Designing an Extractables and Leachables Study

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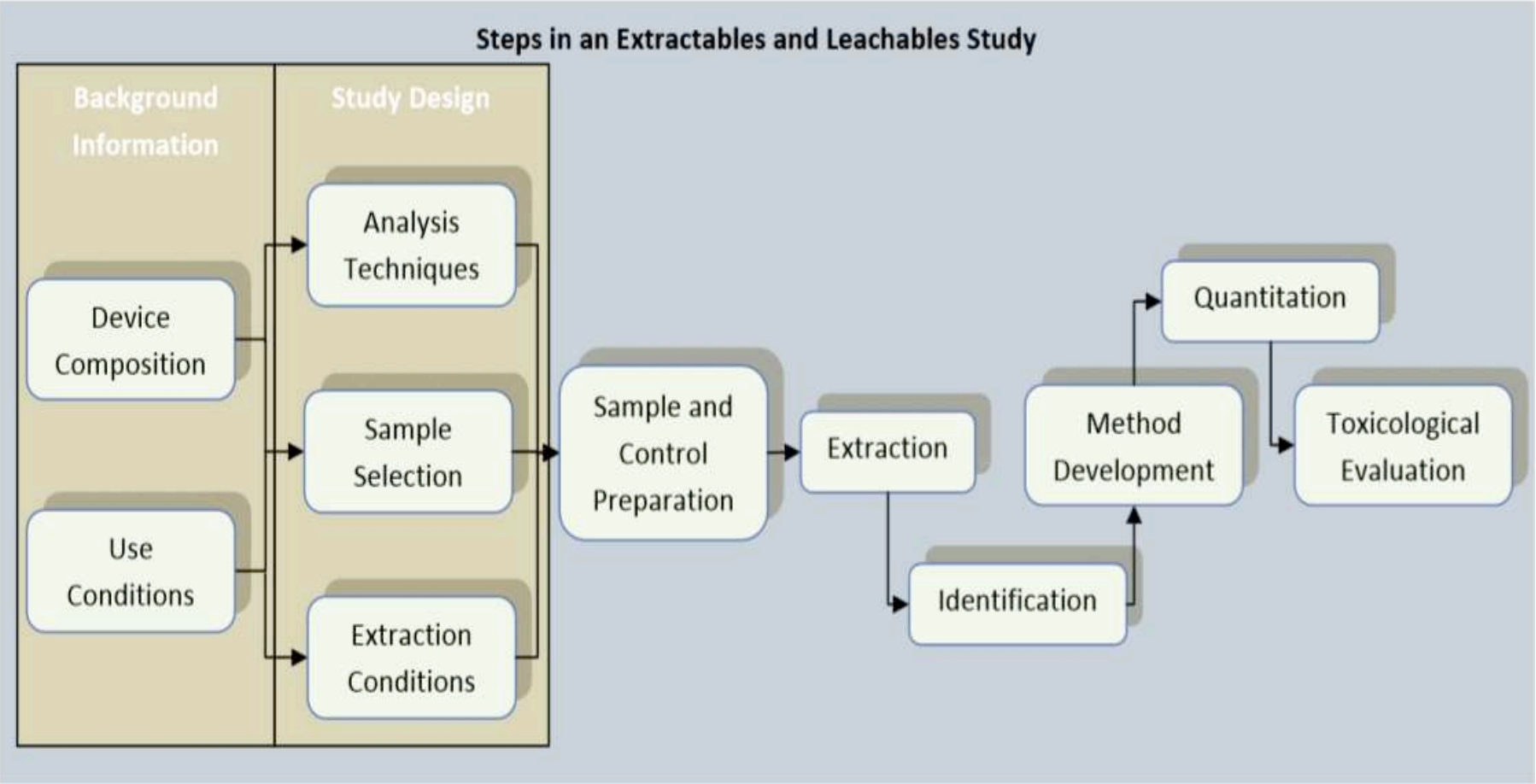
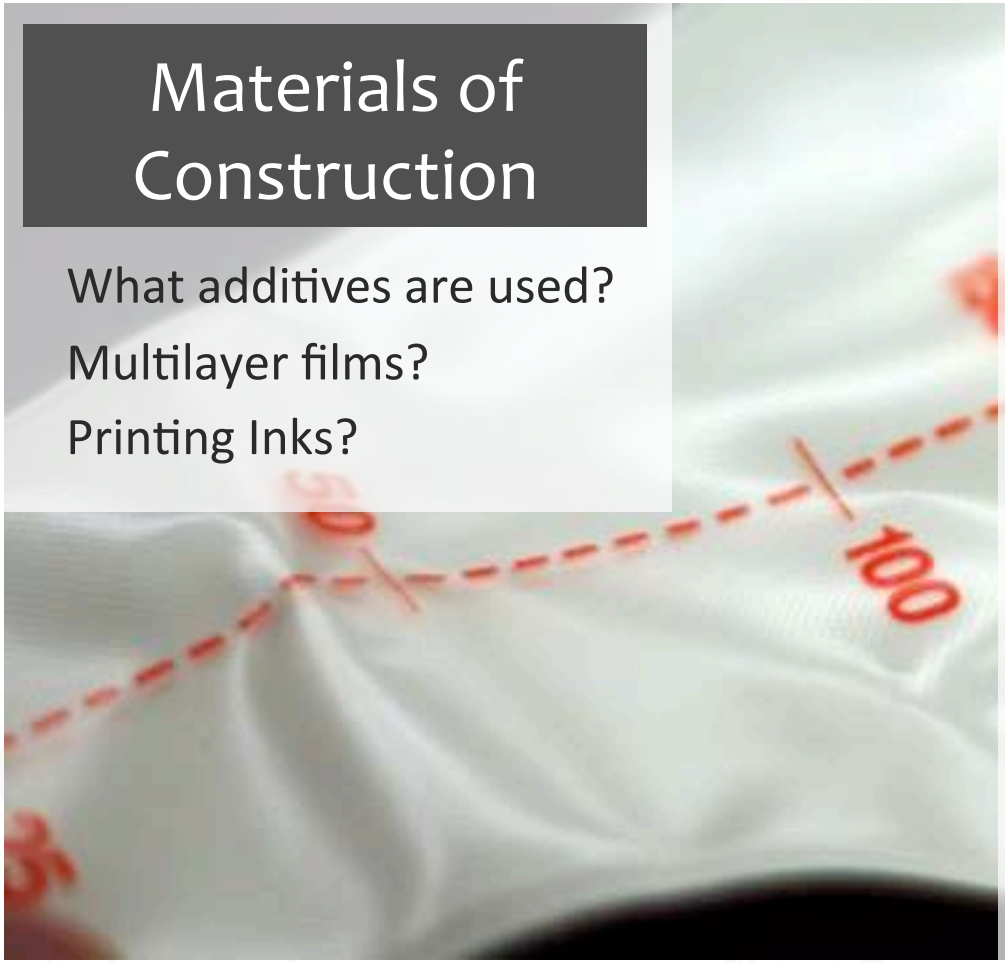
Overview


Steps in an Extractables and Leachables Study
Background Information
Study Design
Device Composition
Use Conditions
Analysis Techniques
Sample Selection
Extraction Conditions
Sample and Control Preparation
Extraction
Identification
Method Development
Quantitation
Toxicological Evaluation

Background Information



Materials of Construction

What additives are used?

Multilayer films?

Printing Inks?

Finished Packaging

Which surfaces does the product contact?

Are there interactions between components?

Is there opportunity for non-product contact components to migrate?

Are there any processing aids used?

Use Conditions

How will it be used?

How should it be extracted?

Extractables

challenge the use condition

- Temperature
- Solvent Strength
- Time

Leachables

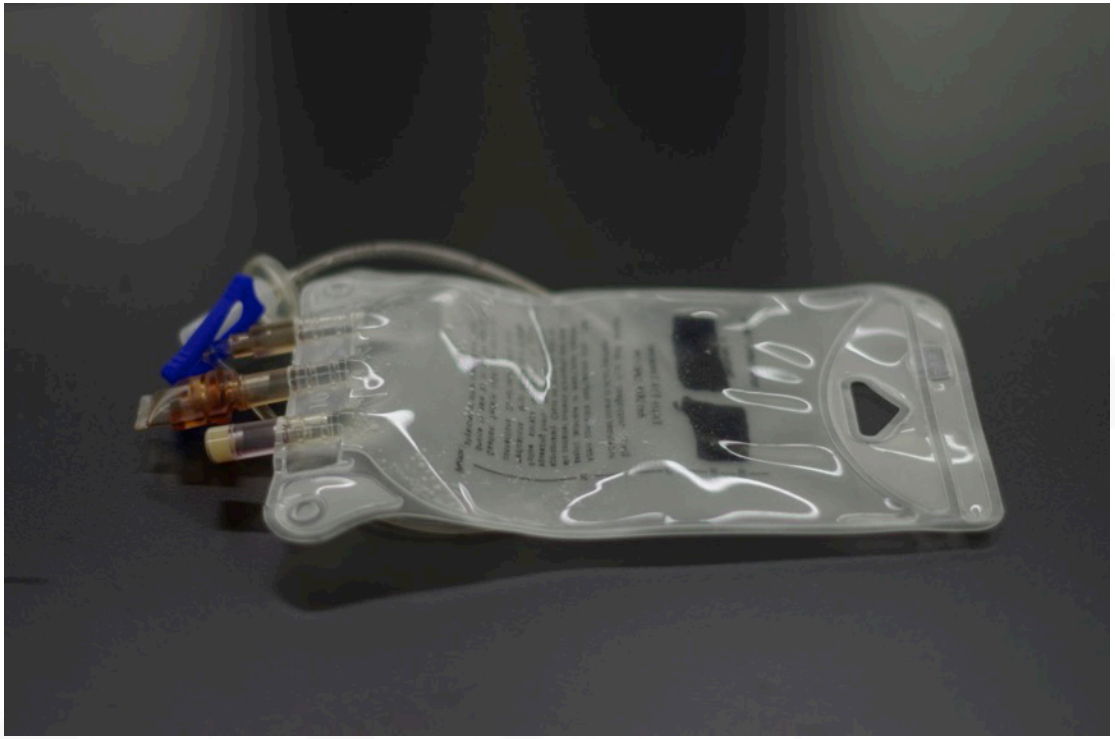
mimic the <u>most stringent</u> use condition

Extraction Strategies

Cut and Cover Extraction

- Simple systems
- Irregularly shaped
- Articles requiring two-sided extraction
- Very large containers

Extraction Strategies



Bags

Small containers

Tubing

Non-permeable

Printed containers

Full Fill Extraction

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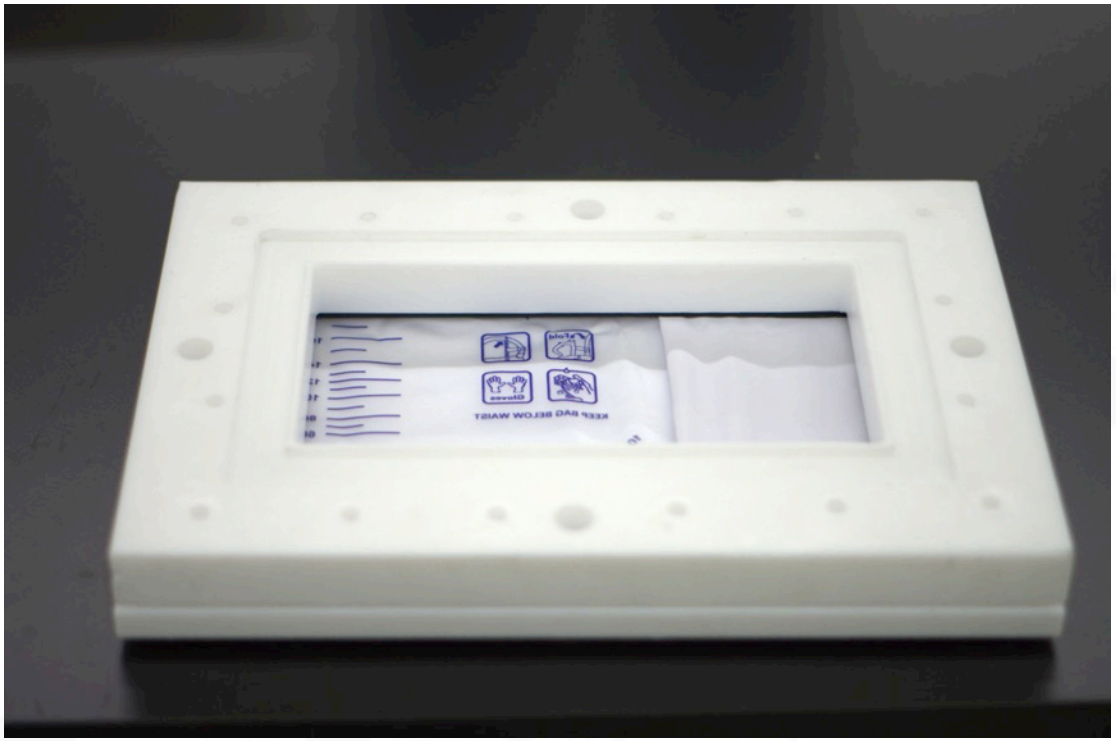
Extraction Strategies



- Multi-layer Printed materials
- Coated materials
- Product contacts one side

One-Sided Extraction

Extraction Strategies

Tubing

Complex systems

In-Line filters

Connectors

Flow Through Extraction

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Extraction Strategies

Direct analysis of the entire article

Very high sensitivity

No risk of volatiles loss

Large Volume Dynamic Headspace

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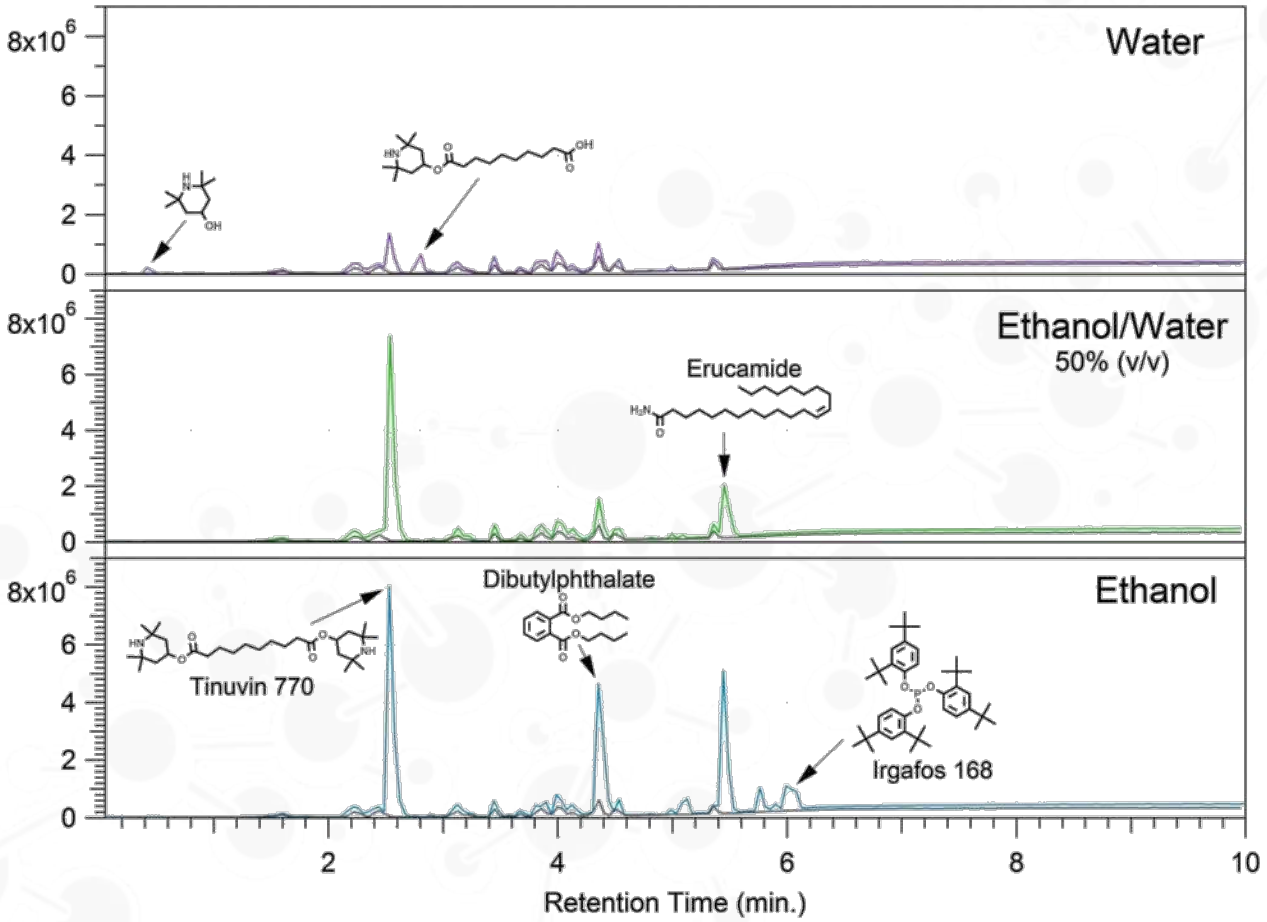
Extraction Solvent

From the background information provided for a container closure system the probable extractables were:

Expected Extractable	Type	Log P	Boiling point
Erucamide	Hydrophobic	8.8	474 °C
Linear Alkanes	Hydrophobic	8.859	250-400 °C
Dibutylphthalate	Hydrophobic	4.72	340 °C
Dimethoxyethane	Volatile	-0.2	85 °C
Irganox 1010	Non-volatile	23	N/A
Irgafos 168	Non-volatile	15.5	N/A
Tinuvin 770	Basic	6.3	N/A
Stearic acid	Acidic	8.23	361 °C
Sodium benzenesulfonate	Anionic	N/A	N/A

Effect of Solvent Polarity



Agilent 1290 Infinity UHPLC; Agilent 6520 QTOF-MS
Column: Agilent Zorbax Eclipse Plus C8; 1.8 µm, 2.1×50 mm
Electrospray Ionization (ESI); Polarity: positive

Extract Preparation

Example:

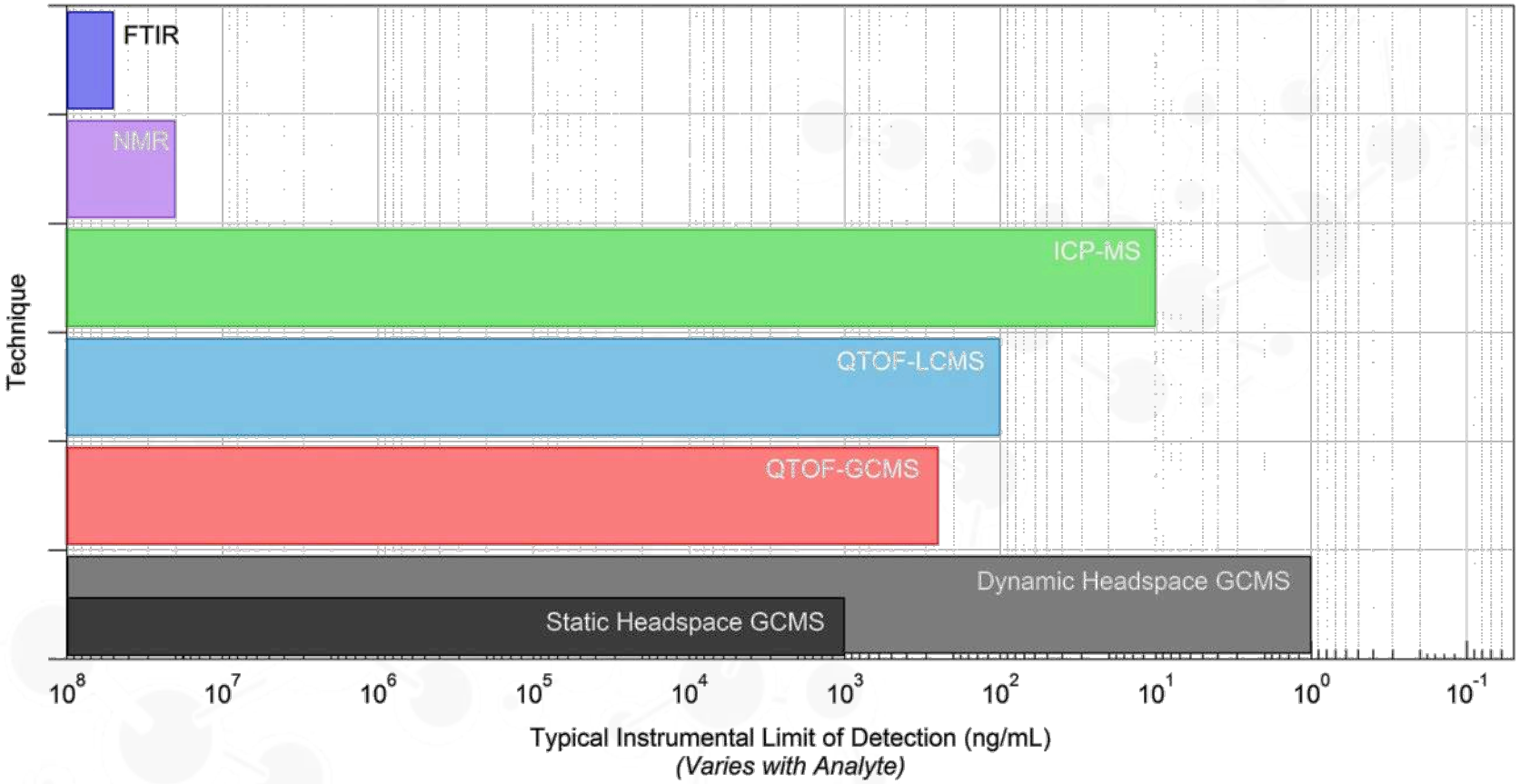
- 250 mL per bag
- Worst case 3 bags per day
- Product contact surface area 310 cm^2
- Safety concern threshold (SCT) = 0.15µg/day

$$AET(\mu g/bag) = 0.15\ \mu g/day\ /3\ bags/day = 0.05 \mu g/bag$$

$$Extract\ Vol.\ (mL) = 310\ cm\uparrow 2\ /6\ cm\uparrow 2\ /mL = 52\ mL$$

$$LOD = 0.05\ \mu g/bag\ /52\ mL/bag \approx 1\ ng/mL$$

Qualitative Analysis



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Concentration of Extracts

Extractables & Leachables can be *lost* during concentration

Loss depends on

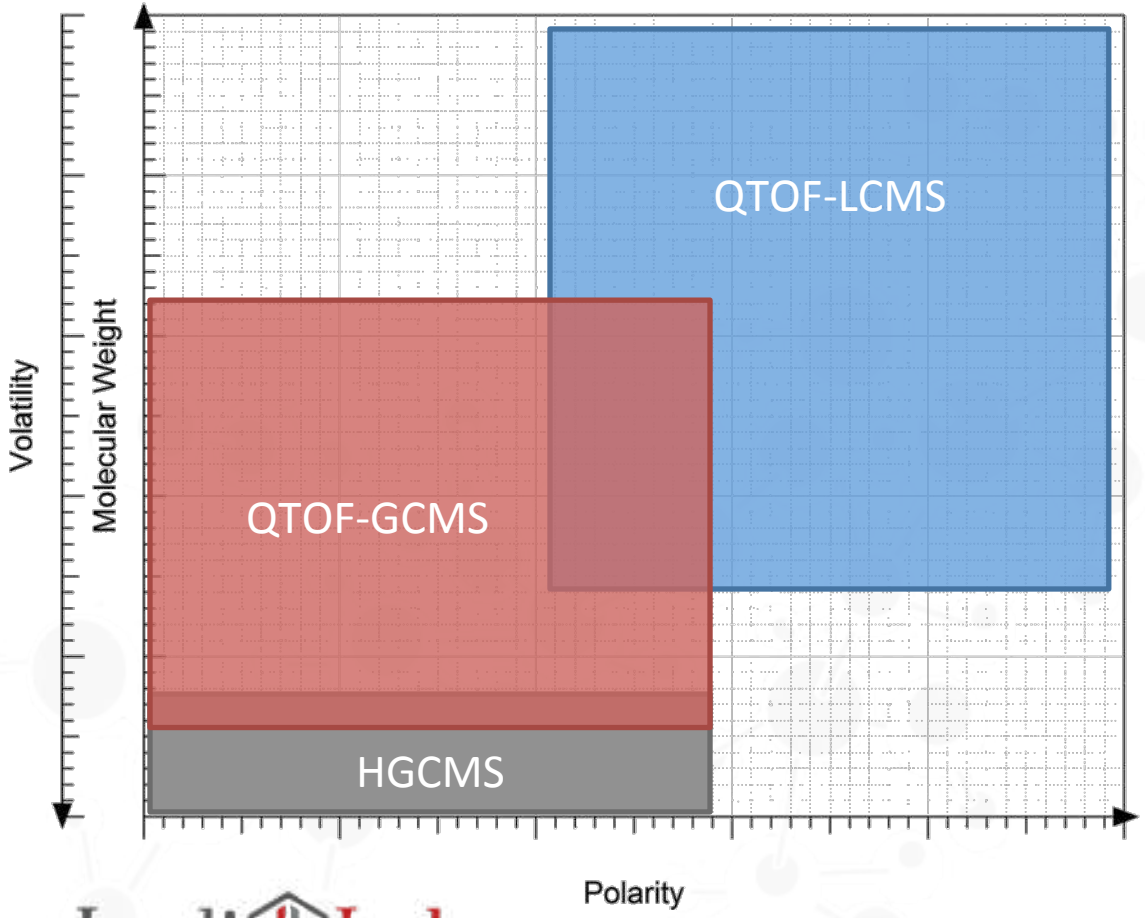
- Volatility of the analyte(s)
- Extract handling

Best Practices

- Mild conditions
- Method validation
- Headspace analysis

Qualitative Analysis

No universal analytical technique exists for E&L analysis



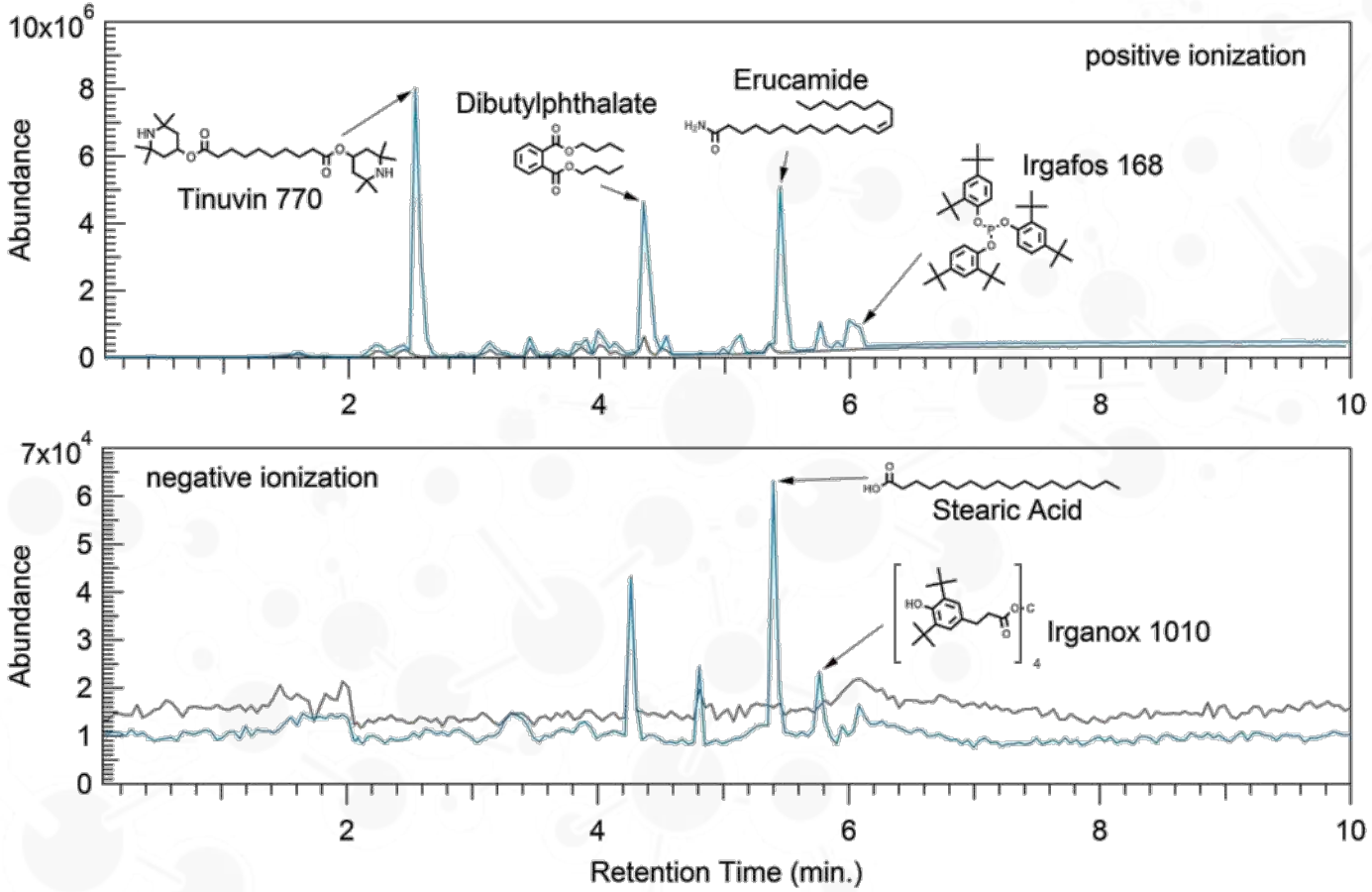
- Headspace GCMS
  - Volatiles
- QTOF-GCMS
  - Volatiles
  - Semi-volatiles
  - Non-polar analytes
- QTOF-LCMS
  - Polar/ionizable
- ICP-MS
  - Metals

Extraction Conditions

--Ethanol Extract--

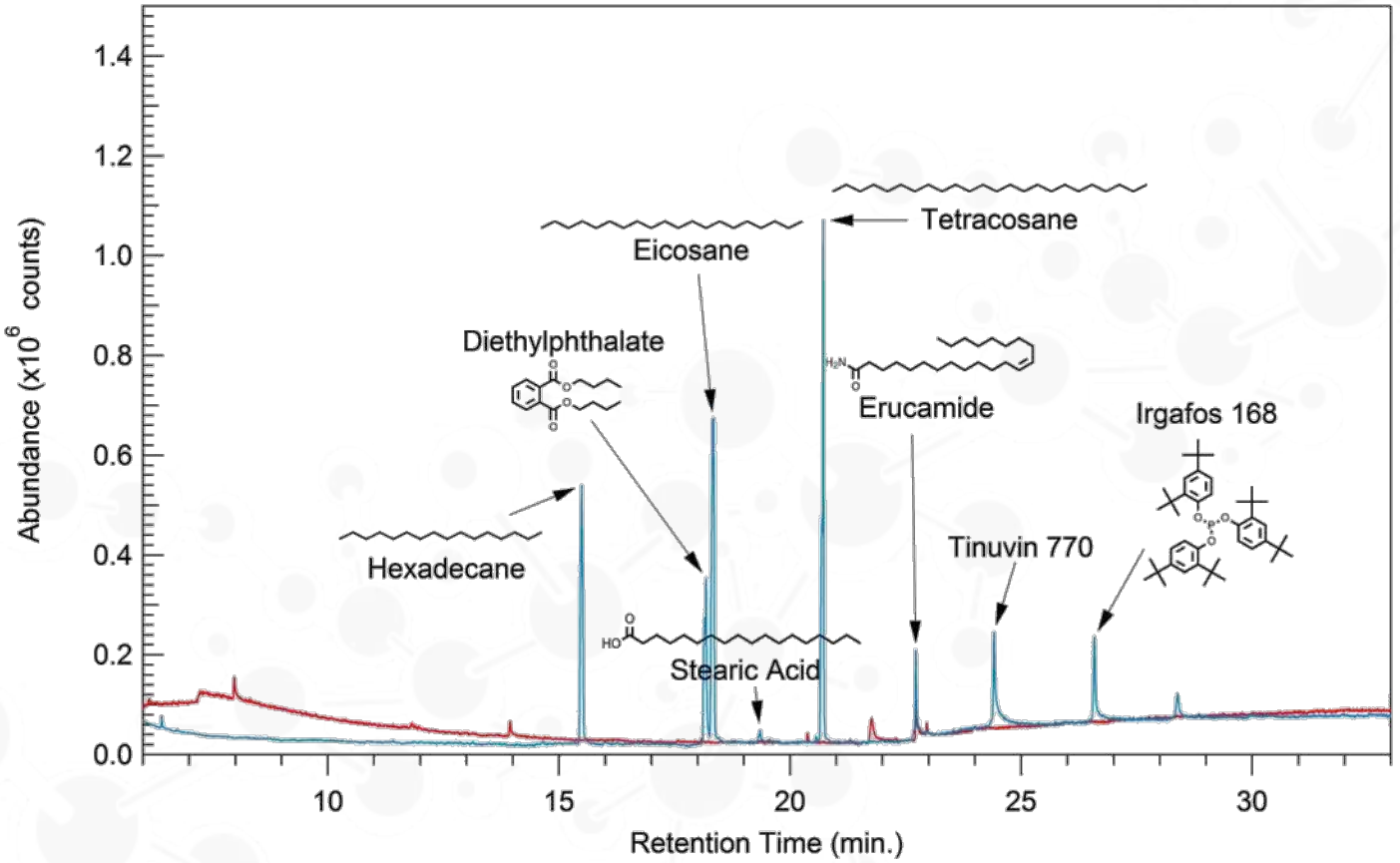
Expected Extractables	Type	Log P	Boiling point
Erucamide	Hydrophobic	8.8	474 °C
Linear Alkanes	Hydrophobic	8.859	250-400 °C
Dibutylphthalate	Hydrophobic	4.72	340 °C
Dimethoxyethane	Volatile	-0.2	85 °C
Irganox 1010	Non-volatile	23	N/A
Irgafos 168	Non-volatile	15.5	N/A
Tinuvin 770	Basic	6.3	N/A
Stearic acid	Acidic	8.23	361 °C
Sodium benzenesulfonate	Anionic	N/A	N/A

Qualitative Analysis



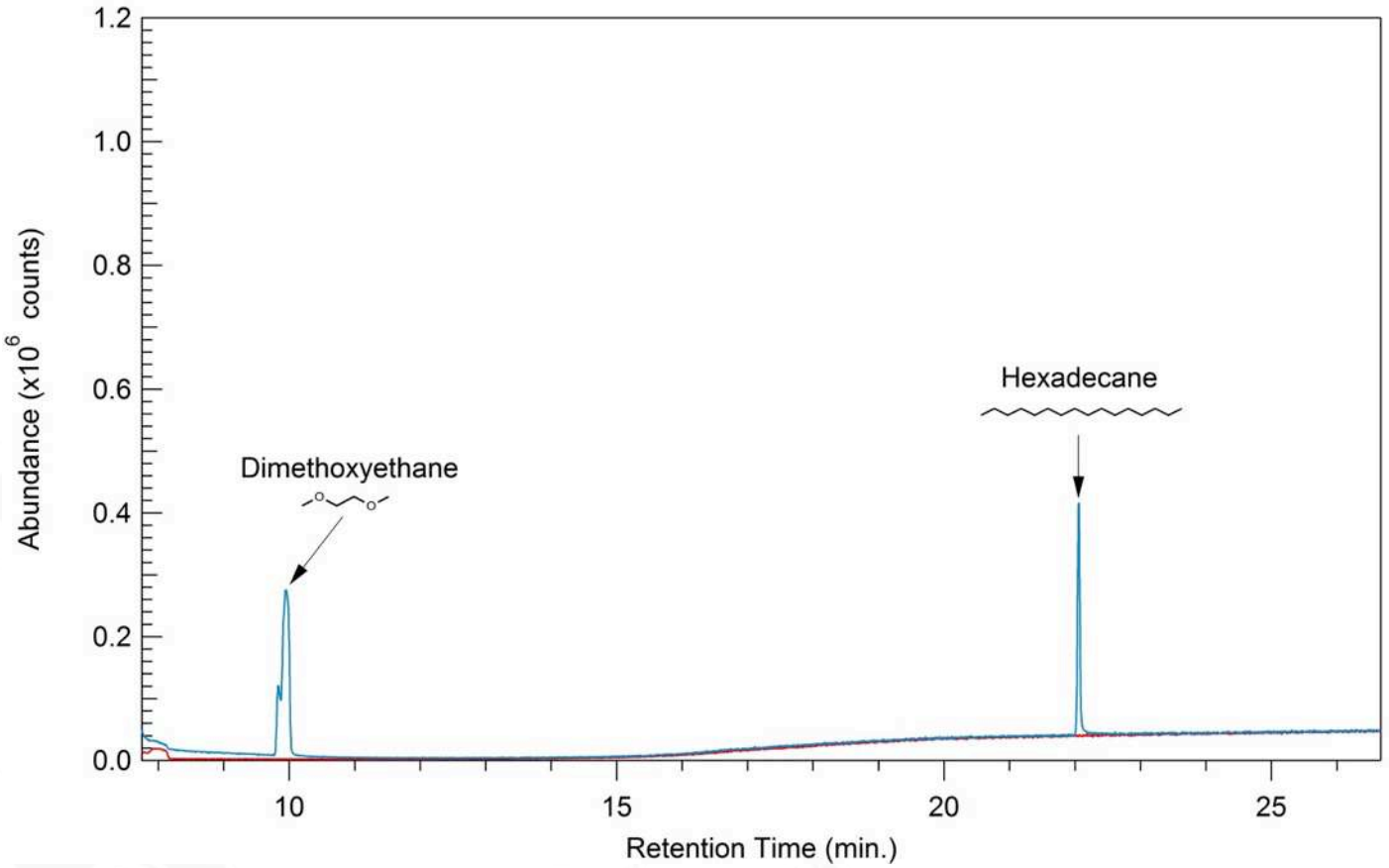
Agilent 1290 Infinity UHPLC; Agilent 6520 QTOF-MS
Column: Agilent Zorbax Eclipse Plus C8; 1.8 µm, 2.1×50 mm
Electrospray Ionization (ESI)

Qualitative Analysis



Agilent 7890B GC; Agilent 7200 QTOF-MS
Column: DB-5MS UI; 0.25 mm × 30 m, 0.25 µm
Electron Impact Ionization

Qualitative Analysis



Agilent 6890 GC; Agilent 5973 inert MSD
Electron Impact Ionization

Qualitative Analysis

Technique	Analyte	Boiling Point (°C)
HGCMS	Dimethoxyethane	85°C
	Hexadecane	286°C
QTOF-GCMS	Linear Alkanes	286-400°C
QTOF-LCMS	Dibutylphthalate	340°C
	Tinuvin 770	>350°C
	Irgafos 168	N.A.
	Stearic Acid	361°C
	Erucylamide	474°C
	Irganox 1010	Non-Volatile

Identification of Unknowns

Database Searches

Commercial Databases (NIST, Wiley)

Jordi Proprietary Additive and Oligomer Databases

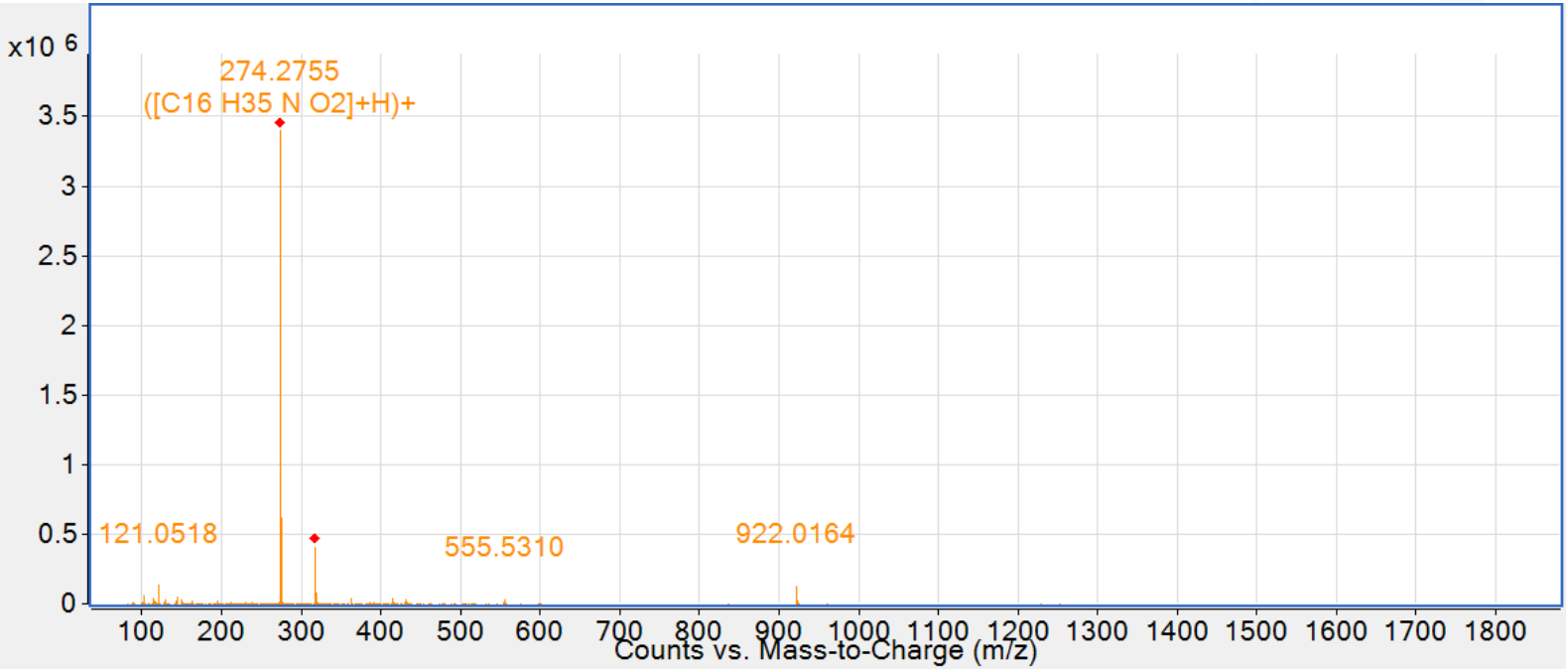
QTOF-GC / QTOF-LC

Molecular Formula Generation (MFG)

MS/MS for QTOF -LCMS

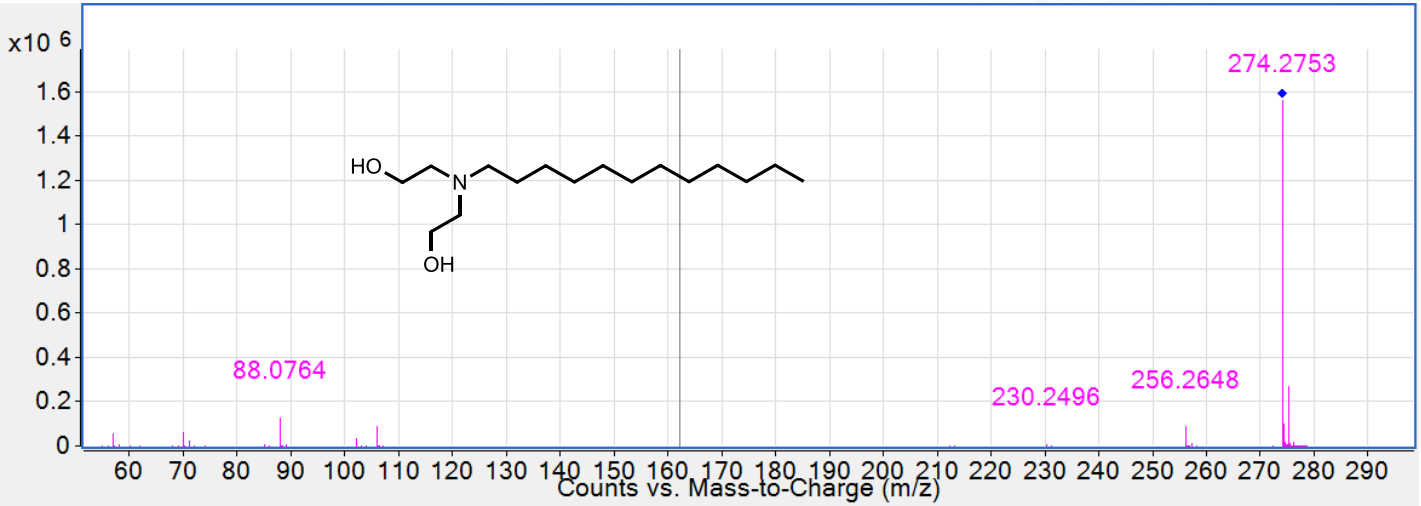
CI for QTOF-GCMS

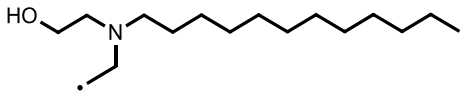
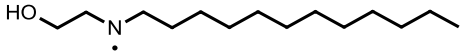
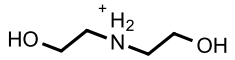
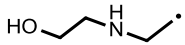
Identification of Unknowns



m/z	Best Match	Species	Mass	Score (MFG)	Diff. (ppm)	DBE
274.2731	C_{16} H_{35} N O_2	[M+H]+	273.2660	94.66	2.73	0

Identification of Unknowns



Fragment Ion	Best Match	Score	Possible Structure
256.2648	$[C_{16}H_{34}NO]+$	97.5	
230.2496	$[C_{14}H_{32}NO]+$	84.16	
106.0869	$[C_4H_{12}NO_2]+$	99.07	
88.0764	$[C_4H_{10}NO]+$	99.09	

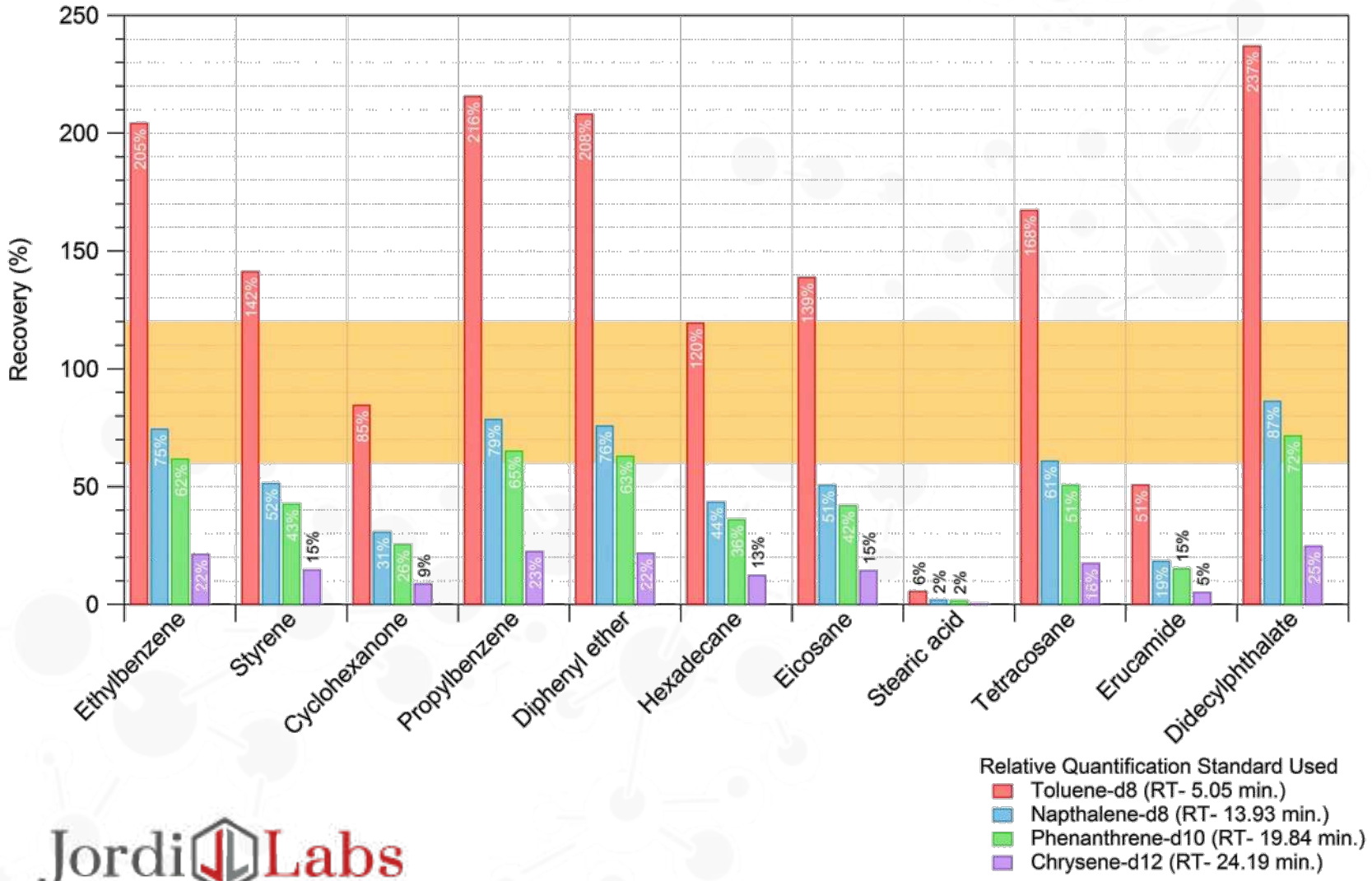
Quantitative Strategies

Relative Quantitation

- Quantification of compounds observed is performed against surrogate standards
- Accuracy depends on the surrogate standard used

Estimated Analyte Conc.= Observed Analyte Peak Area/Surrogate Peak Area ×Surrogate Conc.

Quantitative Strategies



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Quantitative Strategies

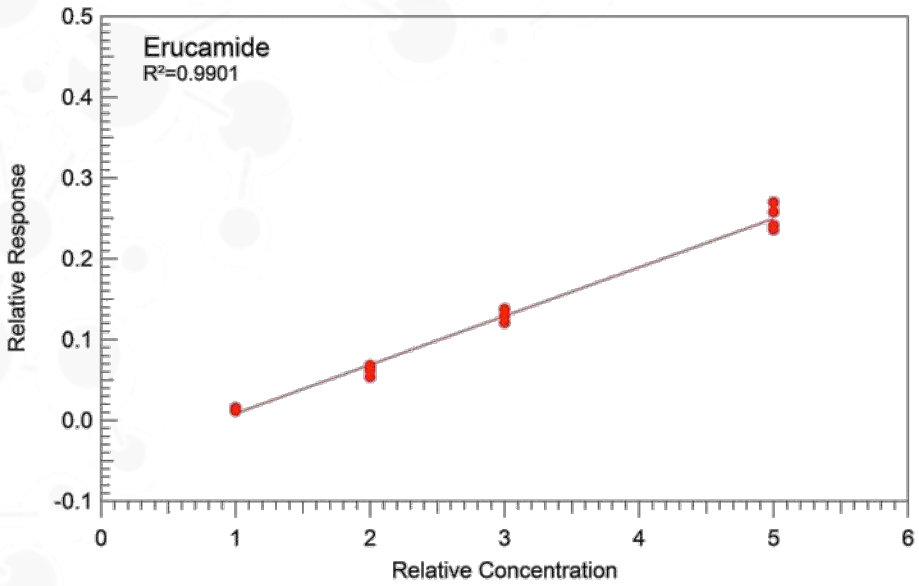
Formal Quantitation

Confirmed compounds are quantified against an analytical standard at a series of concentrations

Methodologies:

- External Standardization
- Standard Addition

Requires high purity analytical standards



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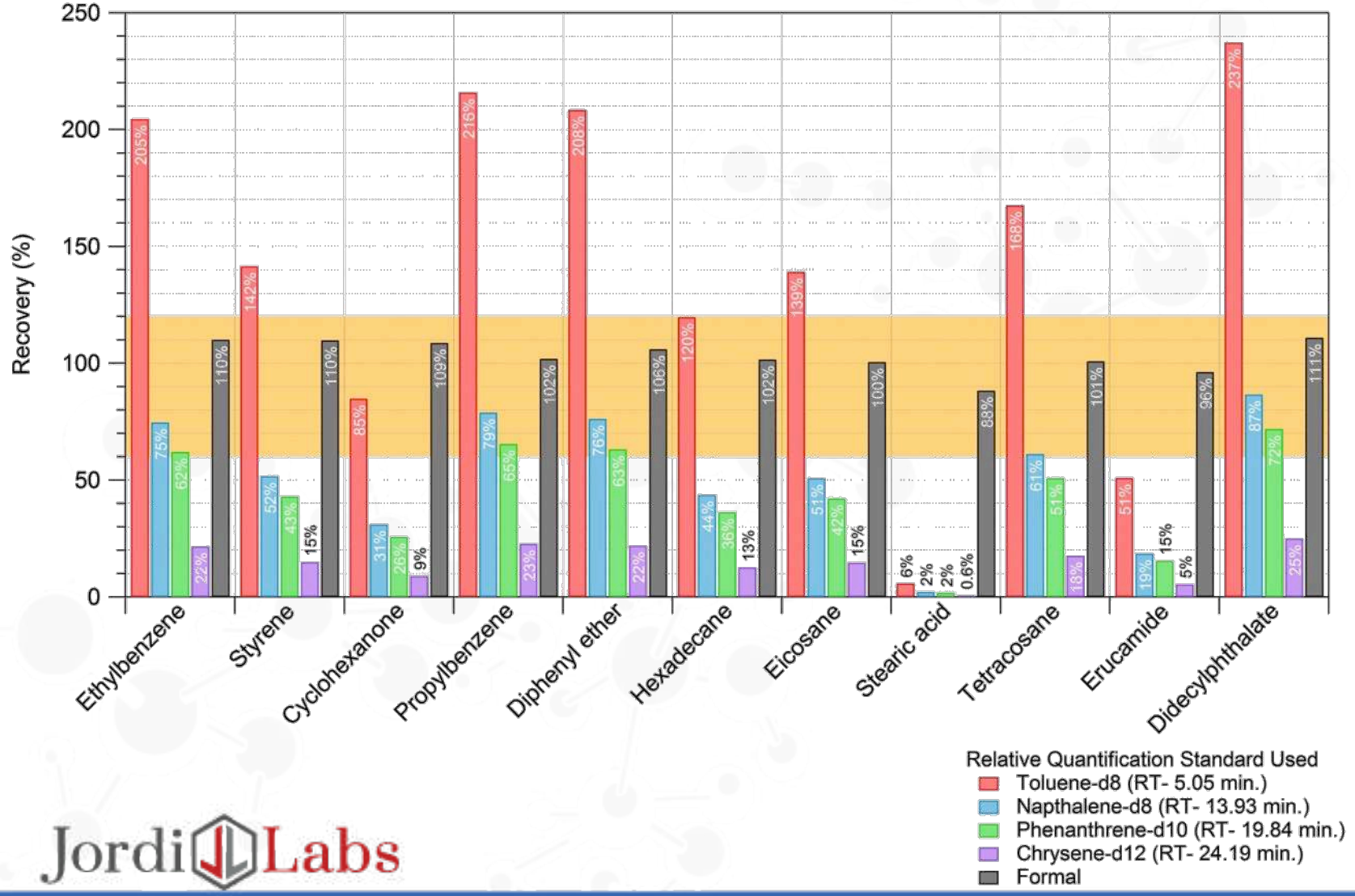
Quantitative Strategies



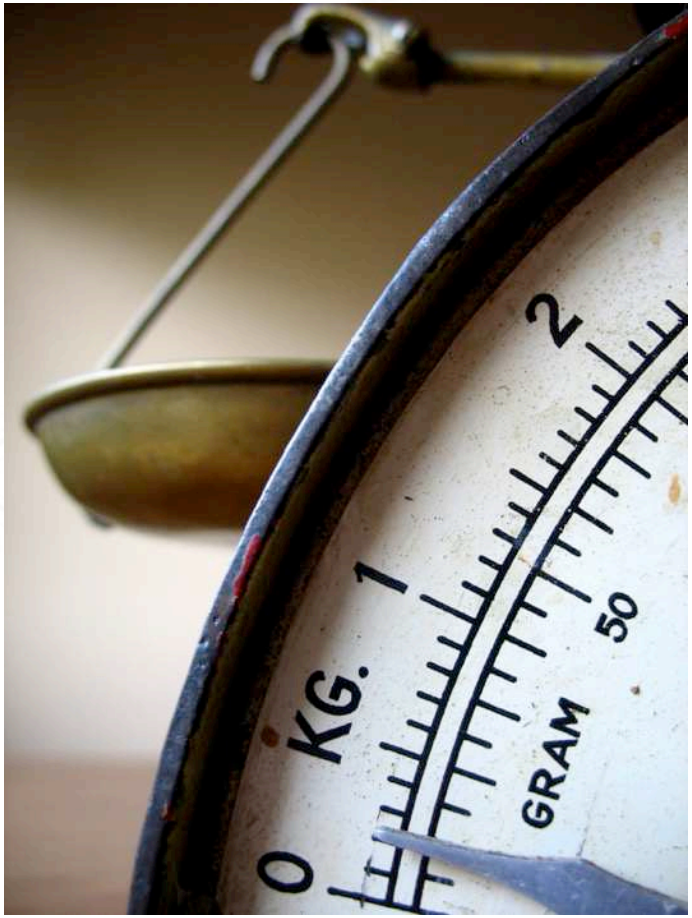
Quantitative Method Development

Quantitative Methods

- Dynamic Headspace GCMS
- UHPLC-UV
- UHPLC-CAD
- QTOF-GCMS

In formal quantitation limit of quantitation (LOQ) can be improved using:

- Targeted MS/MS
- Large Volume Injection



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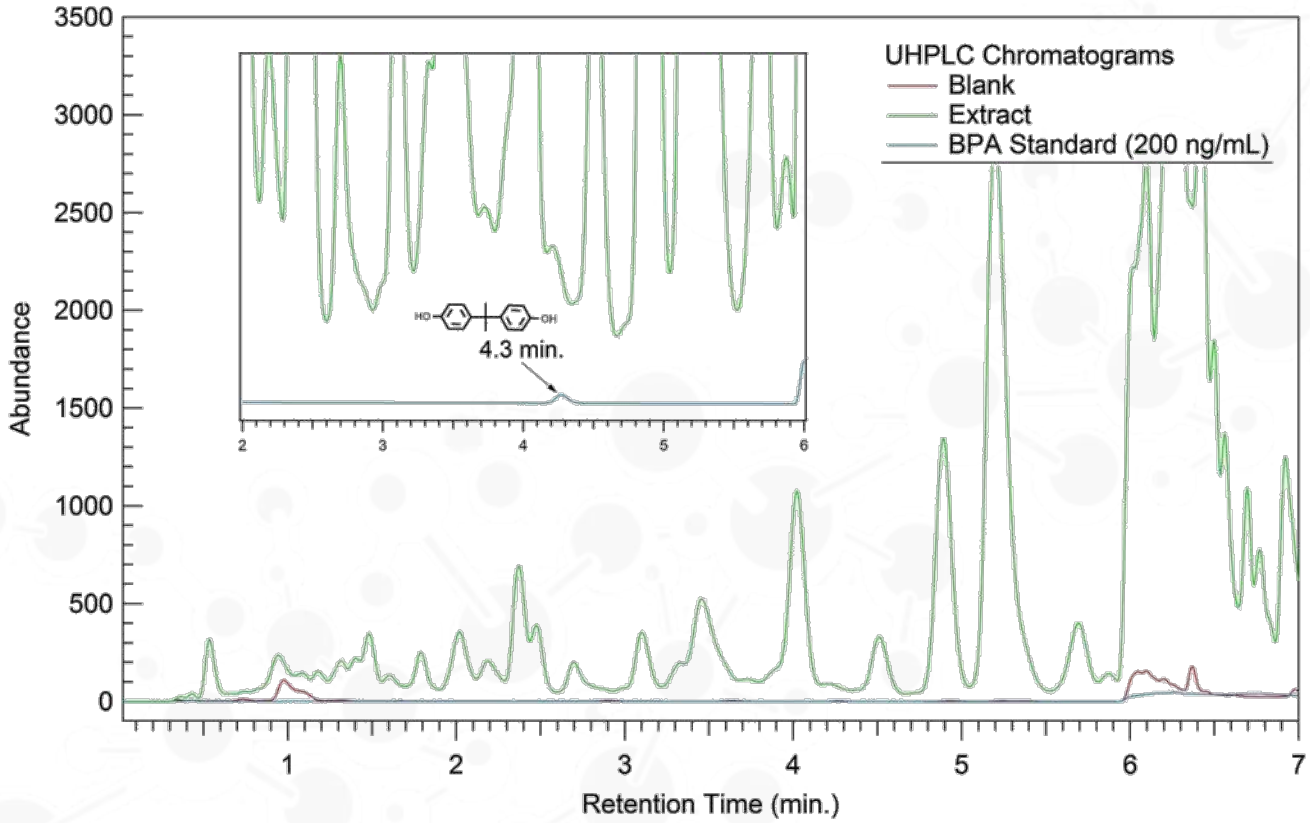
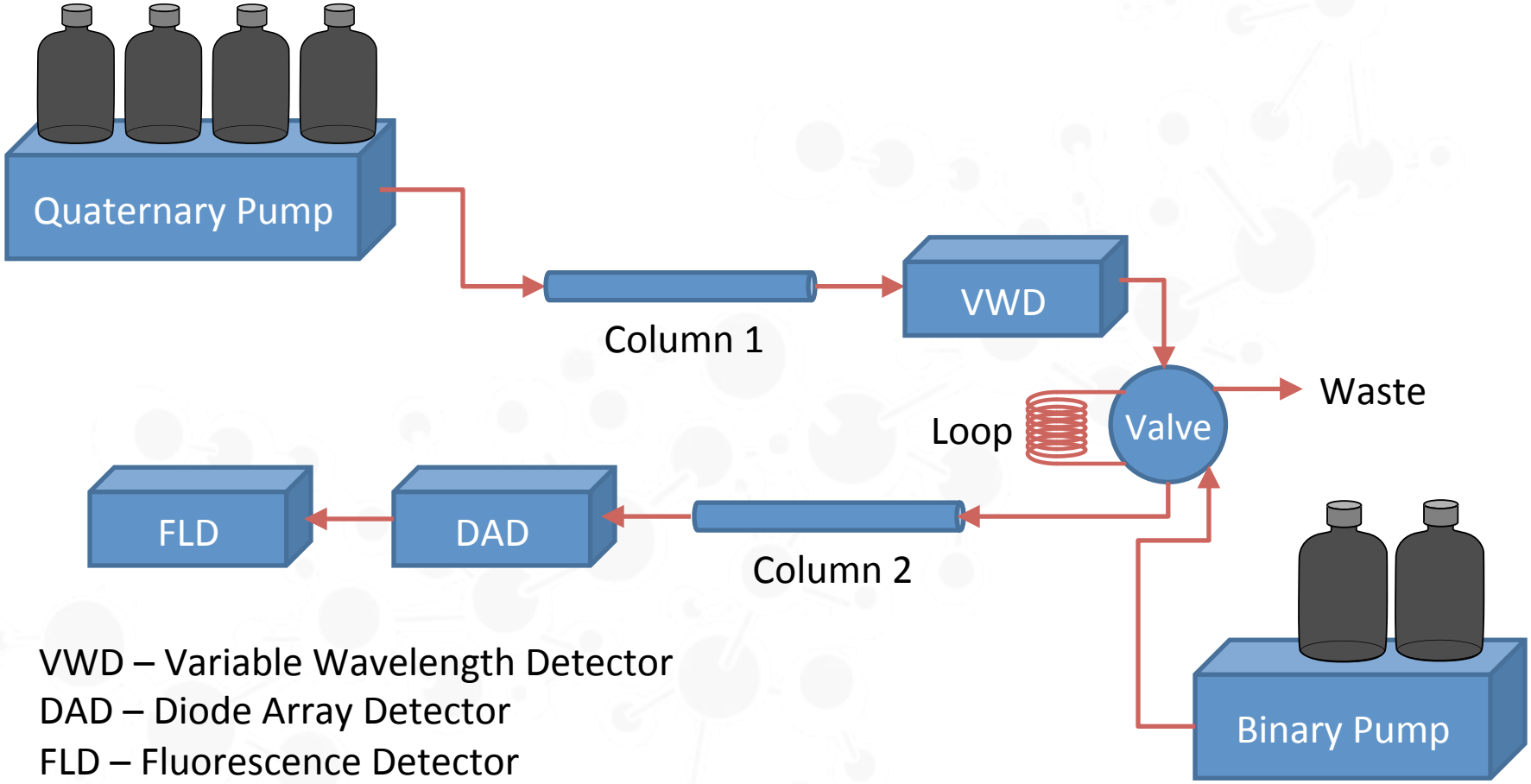
Quantitative Method Development



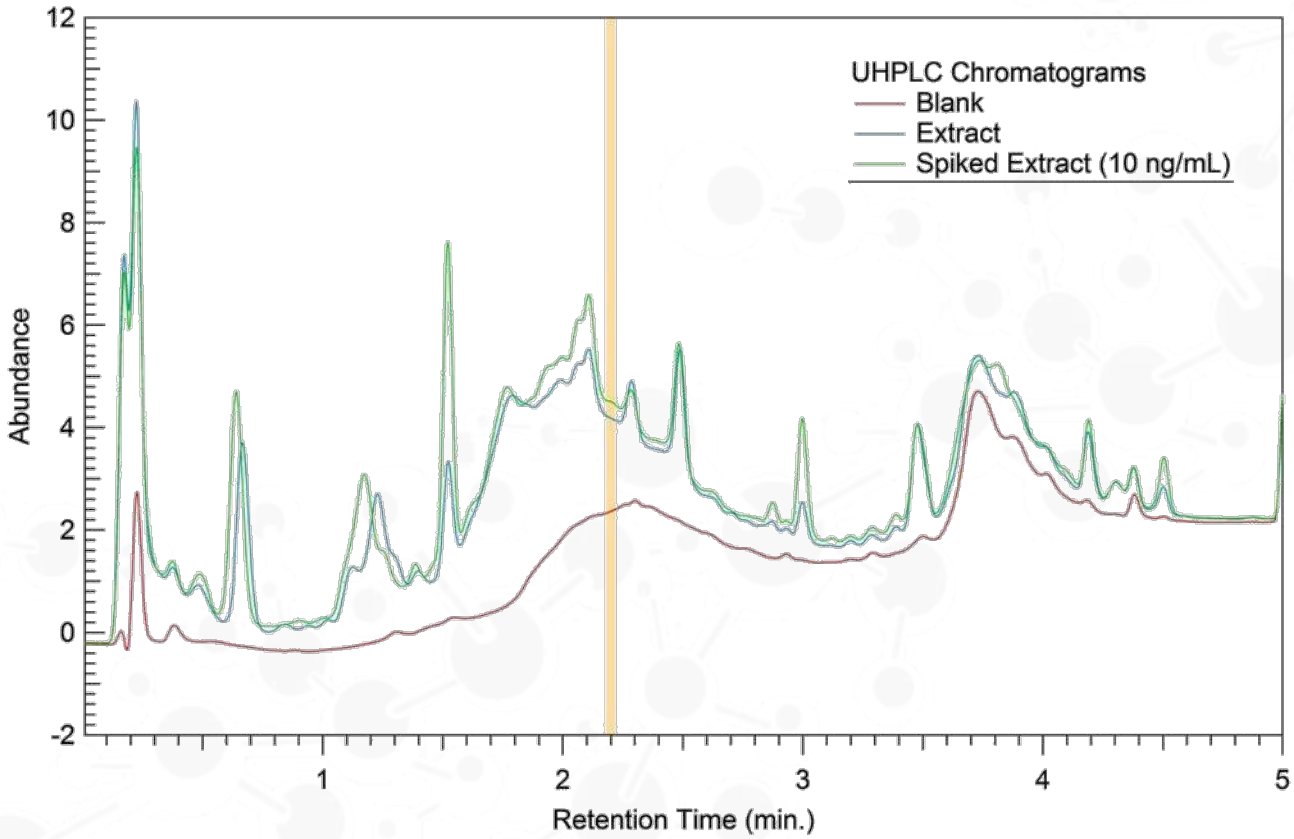
Agilent 1290 Infinity UHPLC
Column: Zorbax SB-C18, 1.8 µm, 100 × 2.1 mm
Mobile Phase: H_2O – ACN Grad.
Detection: 230 nm (DAD)

2D UHPLC



VWD – Variable Wavelength Detector
DAD – Diode Array Detector
FLD – Fluorescence Detector

Quantitative Method Development



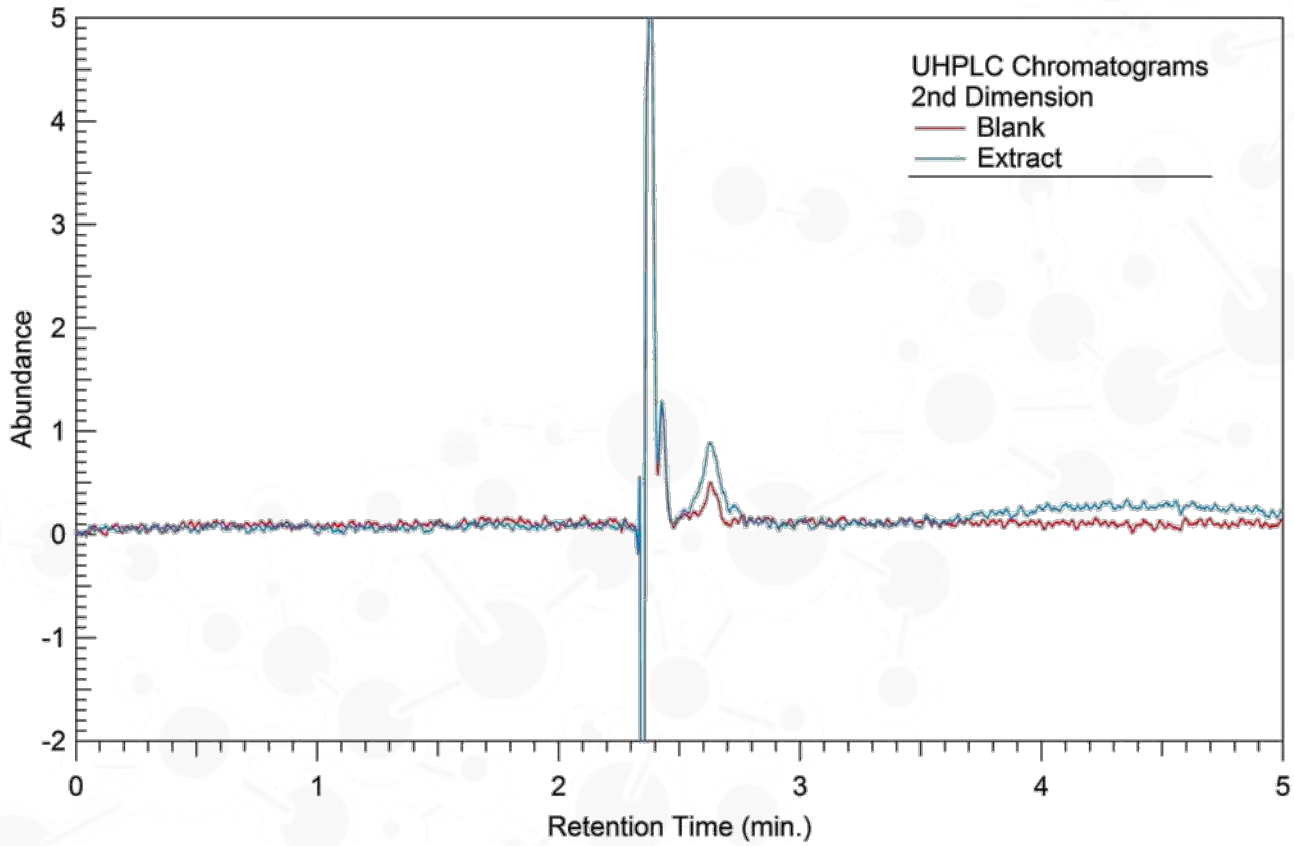
Column: Zorbax SB-C18; 1.8 µm, 2.1×50 mm

Mobile Phase: H_2O – ACN Gradient

Detection: 230 nm (VWD)

Collection Mode: Heart-cutting; 2.18-2.22 minutes (40 µL)

Quantitative Method Development

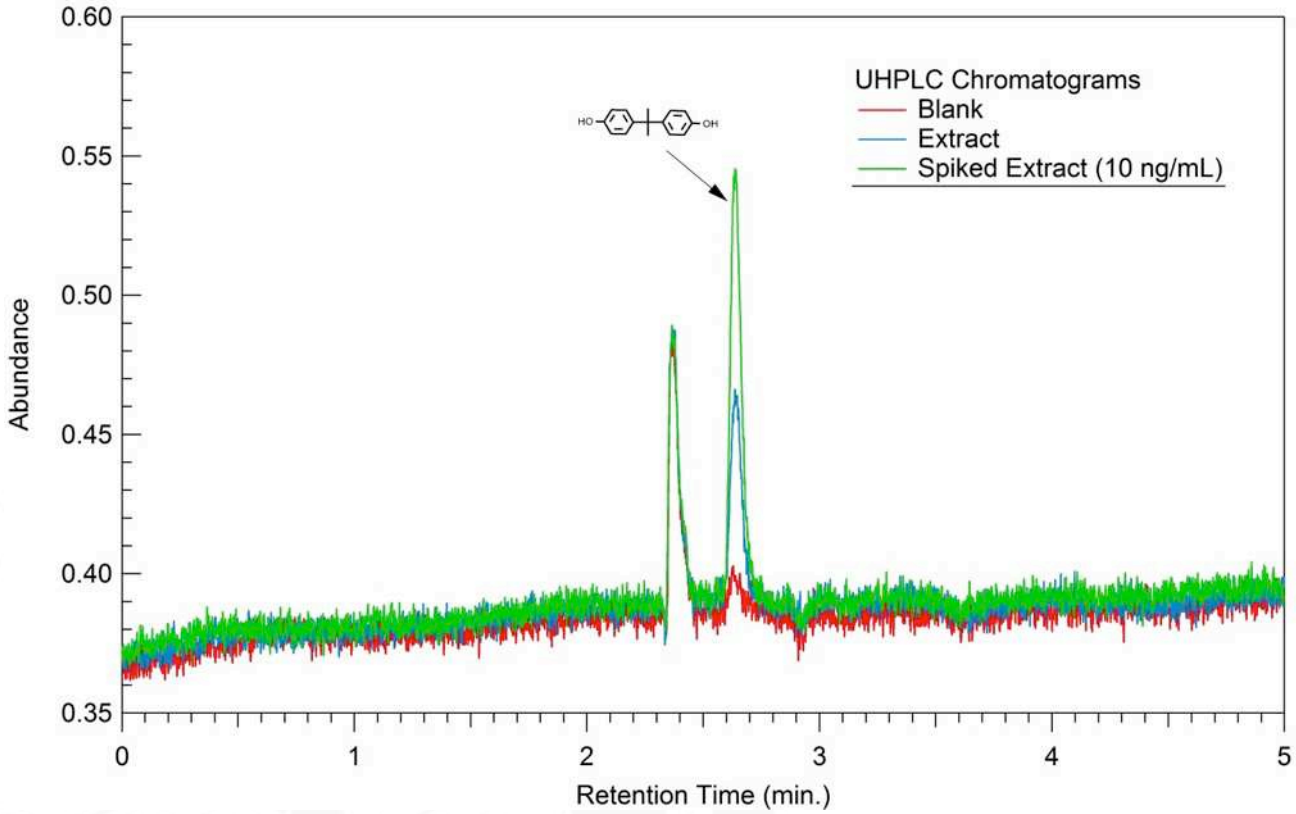


Column: Eclipse Plus Phenyl-Hexyl; 1.8 µm, 2.1×50 mm

Mobile Phase: H_2O – ACN Isocratic

Detection: 230 nm (DAD)

Quantitative Method Development



Column: Eclipse Plus Phenyl-Hexyl; 1.8 µm, 2.1×50 mm

Mobile Phase: H_2O – ACN Isocratic

Detection: Fluorescence; 225 nm excitation, 310 nm emission

A SUCCESSFUL STUDY HAS:

1. Appropriate Extraction Conditions
2. Careful Concentration of Extracts
3. Definitive Identifications
4. Accurate Quantification

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