

Applying non-targeted analysis workflows to the detection and identification of extractables and leachables in medical device polymers

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Overview

- Application of a single processing method with a novel software application - Insight Profiler, to identify E&L compounds in medical polymer materials.
- A simple screening workflow applied in Insight Profiler software enabled detection of E&L compounds in foam extracts extracted in isopropanol or water that were not detected in representative blanks.
- Application of SICRIT to the LC-DIA-MS/MS method extended the chemical space enabling detection of additional E&L compounds that were not detected using ESI.

1. Introduction

Extractables and leachables (E&L) from medical device polymers present toxicological risks during clinical use and regulatory frameworks such as ISO 10993 require chemical characterization to ensure patient safety. In this study, high-resolution LC-MS/MS was applied to the analysis of different polymer materials used in medical devices for sleep apnea, followed by automated data processing in a novel non-targeted analysis software platform, Insight Profiler.

2. Materials and Methods

Samples were prepared in five technical replicates from four different medical polymers (mattress extract, silicone foam, polyesterurethane and polyetherurethane) extracted in water or isopropanol for analysis by HRMS (LCMS-9050 Q-TOF mass spectrometer, Shimadzu Corporation). Samples were analysed in positive and negative ion mode.

LC Separation (cycle time 20 minutes)

- Shim-pack XR-ODS III (2.0 x 150 mm 2.2 µm); 40°C, flow rate 0.4 mL/min
- Binary gradient; water + 0.1 % formic acid and methanol

Electrospray Ionization (ESI)

- Temperature 300 °C; Voltage 4.5 kV (ESI +) / -3.0 kV (ESI -)

Soft Ionization by Chemical Reaction in Transfer (SICRIT)

- Temperature 500 °C; Voltage 1.8 kV; Frequency 45 kHz

LC-MS/MS Mass Spectrometry Detection (cycle time 1.125 sec)

- TOF MS survey scan (m/z 70-1250; 100 msec)
- 41 DIA-MS/MS mass scans (m/z 40-1250; 25msec; precursor isolation 20 Da for m/z 70-500 and precursor isolation 35 Da for m/z 500-1250)
- Collision energy spread 5-55V; External mass calibration

Data Processing

- Data processing in Insight Profiler software considered a feature detection, alignment, statistical analysis and compound identification in a single method.
- Compound screening included the ELSIE chemical list hosted within EPA's CompTox Chemicals Dashboard, FDA-CLAP and NIST 2023.
- Statistical comparisons were made between samples and blanks considering consistent detection of features in 4/5 replicates for Volcano Plot analysis to find potential E&L compounds in samples. Data filtering and analysis were performed automatically in the method.

2.1 Automated processing in Insight Profiler

Insight Profiler software has been developed to automate complex data processing in non-targeted analysis applications including E&L under a single processing method cascade.

Feature Detection and Alignment
Detects and aligns all ion signals that behave as a peak.

Statistics and filters
Applied to find ion signals of significance and to remove ions of high variance.

Compound identification and batch processing
Using large scale screening lists and multiple libraries to identify ion signals of interest.

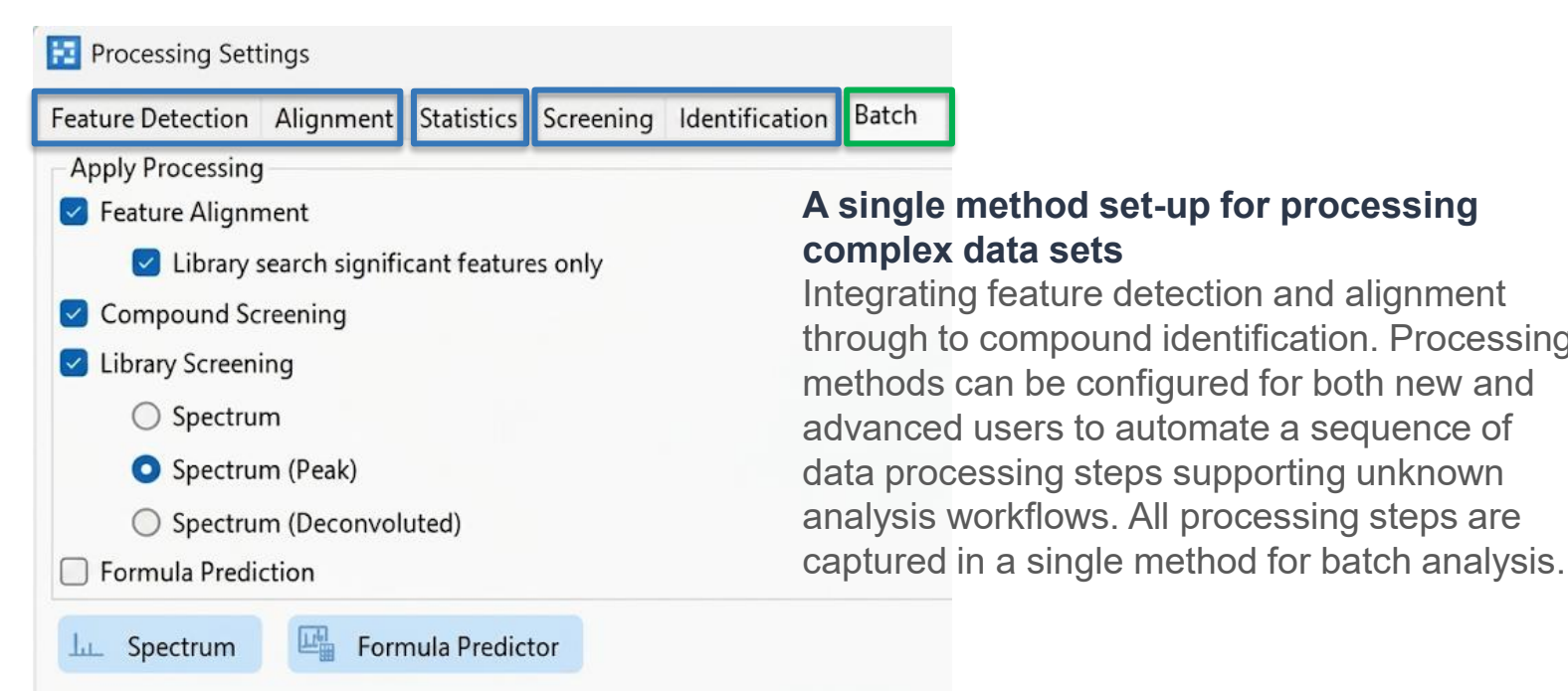


Figure 1. The Insight Profiler processing application method editor, designed to create a single workflow for feature detection of unknowns to compound identification.

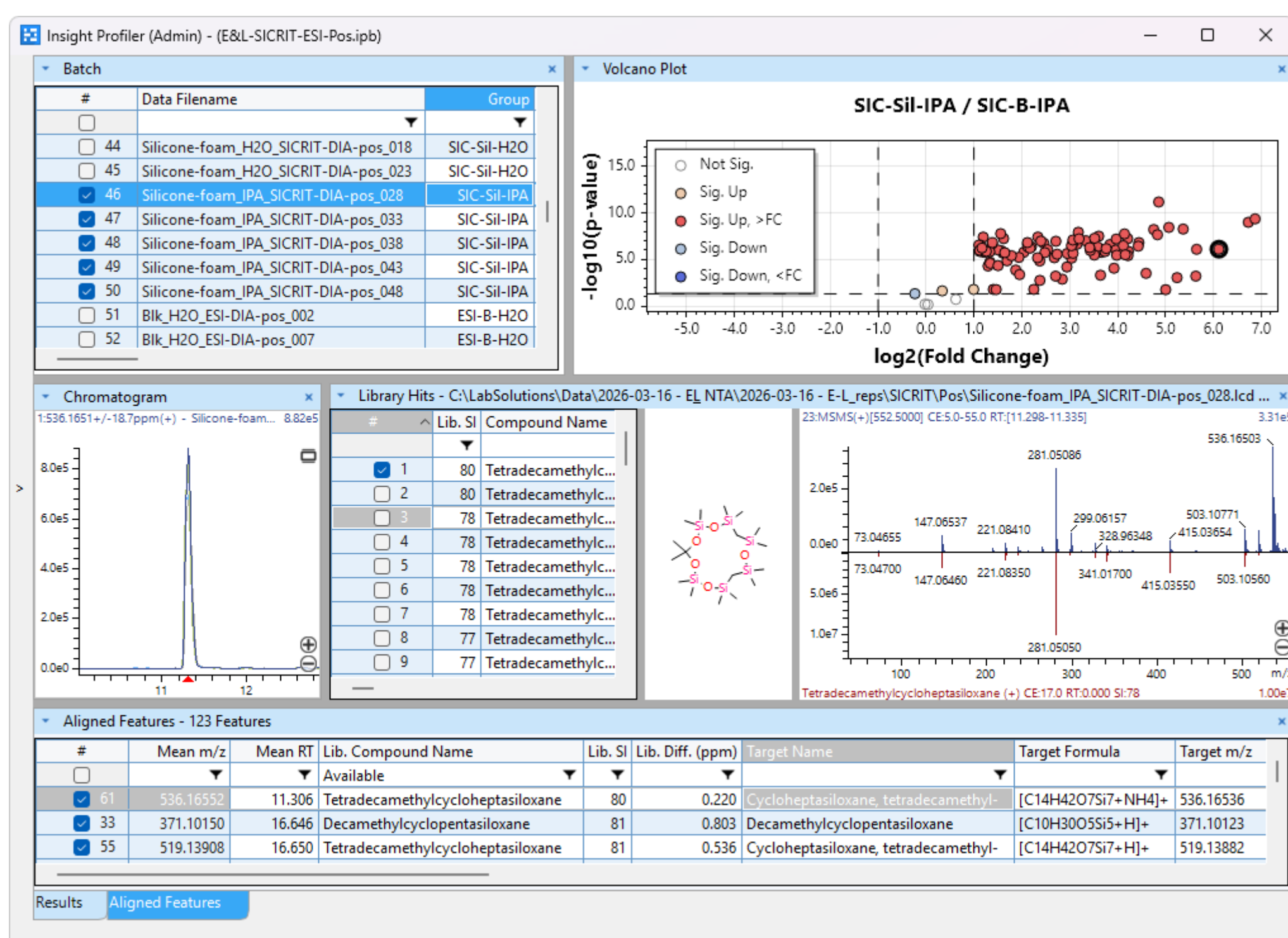


Figure 2. Insight Profiler was applied to process data from foam extracts and blanks following non-targeted analysis (LC-DIA-MS/MS). Interactive and intuitive data review enables analysis of E&L screening targets in the samples. Volcano plot analysis highlights features present in samples relative to the blank extraction. Chromatogram and library identification are linked with results tables and plots to help data interpretation, and different comparisons can be made without re-processing data. The example highlights Tetradecamethylcycloheptasiloxane which was best detected using SICRIT in the silicone foam extract.

3. Results

3.1 Detection of E&Ls in medical foam extracts by ESI

ISO 10993-18 is part of the ISO 10993 series for biological evaluation of medical devices. It provides a framework for chemical characterization of materials to identify substances that could leach from a device during clinical use. Given this regulatory framework, the objective is to assess biological risk and consider the impact of potential patient exposure by identifying E&L components in medical devices. LabSolutions Insight Profiler software was used to screen for E&L compounds in medical foam extracts which were largely ionized by ESI (Figure 3).

Mattress extract

1,4,7-Trioxacyclotridecane-8,13-dione
1,6-Dioxacyclododecane-7,12-dione
2,2'-Methylene-bis(6-tert-butyl-4-methylphenol)
2,6-Di-tert-butyl-4-methoxyphenol
2-Hydroxyethyl benzoate
3,5-Di-tert-butyl-4-hydroxybenzaldehyde
7,9-Di-tert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione
Acetyl tributyl citrate
Acridine
Benzaldehyde
Bis(1,2,2,6,6-pentamethyl-4-piperidyl) sebacate
Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate
Bis(2-ethylhexyl) adipate
Bis(p,p'-tert-octylphenyl)amine
Caprolactam
Dibutyl adipate
Dipropyl adipate
Erucaamide
Irganox 1098
Irganox 565
N,N-Dimethylaniline
N-Benzyl-N,N-dimethyl-1-tetradecanaminium cation
N,N'-Diacetylenediamine
N,N'-Dibutylformamide
Oleamide
Poly THF n4-12
Tetradecamethylcycloheptasiloxane
Trans-1,2-Cyclohexanediol

Polyesterurethane

1,3-Bis(2-hydroxyethoxy)benzene
1,4,7-Trioxacyclotridecane-8,13-dione
1-Dodecyl-2-pyrrolidinone
3,5-Di-tert-butyl-4-hydroxybenzaldehyde
Docosanamide
Elaidic Acid
Erucaamide
N,N-Bis(2-hydroxyethyl)dodecanamide
N-Lauryldiethanolamine
Octadecanamine
Octyl decyl phthalate
Stearamide
Stearoyl Ethanolamide
Tetradecyltrimethylammonium cation

Silicone foam

1,4,7-Trioxacyclotridecane-8,13-dione
2,3-Dihydroxypropyl octadecanoate
Acetyl tributyl citrate
Bis(2-ethylhexyl) adipate
Bis-(3,4-dimethylidibenzylideneesorbitol)
Bis(p,p'-tert-octylphenyl)amine
Decamethylcyclopentasiloxane
Diisodecyl phthalate
Di-n-octyl phthalate
Erucaamide
Hexamethylcyclotrisiloxane
N-Benzyl-N,N-dimethyl-1-tetradecanaminium cation
N-Lauryldiethanolamine
Octamethylcyclotetrasiloxane
Oleamide
Stearamide
Tetradecamethylcycloheptasiloxane
Tris-(2,4-di-tert-butylphenyl) phosphate

Polyetherurethane

3,5-Di-tert-butyl-4-hydroxybenzaldehyde
Benzaldehyde
Bis(p,p'-tert-octylphenyl)amine
Dibutylphthalate
Erucaamide
N,N,N'-Trimethyl-n'-(2-hydroxyethyl)bis(2-aminoethyl) ether
N,N-Dibutylaniline
N-Butyldiethanolamine
N-Lauryldiethanolamine
Tetradecamethylcycloheptasiloxane

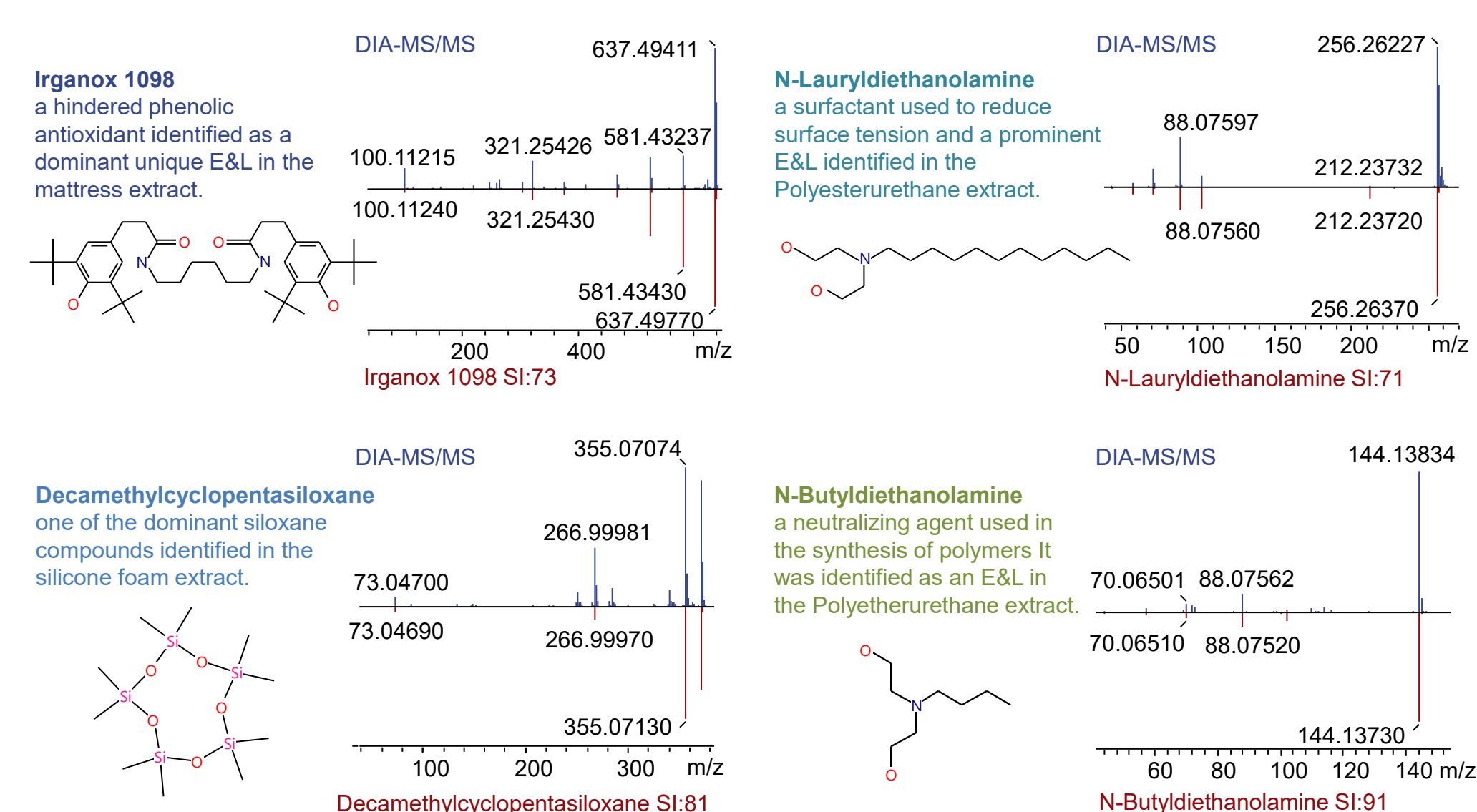


Figure 3. E&L compounds identified by MS/MS library matching in the medical foam extracts by LC-MS/MS with ESI. Compound screening included ELSIE, FDA-CLAP and NIST 2023. Examples of MS/MS library match for dominant E&Ls identified in each extract are highlighted.

3.2 Application of SICRIT in E&L analysis

Analytical strategies to identify E&L components typically include HRMS LC-MS/MS for semi-volatile/non-volatile organic compounds and GCMS for volatiles/SVOCs. To explore if SICRIT could extend the chemical space for LC-MS/MS and reduce complexity in data acquisition and processing, samples were analysed using both ESI and SICRIT and data were processed together for comparison. Figure 4 highlights examples of E&L compounds identified in the mattress extract (IPA) that were better detected using SICRIT compared to ESI.

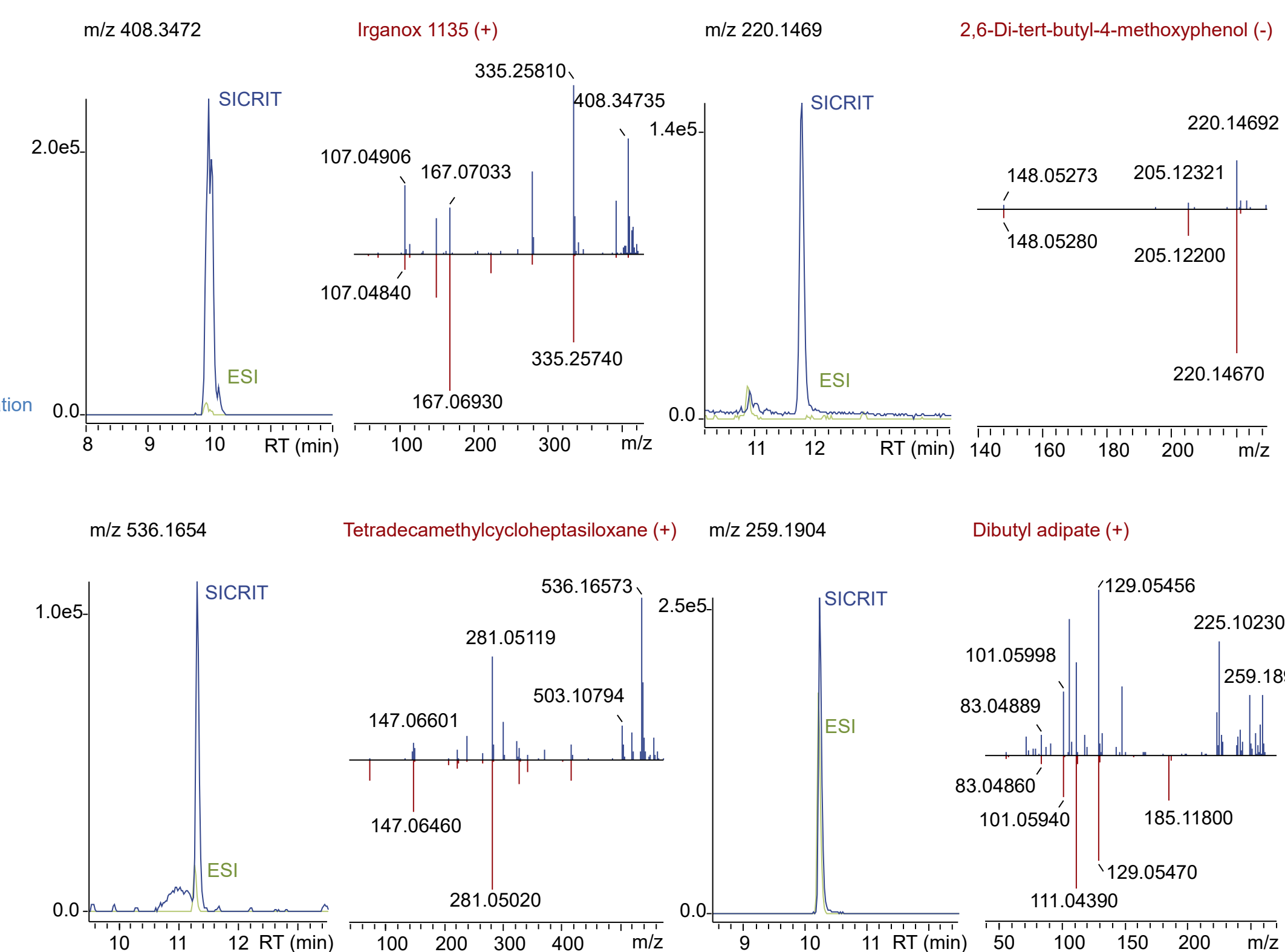


Figure 4. Chromatograms and MS/MS spectra for E&L compounds identified in the mattress extract (IPA) that were better detected using SICRIT compared to ESI.

4. Conclusions

- The inherent challenges in reporting E&L reflect both the complexity of the chemical space, and complexity of data analysis. To simplify a screening workflow for E&L analysis, two complementary ionization techniques for LC-MS/MS (ESI and SICRIT) have been applied to the analysis of medical foam extracts and a software application able to automatically process all data with a single method has been developed.
- Compound screening included the ELSIE chemical list hosted within EPA's CompTox Chemicals Dashboard, FDA-CLAP and NIST 2023 and revealed several E&L compounds identified in the foam extracts.
- Insight Profiler streamlines the data analysis workflow for E&L analysis.

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