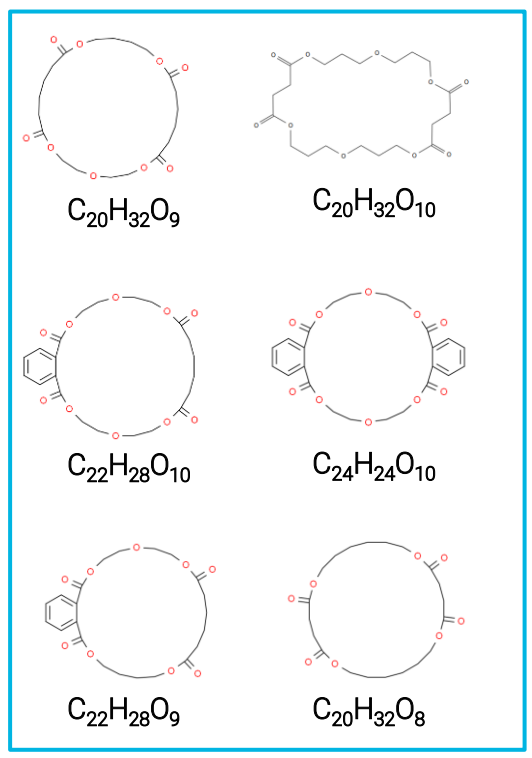

Figure 7. Proposed Cyclic Structures in Sample C.

Highest Abundant of Compounds by Sample

Table 3 lists the major compounds in each sample with Sample A cyclic nylons and amides, Sample B breakdown products of Irganox 1076; and Sample C) amides and cyclic esters. Compounds $C_{20}H_{32}O_8$, $C_{19}H_{30}O_9$, and $C_{19}H_{30}O_8$ have nearly identical MS/MS spectra and therefore their structure should be modifications of $C_{20}H_{32}O_9$.

Table 3. Formulas of Similar Cyclic Known/Unknowns

Compound Name	RT (min)	Neutral Mass	Formula
Palmitamide	17.59	255.2562	$C_{16}H_{33}NO$
Stearamide	18.129	283.2876	$C_{18}H_{37}NO$
2-Allyl-3-hydroxy-2methylsuccinic Acid 1-Ethyl Ester	9.007	216.0998	$C_{10}H_{16}O_5$
1,4,7,17, 20-Hexaoxycyclohexacosane-8,13,21,26-tetrone	12.32	432.1994	$C_{20}H_{32}O_{10}$
1,4,7,17,19-Pentaoxyacyclophentacosane-8,13,20,250tetrone	13.388	416.2046	$C_{20}H_{32}O_9$
2,4,6-tritert-butylphenol, Antioxidant TMOZ	17.36	262.2297	$C_{18}H_{30}O$
2,5,8,15,20-Benzophentaoxacyclotricosin-1,9,14,21-tetrone	14.324	436.1733	$C_{22}H_{28}O_9$
2,13-Dimethyl-1,4,12,15-tetraoxacyclodeocosane-5,11,16,22-tetrone	14.304	400.2095	$C_{20}H_{32}O_8$
Modification of $C_{20}H_{32}O_9$ (-CH_2)	12.944	402.1884	$C_{19}H_{30}O_9$
Modification of $C_{20}H_{32}O_9$ (-COH_2)	13.95	386.1936	$C_{19}H_{30}O_8$
Modification of $C_{22}H_{28}O_9$ (-COH_2)	13.808	422.1582	$C_{21}H_{26}O_9$

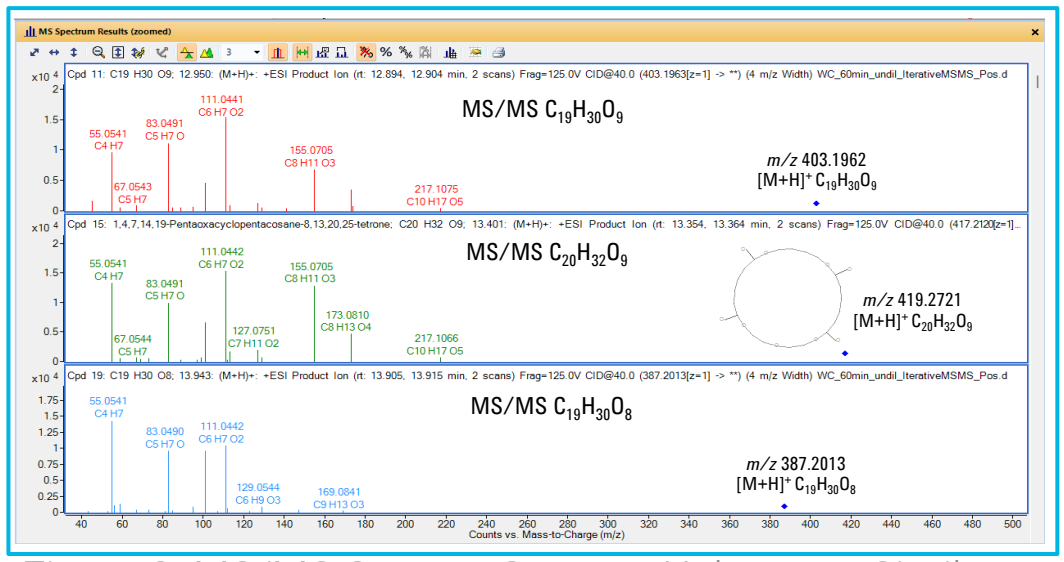

Figure 8. MS/MS Spectra Suggest Unknowns Similar

Conclusions

- Revident LC/Q-TOF provides high resolution mass spectral data needed for enhanced compound ID.
- MassHunter Explorer enables project-based nontargeted analysis linked with compound ID.
- ChemVista facilitates building custom application-focused databases usable with SIRIUS.
- SIRIUS MSMS provides means to utilize custom databases to help with known/unknowns analysis.

References

1. The FFCmigex database contains detailed information of more than 4,000 FCM and over 24,000 database entries at https://www.foodpackagingforum.org/fccmige
2. FCCdb is a created by the Food Packaging Forum Foundation (FPP) of compounds that are intentionally used food contact chemicals (FCC).

https://www.agilent.com/en/promotions/asms

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