Best Practices for OINDP Pharmaceutical Development Programs Leachables and Extractables

V. The Controlled Extraction Study

PQRI Leachables & Extractables Working Group

PQRI Training Course
12-13 April 2007
Chicago, IL

Definition

- A Controlled Extraction Study is a laboratory investigation into the qualitative and quantitative nature of extractable profiles from critical components of an OINDP container/closure system

PQRI Safety Thresholds and Best Practices for Extractables and Leachables in OINDP November 2005

Top Ten Reasons Why Controlled Extraction Studies are Needed

- To make an informed selection of materials.
- To meet regulatory expectations.
- To control leachables.
- To control materials from lot to lot.
- To correlate extractables data to leachables.
- To evaluate the safety of the materials.
- To predict worst case of end-of shelf life leachables.
- To qualify packaging materials.
- To obtain a comprehensive extractables profile.
- Because USP testing does not provide applicable data.

Course Objectives

- Purpose of a Controlled Extraction Study
- PQRI Best Practice Recommendations
  - Controlled Extraction Study Example Data
    - Qualitative and Quantitative Profiles
    - Method Optimization
- Conclusion

The Purpose of a Controlled Extraction Study is to systematically and rationally identify and quantify potential leachables, to the extent practical, and within certain defined analytical threshold parameters.

Utility of Extractable Information

- Obtain Data for Risk Assessment
  - Provide Information to Toxicologists for Preliminary Risk Assessment
  - Apply Threshold Principles
- Provide Basis for Leachable Methods
- Correlate Extractable Data to Leachables Data
- Develop Routine Extractable Tests
- Establish Control Criteria

Study Strategy

- When to Begin
  - Early in Development Phase
    - Establish Team and Obtain Extractable Information
- Where to Begin
  - Select Critical Components
    - Knowledge of Materials
  - Extraction Solvents/Techniques
  - Analytical Methods
- Where to End
  - Application of the AET
  - Identification Categories
  - Data Evaluation and Reporting
  - Control of Leachables

Critical Components

- MDI, DPI, Nasal Inhalation Solutions and Sprays
  - Patient Contact
  - Product Contact
  - Device Performance
  - Secondary Packaging
  - Ancillary Components

Typical Materials

- OINDP Components
  - Valves (Gaskets/O-rings)
  - Mouthpiece
  - Canister
  - Secondary Packaging
  - Pump Components
  - Actuator
  - Containers
  - Blisters
  - Labels/Adhesives/Inks
- Extractables (0.01-1000ug)
  - Solvents
  - Monomers/Dimers/Trimers
  - Curatives
  - Photo Initiators
  - Plasticizers
  - Lubricants
  - Processing Aids
  - Antioxidants
  - Cleaning Residues
  - Reaction/Degradation and Breakdown Products

Knowledge of Materials/Processes

- Materials of Composition
  - Base Material
  - Additives and Processing Aids
- Polymerization Process
- Fabrication process
- Cleaning and Pretreatment
- Component Storage and Shipping

Extractable Profiles

- Qualitative
  - Comprehensive
- Quantitative
  - Worst Case Leachables
- Component Control
  - Acceptance Criteria

Challenges / Choices

- What Components?
- How Many Components ?
- What Volume of Solvent?
- What Reference Material Should be Selected?
- What Solvents?
- What Extraction Techniques?
- What Analysis Conditions?

Considerations

- Extraction should be vigorous, but not so aggressive as to alter the qualitative and/or quantitative nature of the extractable profile
- Must be technically justified and optimized to produce extractables profiles at least equivalent to leachable profiles obtained under worst case conditions

Jenke, DR. PDA J Pharm Sci Technology, 2003

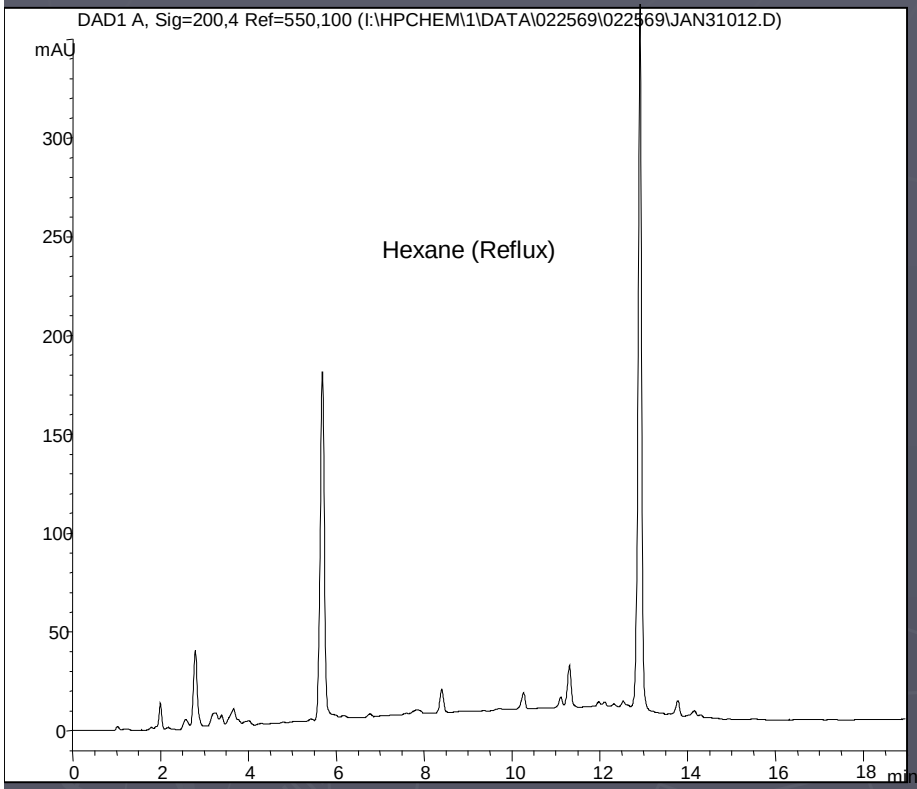
PQRI Best Practices Recommendations

Ten Principal Objectives

#1 Controlled Extraction Studies should employ vigorous extraction with multiple solvents of varying polarity.

- Range of Polarities
- Range of Boiling Points
- One of Similar Extracting Properties to Drug Product Vehicle
- Relatively Non-reactive
- High Purity
- Easily and Safely Handled
- Readily Available

Solubility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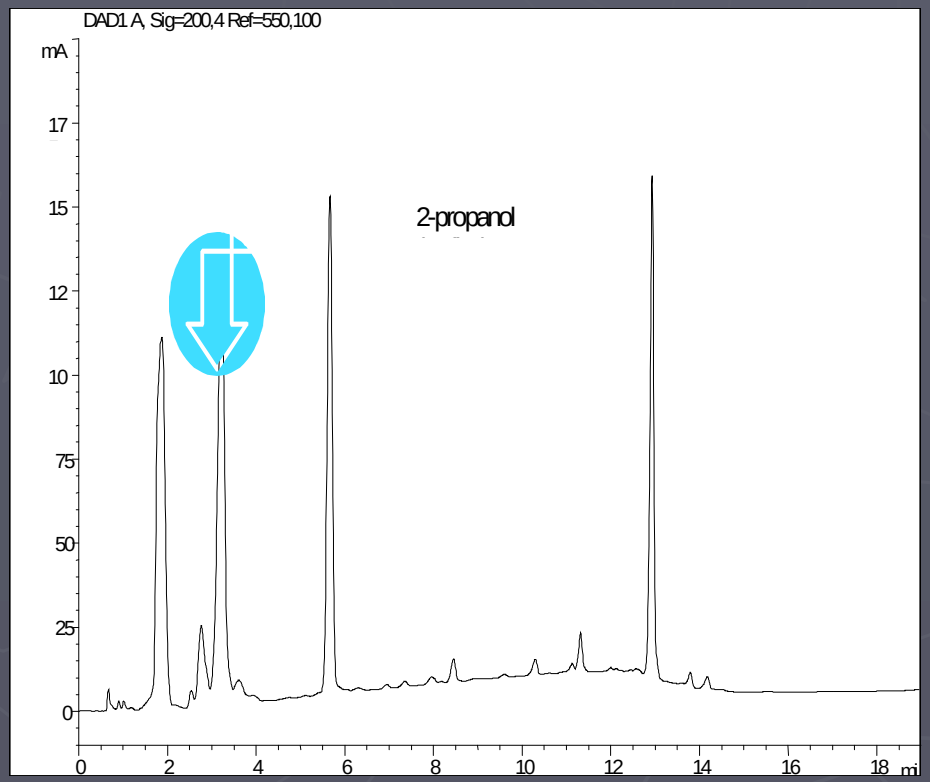
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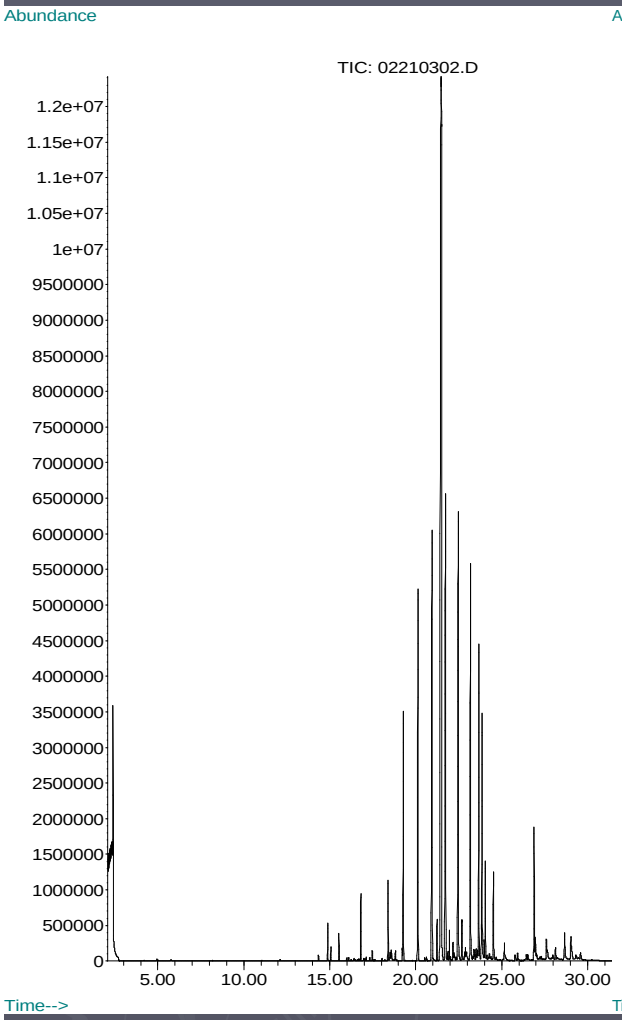
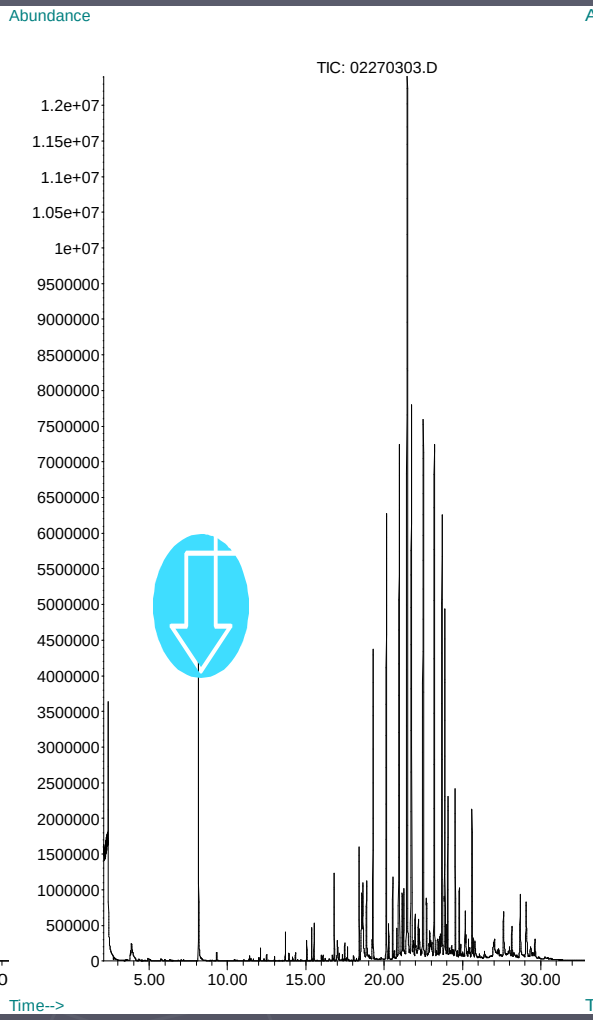
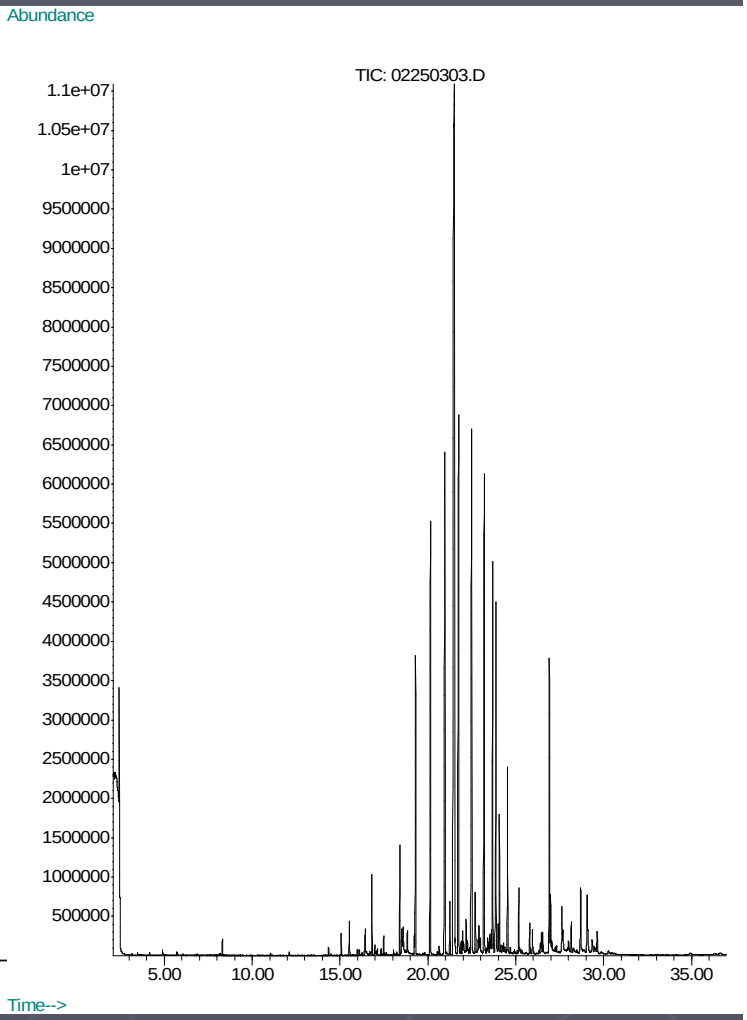
Thermolysis



Methylene Chloride

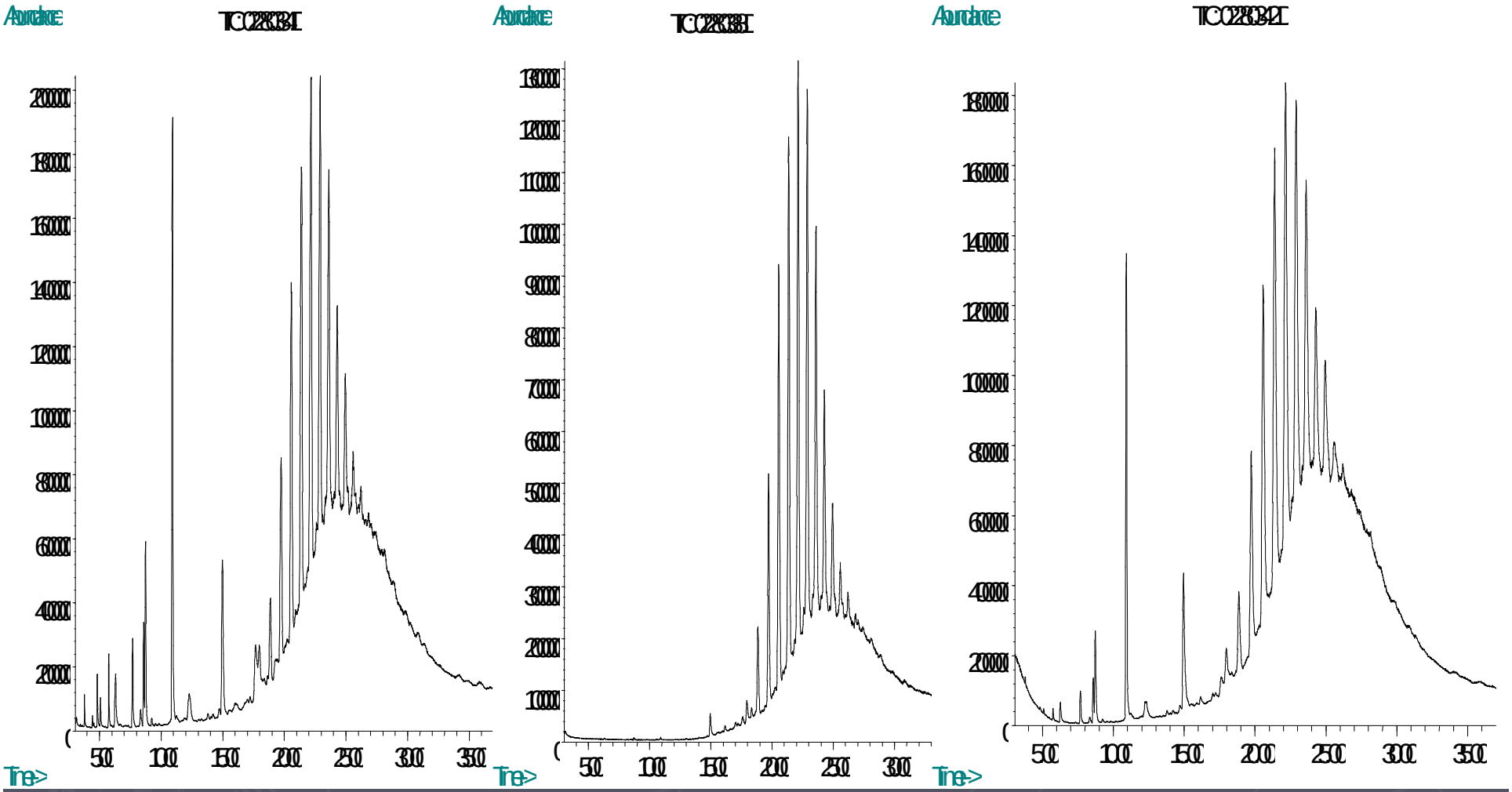


2-propanol



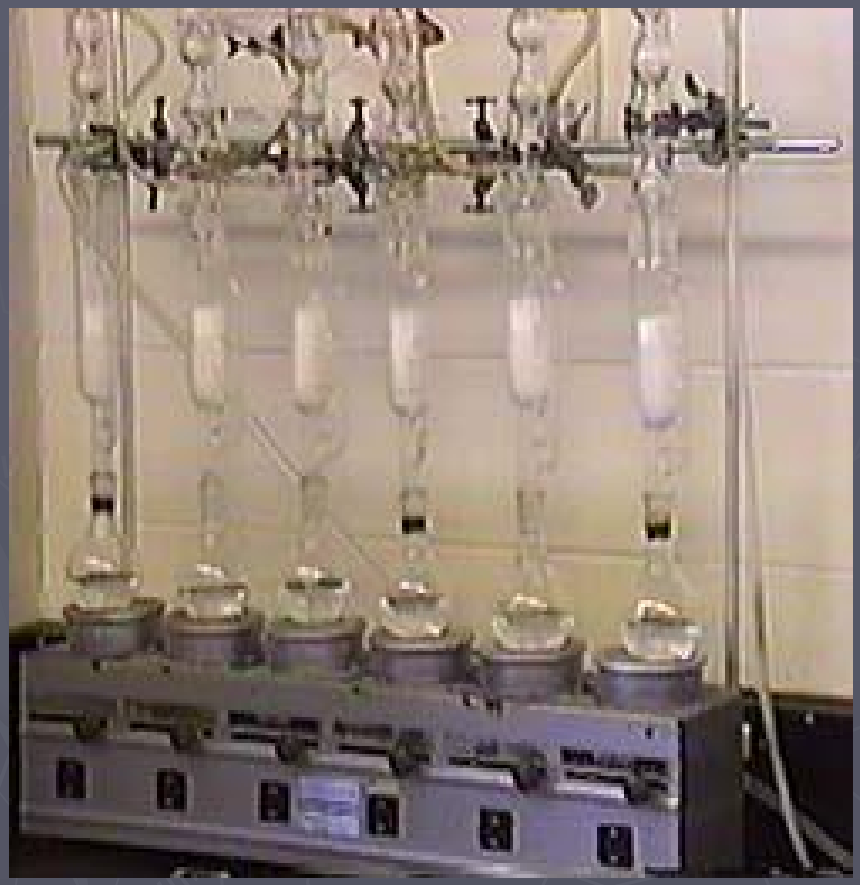
Hexane

Extractable Yield

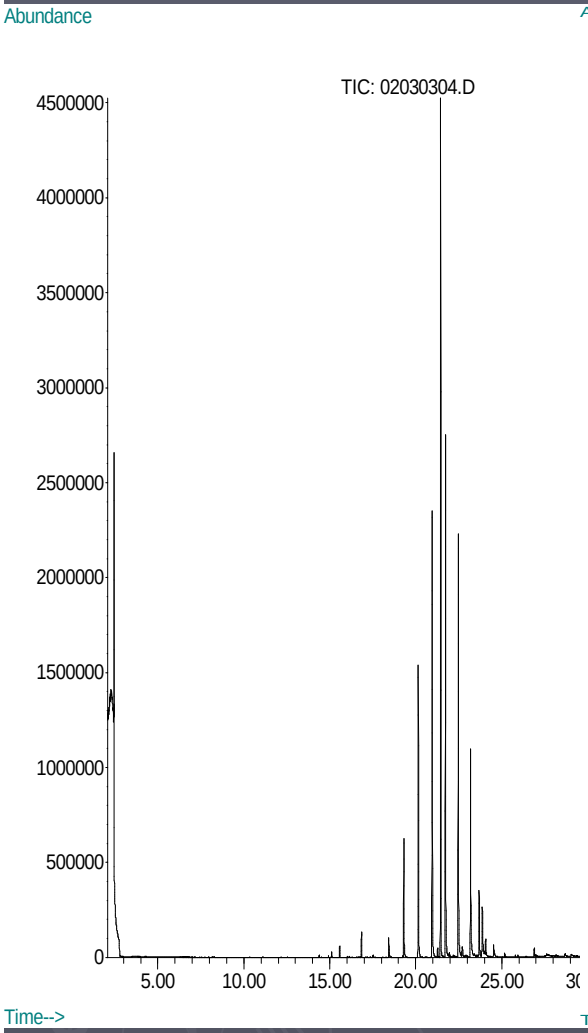


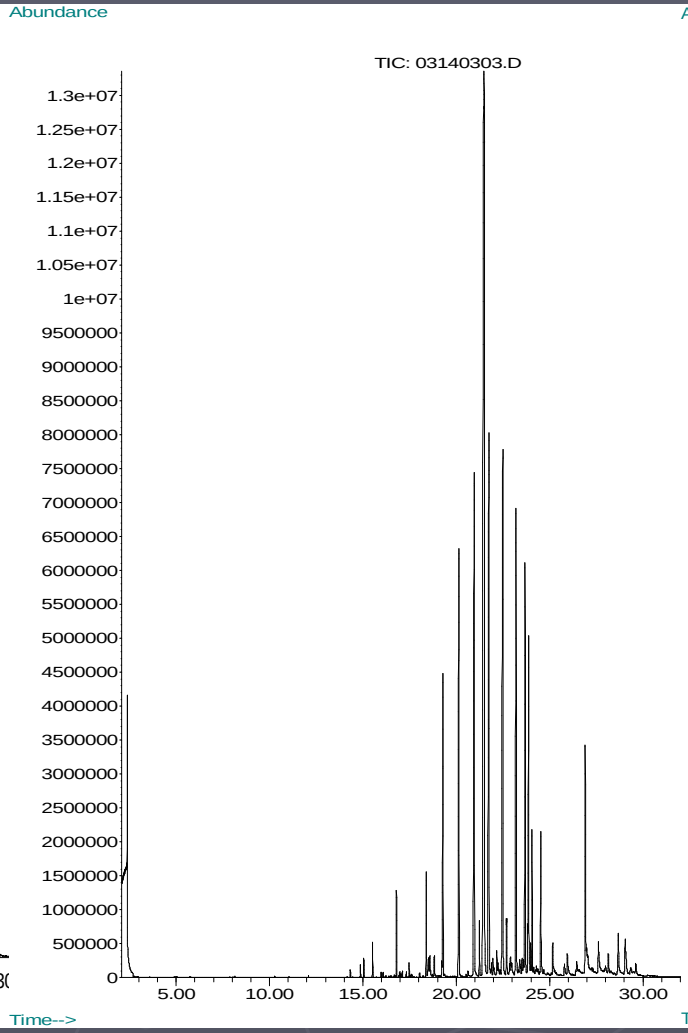
Methylene Chloride | 2-propanol | Hexane

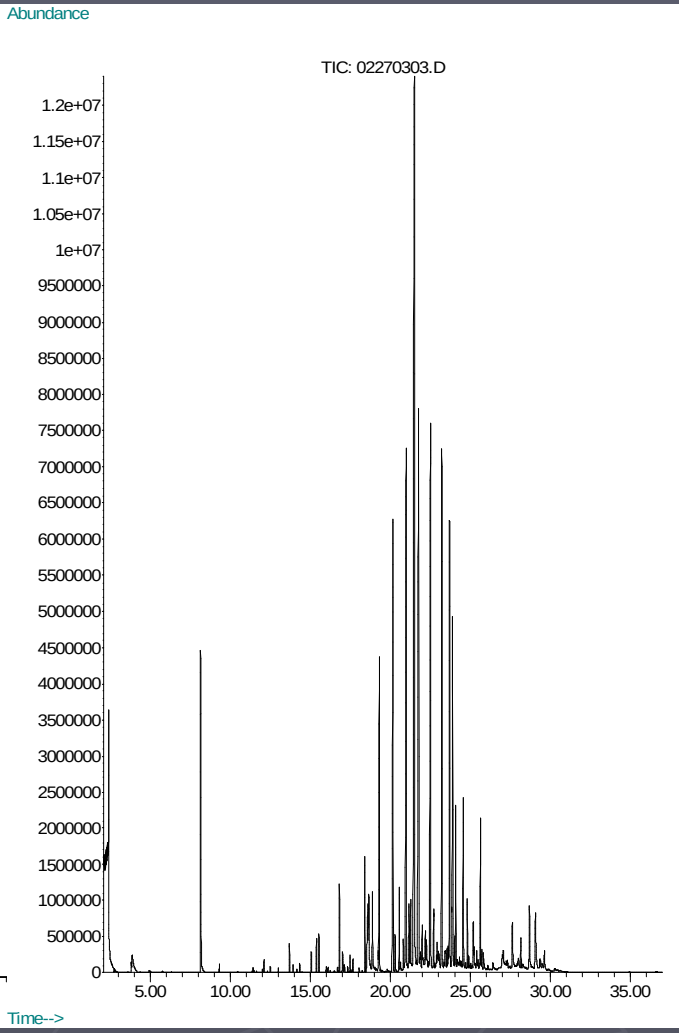
#2 Controlled Extraction Studies should incorporate multiple extraction techniques.



Sulfur Cured Elastomer





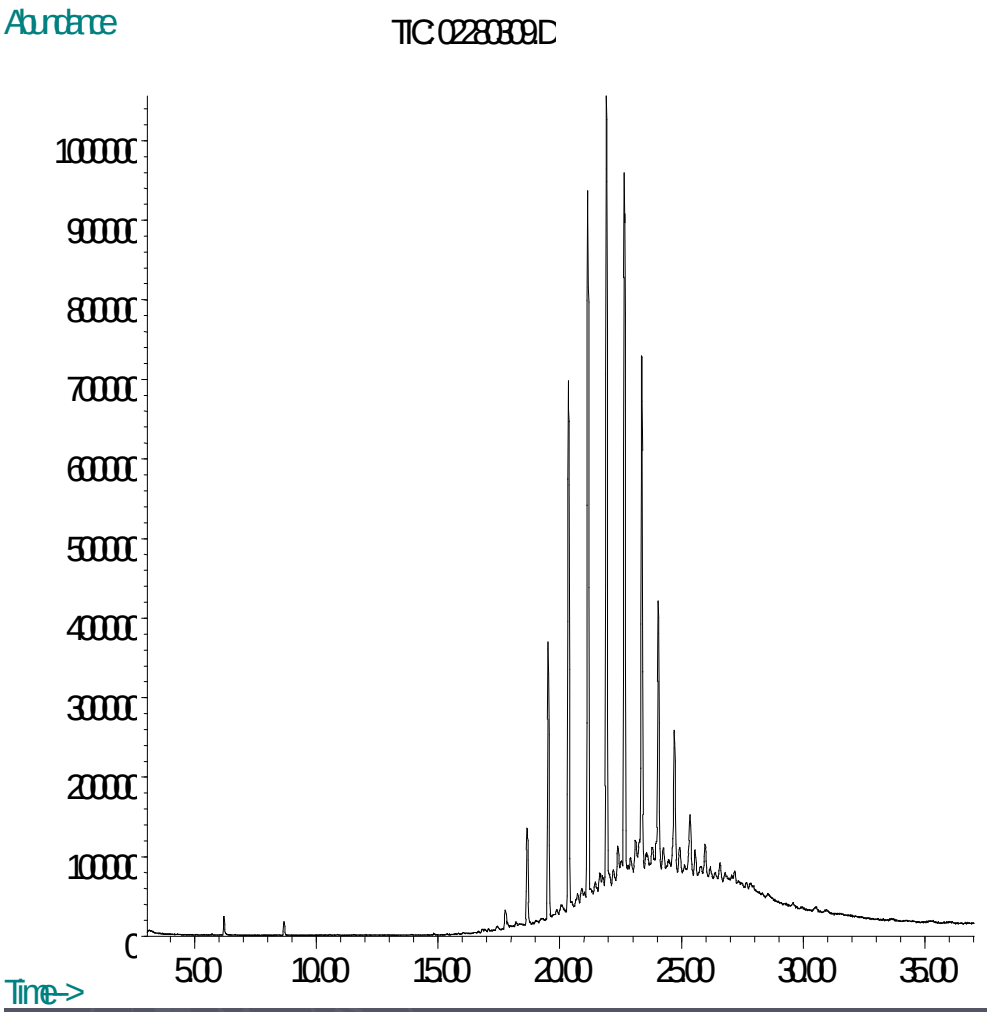


Sonication

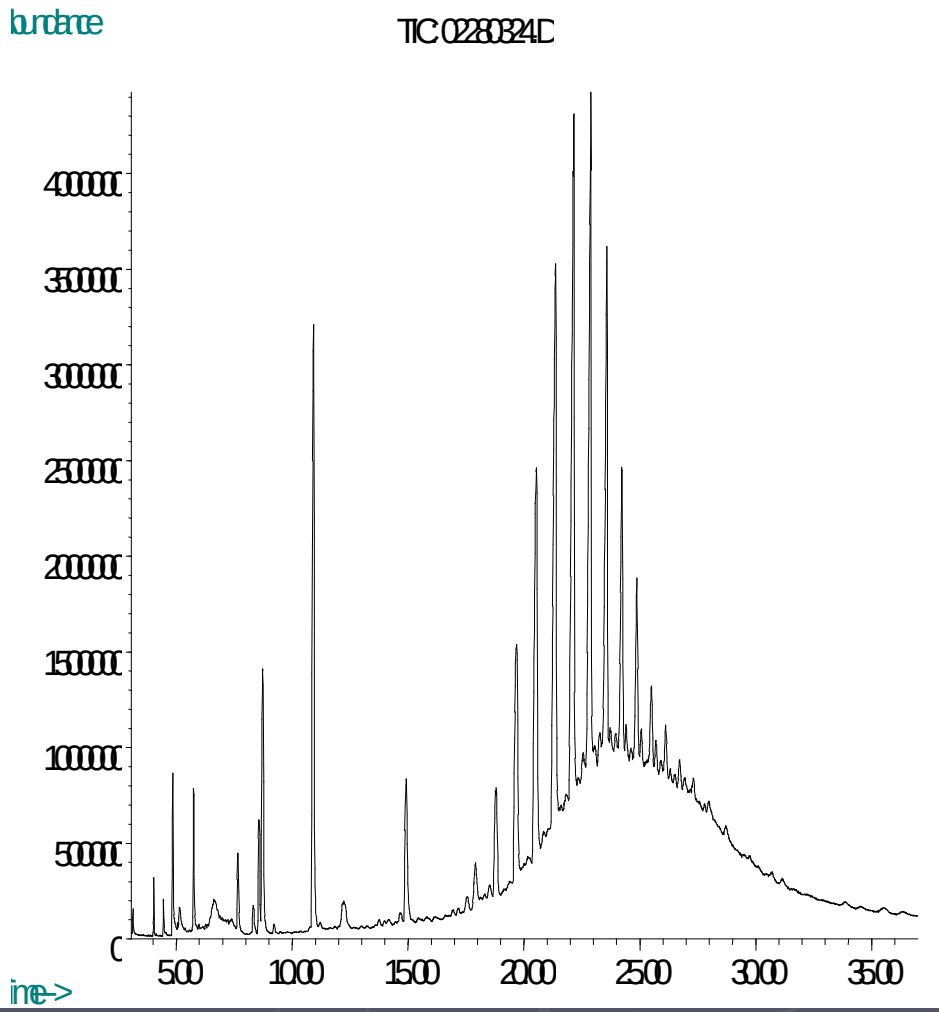
Soxhlet

Reflux

Peroxide- Cured Elastomer

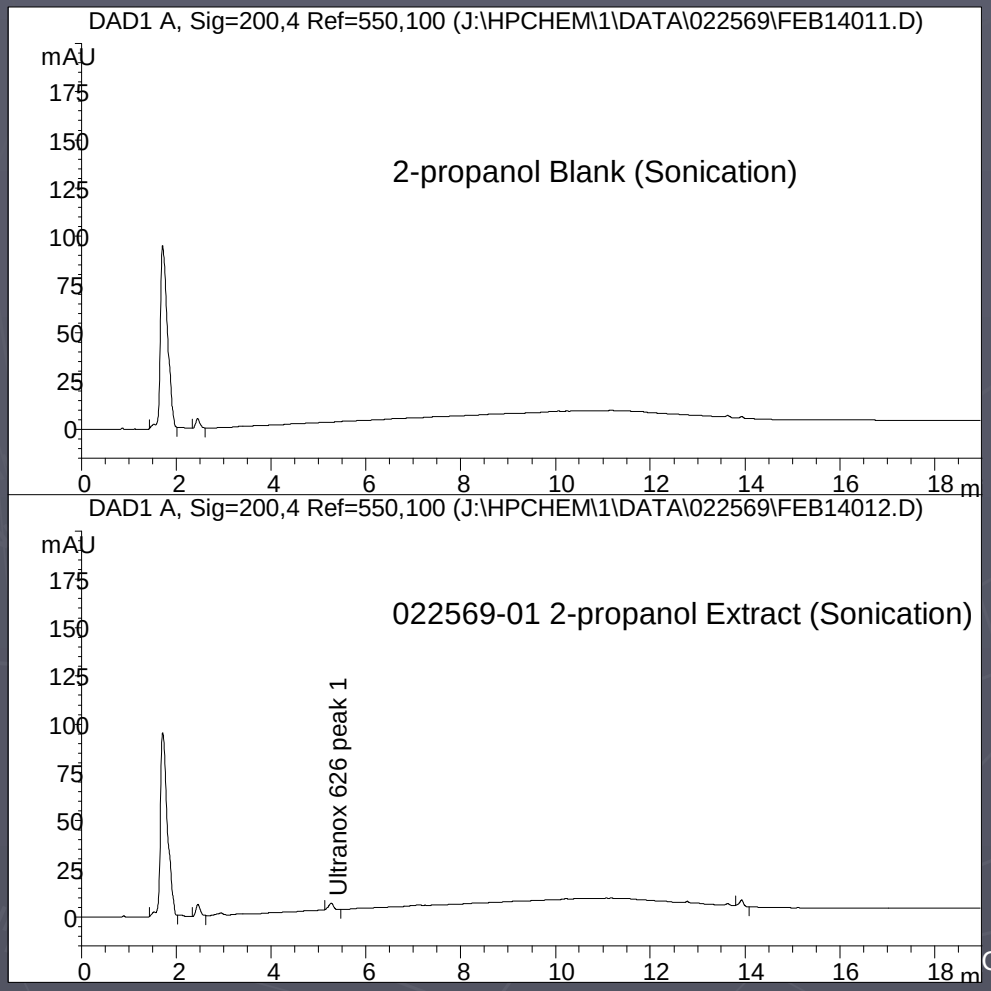


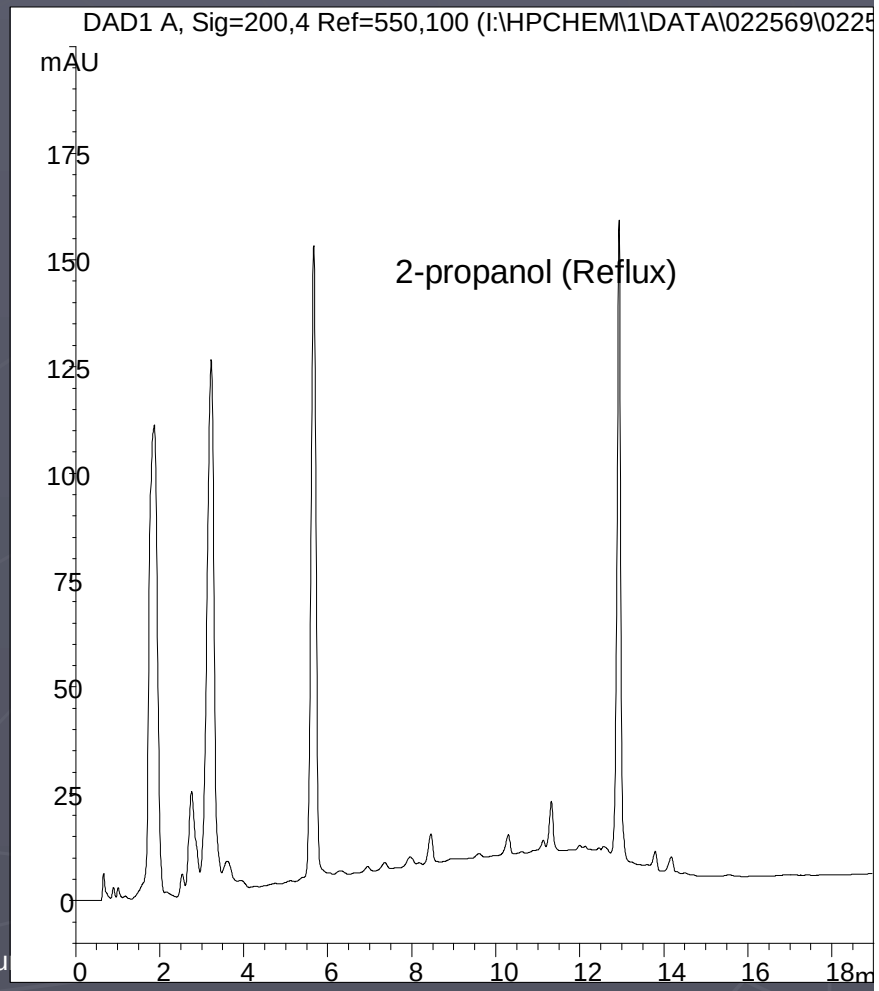
Sonication



Reflux

Polypropylene

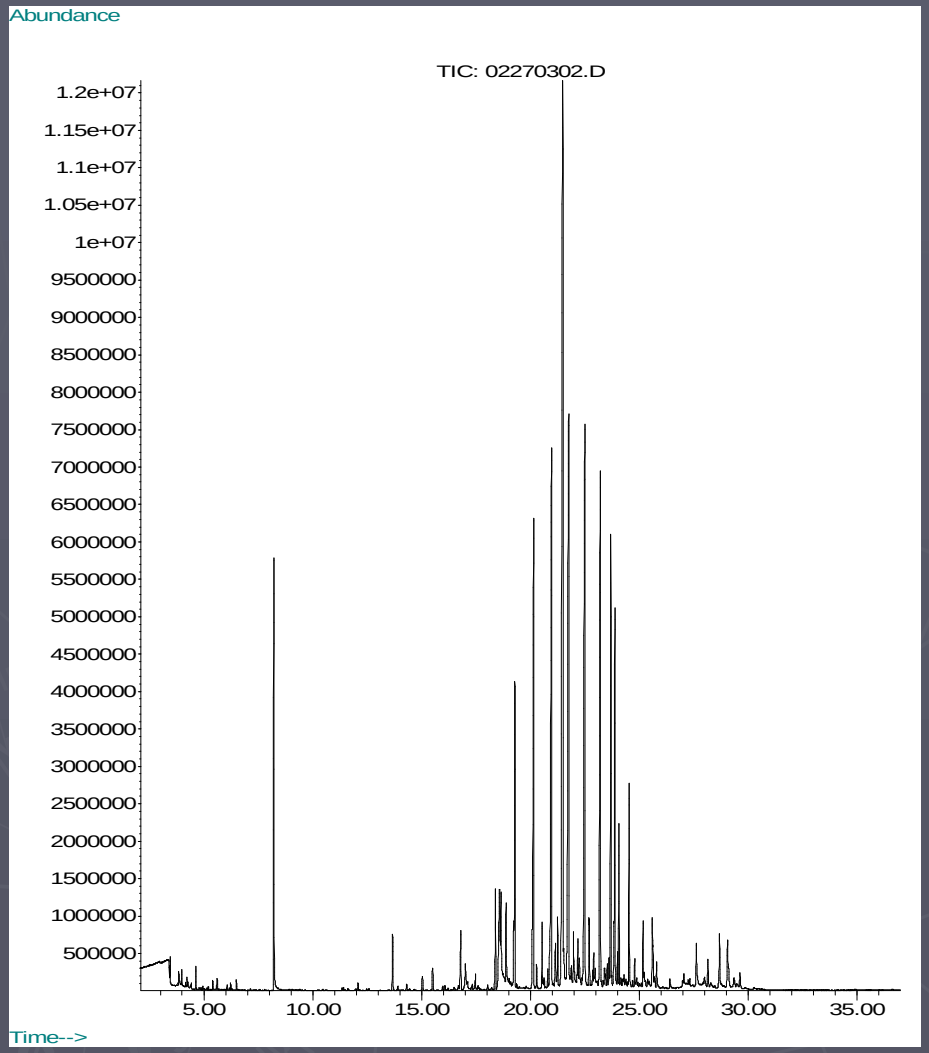




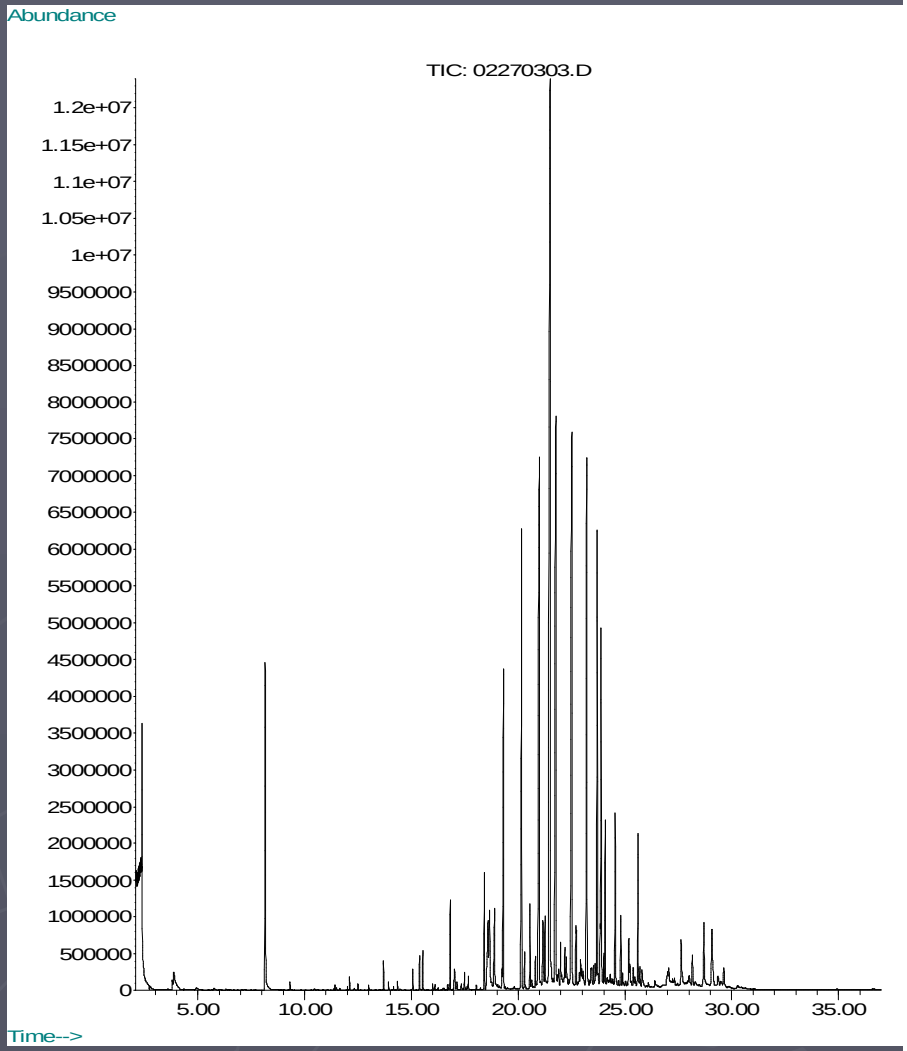
#3 Controlled Extraction Studies should include careful sample preparation based on knowledge of analytical techniques to be used.

- Preparation of Extracts
  - Sampling, Sample:Surface Ratio, Solvents, Conditions
- Test Sample Preparations
  - Instrumental Techniques
  - Concentration/Dilution

Sample Introduction



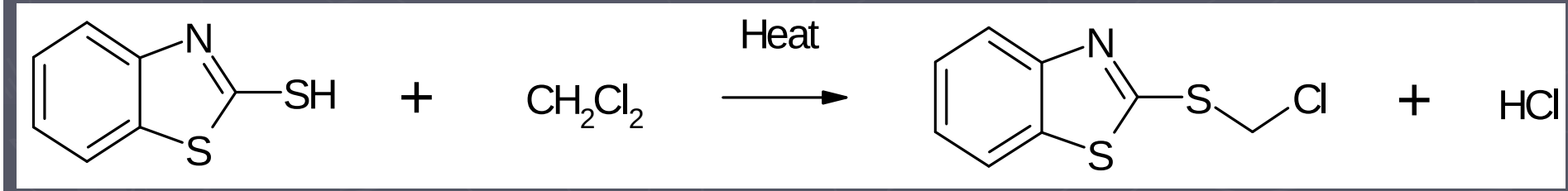
2- Propanol Extract



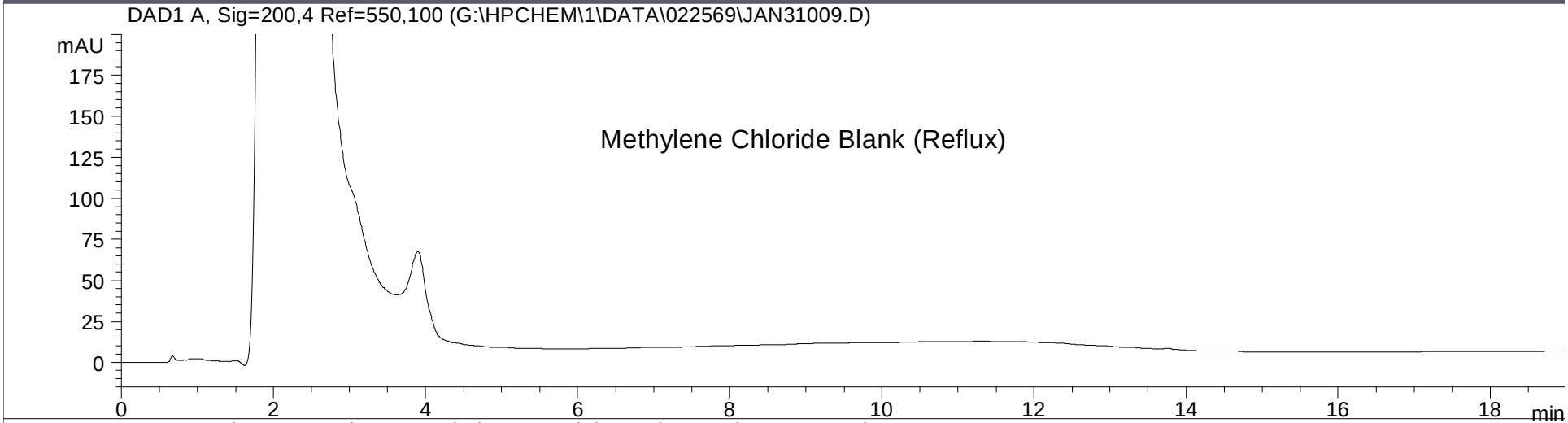
Reconstituted in Methylene Chloride

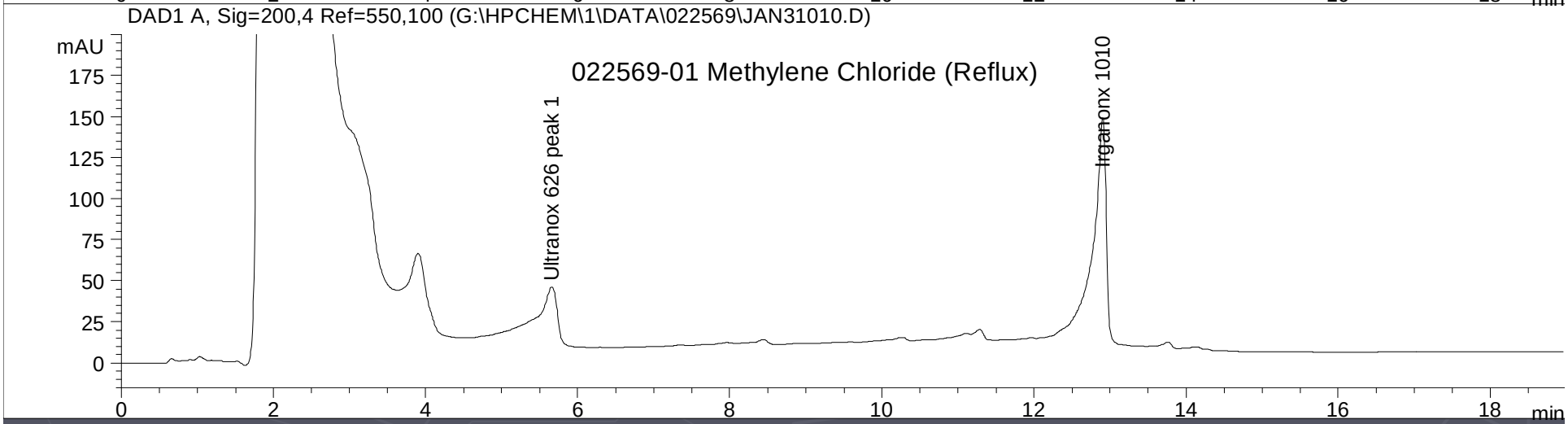
Artifacts

- 2-(chloromethylthio)benzothiazole

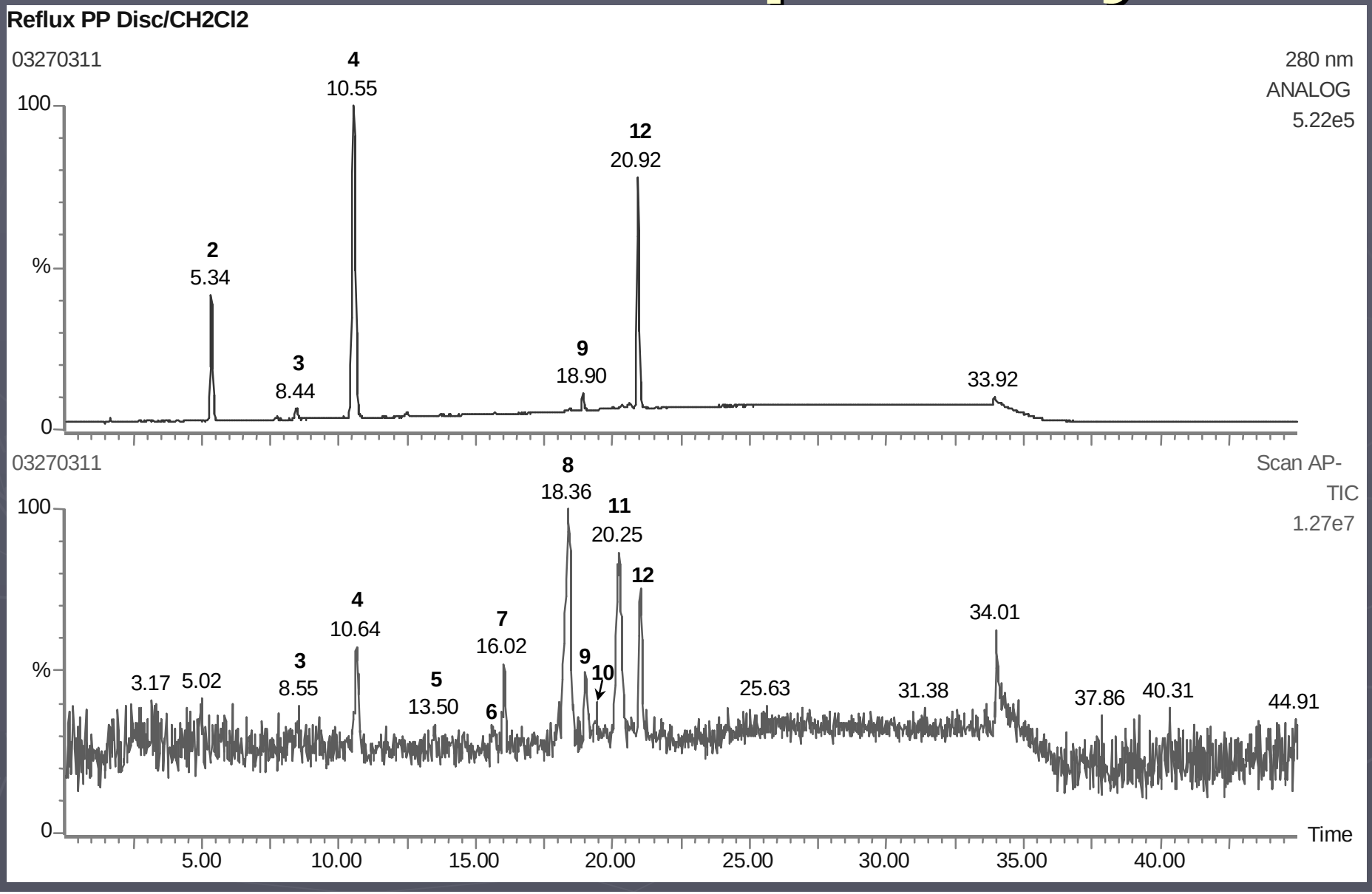


Solvent Compatibility





Solvent Compatibility



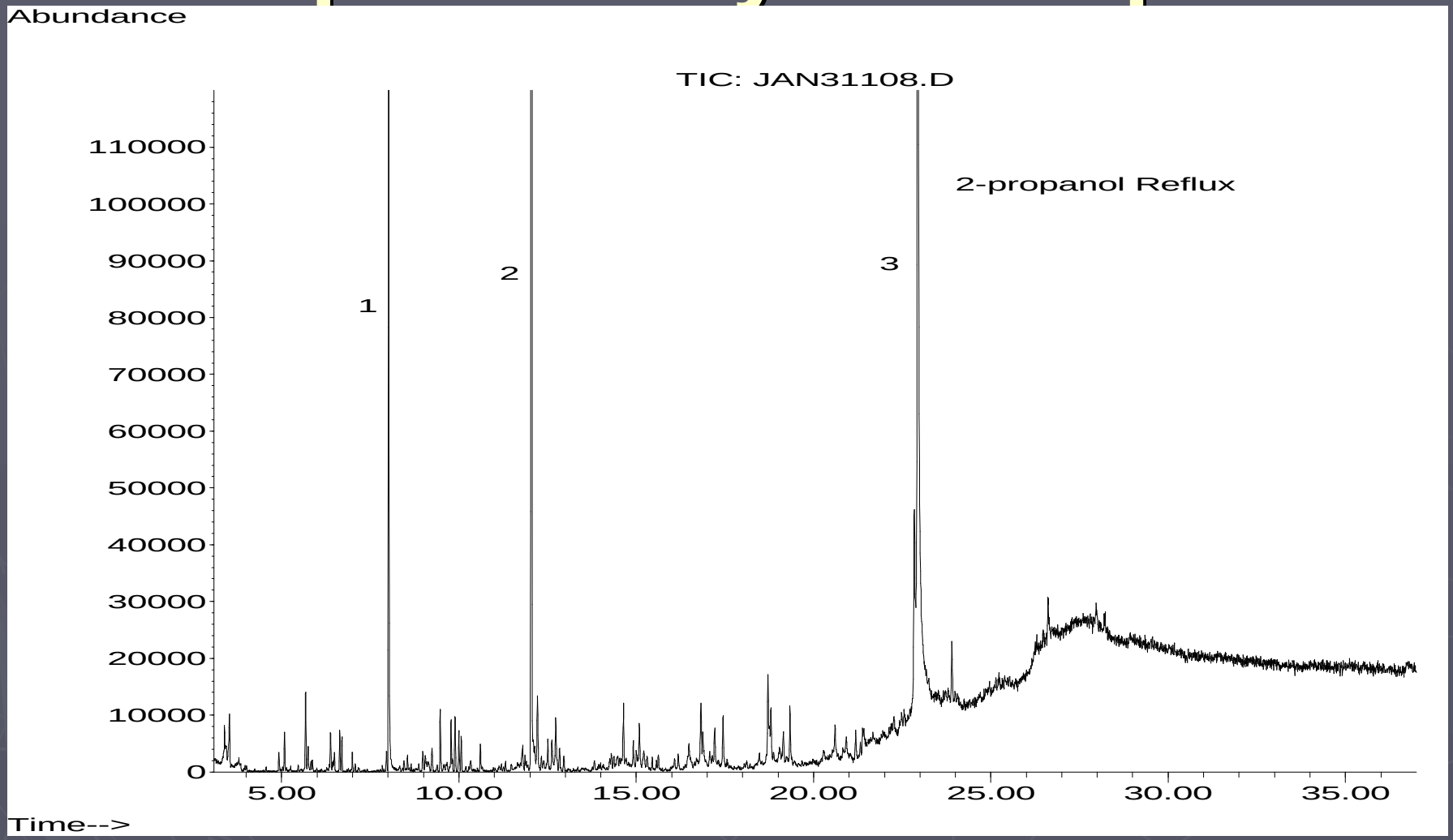
#4 Controlled Extraction Studies should employ multiple analytical techniques

- Gas Chromatography/Mass Spectrometry (GC/MS)
- Liquid Chromatography/Mass Spectrometry (LC/MS)
- Liquid Chromatography/Diode Array Detection (LC/DAD)
- Gas Chromatography/Flame Ionization Detection (GC/FID)
- Liquid Chromatography/Ultraviolet Detection (LC/UV)
- Fourier Transform Infrared Spectroscopy (FTIR)
- Inductively Coupled Plasma/Mass Spectroscopy (ICP/MS)
- Inductively Coupled Plasma/Optical Emission Spectroscopy (ICP/OES)
- Scanning Electron Microscopy. Energy Dispersive X-Ray (SEM/EDX)

Qualitative System Suitability

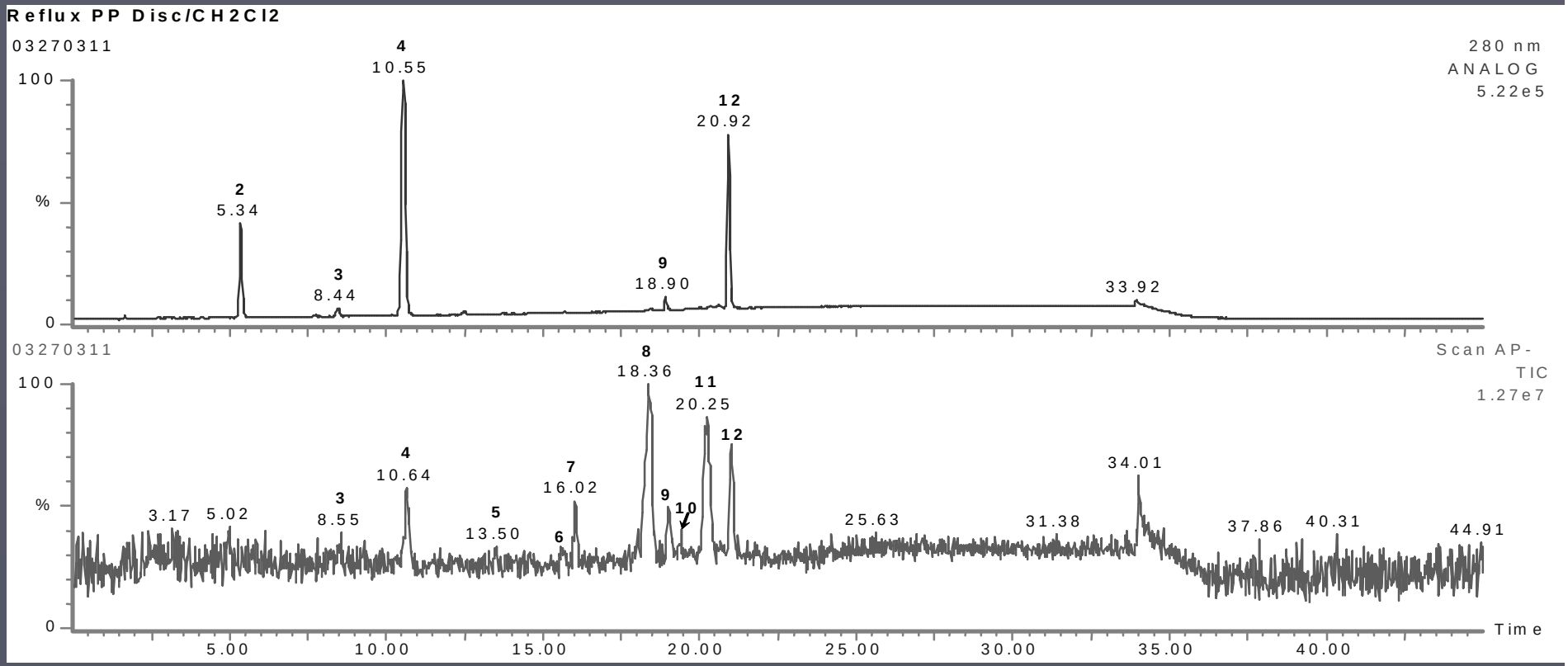
Compound	Suggested Technique	Recommended Target Concentration (ug/ml)
2-Mercaptobenzothiozole	GC or LC	50
Tetramethylthiuramdisulfide	GC or LC/UV	50
Butylatedhydroxytoluene	GC or LC	50
Irganox 1010	LC	50
Diphenyl Amine	LC	50
Bis-(2-ethylhexyl) phthalate	GC or LC	50
Bis (dodecyl) phthalate	GC or LC	50
Stearic Acid	GC or LC/MS	100
2-ethylhexanol	GC	50
Pyrene	GC or LC/UV	1

Complimentary Techniques



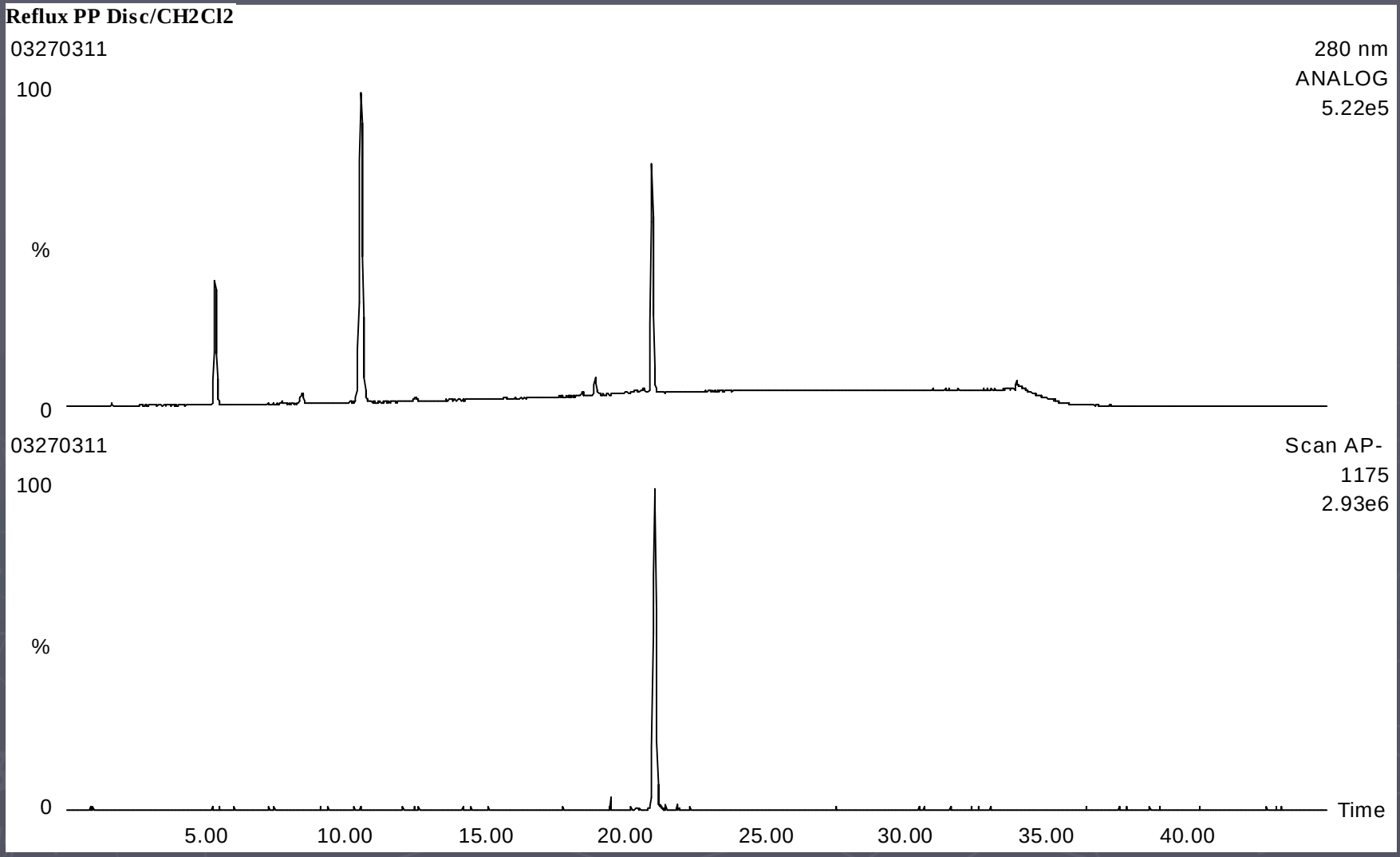
GC/MS of polypropylene 2-propanol extract: 1 = 2,6-di-methyl benzaldehyde; 2 = 2,4-di-*tert*-butylphenol; 3 = glycerol monostearate.

Complimentary Techniques



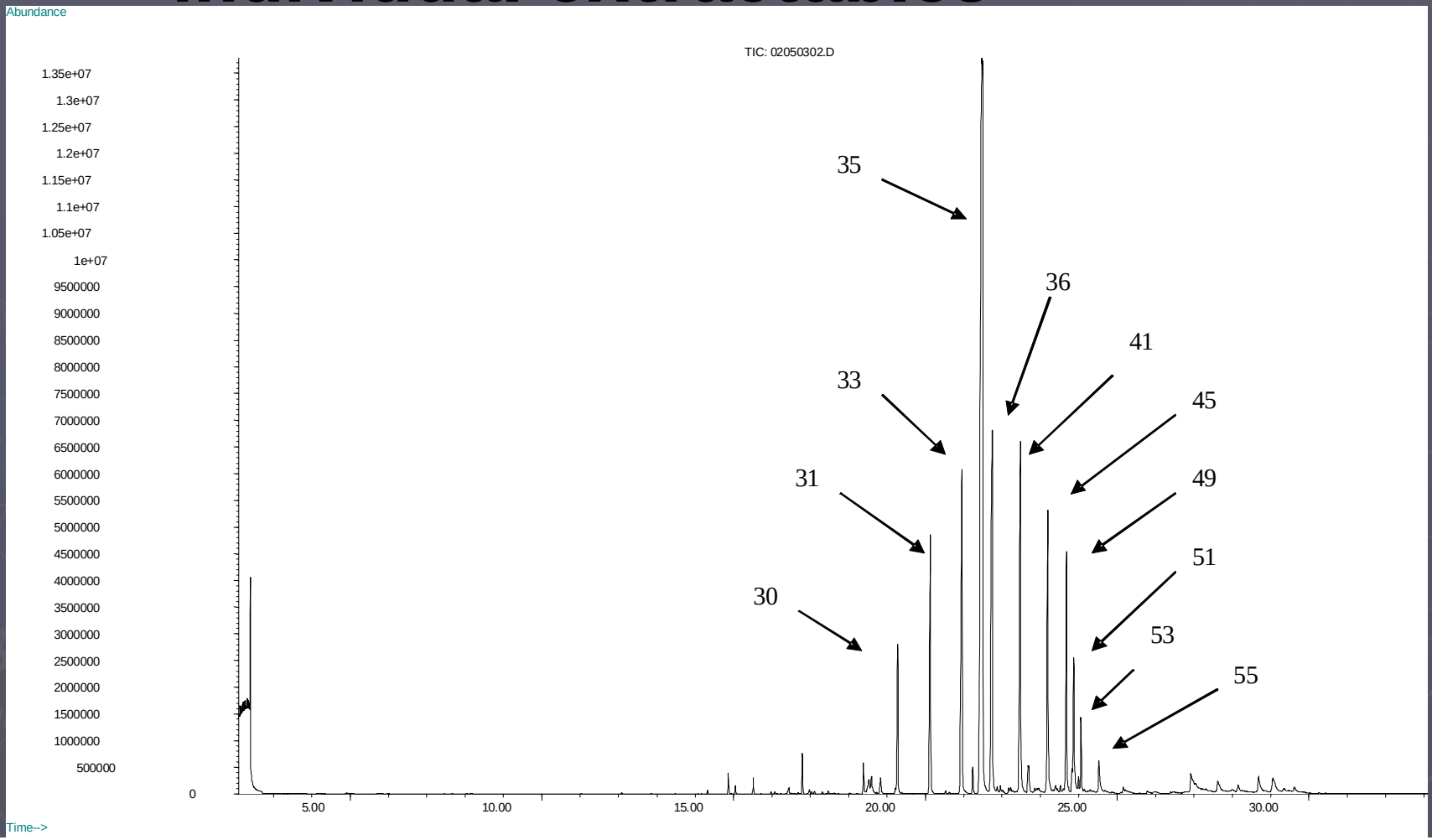
5.3	Bis(dimethylbenzylidene) sorbitol isomer	18.4	Glycerol monopalmitate / Glycerol monostearate
8.6	Unknown	19.0	Irganox 1010 fragment
10.6	Di-tert-butylphenol	19.4	Irganox 1010 related
15.6	Tetradecanoic acid	20.3	Octadecanoic acid
16.0	Hexadecanoic acid	21.0	Irganox 1010

Compound Specific Detection



HPLC-UV chromatogram and m/z 1175 extracted ion current profile

#5 Controlled Extraction Studies should include a defined and systematic process for identification of individual extractables



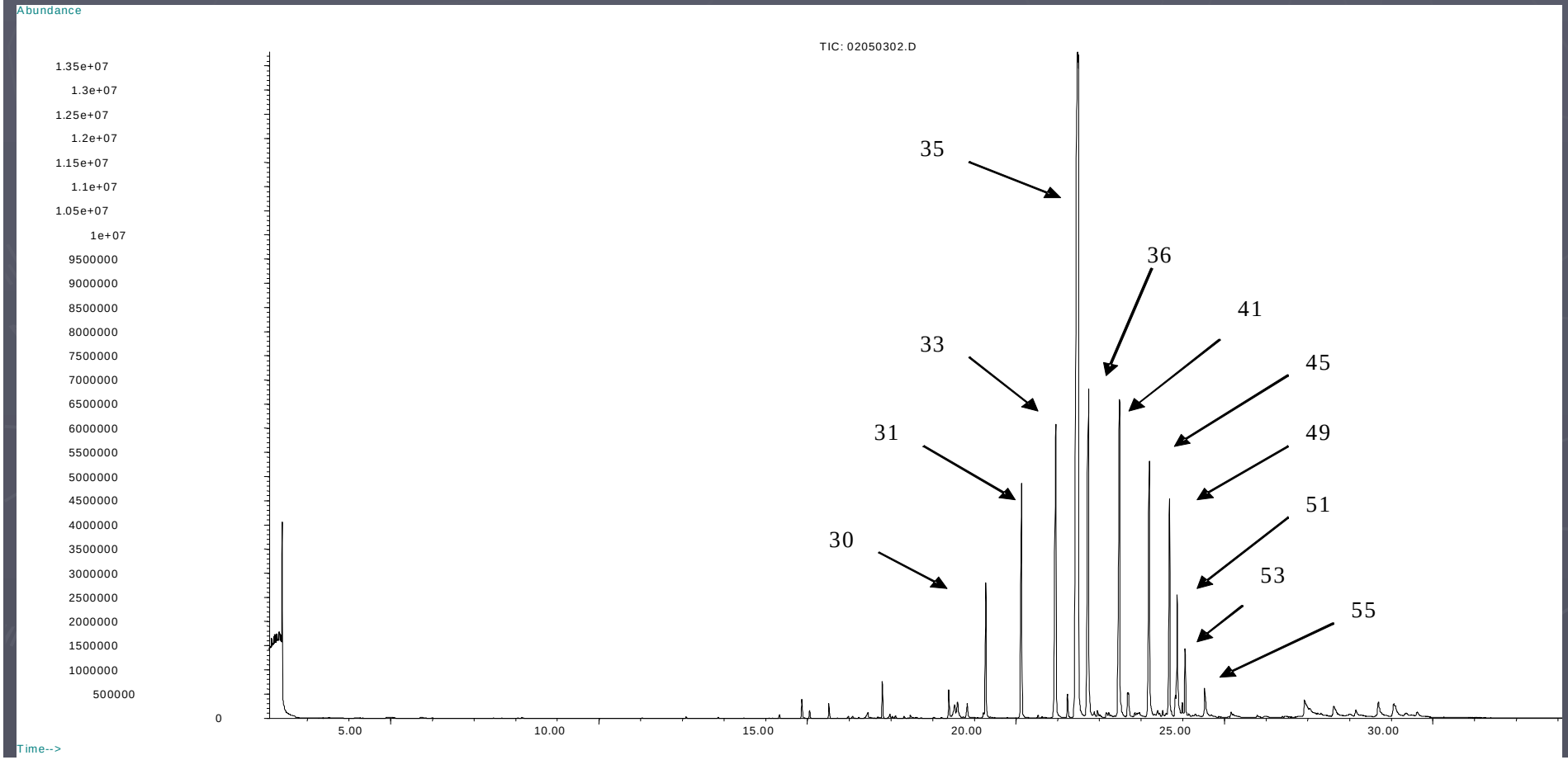
Identification Categories

- Confirmed:
  - **Mass spectrometric fragmentation behavior**
  - **Confirmation of molecular weight or confirmation of elemental composition**
  - **Mass spectrum matches automated library or mass spectrum and chromatographic retention index match authentic specimen**
- Confident:
  - **Sufficient data to preclude all but the most closely related structures have been obtained**
- Tentative:
  - **Data have been obtained that are consistent with a class of molecule only**

Confirmed Peak 21.47 min

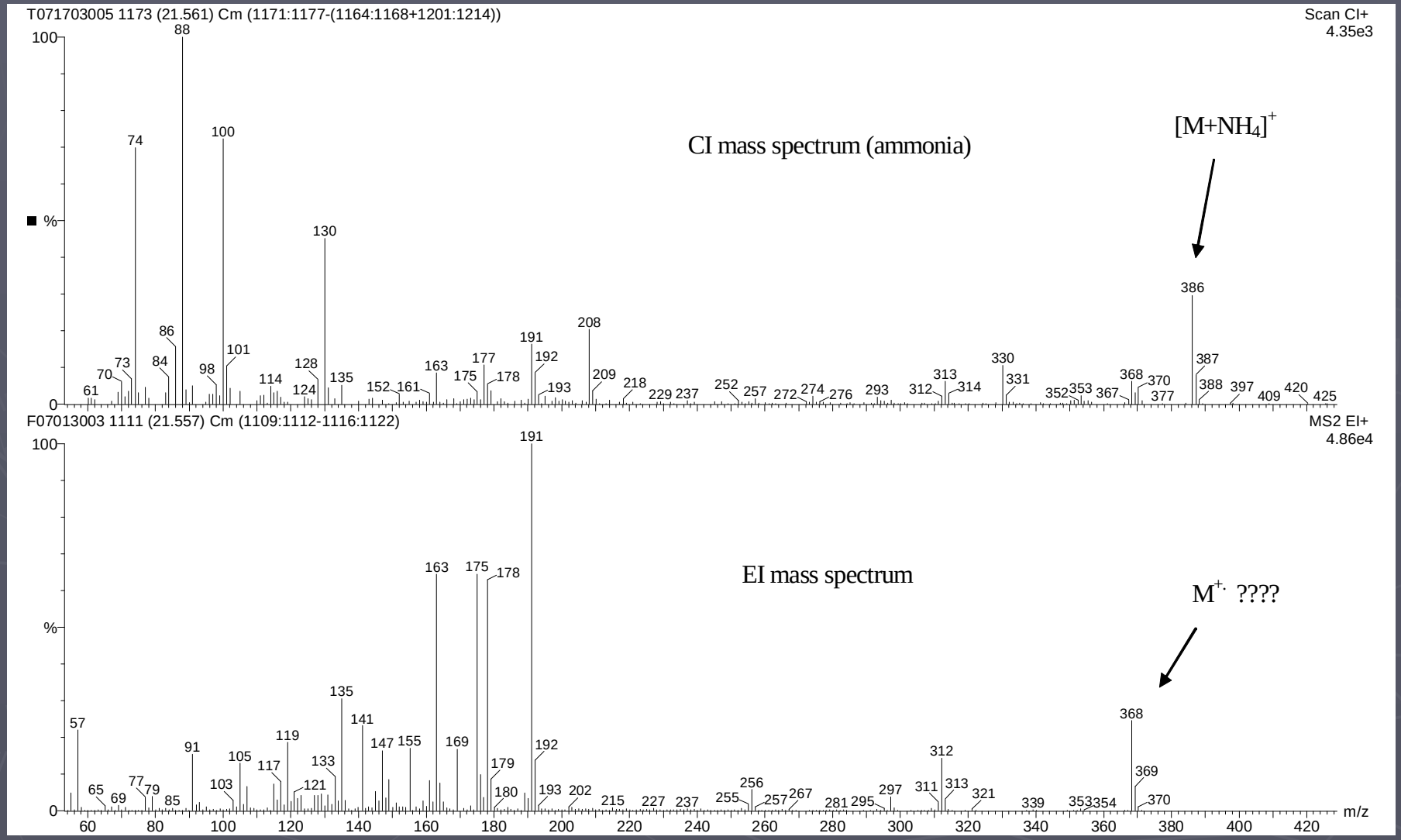
2,2’-methylene-bis-(-6-*tert*-butyl)-4-ethylphenol

Confirmation of Molecular Weight; Fragmentation Behavior; Mass Spectral Library Match; RT Match to Authentic Standard



Confirmed Peak 21.47 min

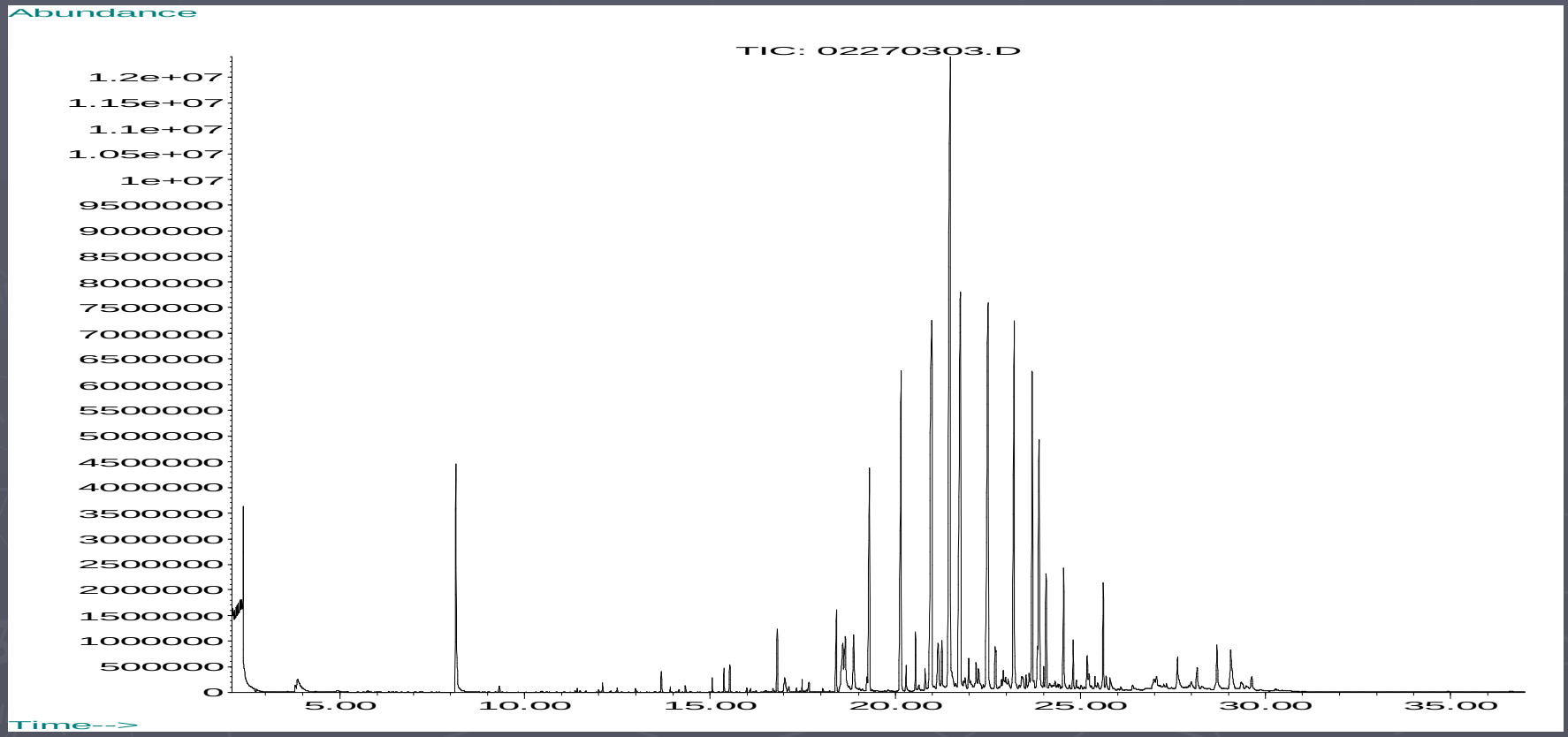
2,2’-methylene-bis-(-6-*tert*-butyl)-4-ethylphenol



Confident Peak 8.15 min

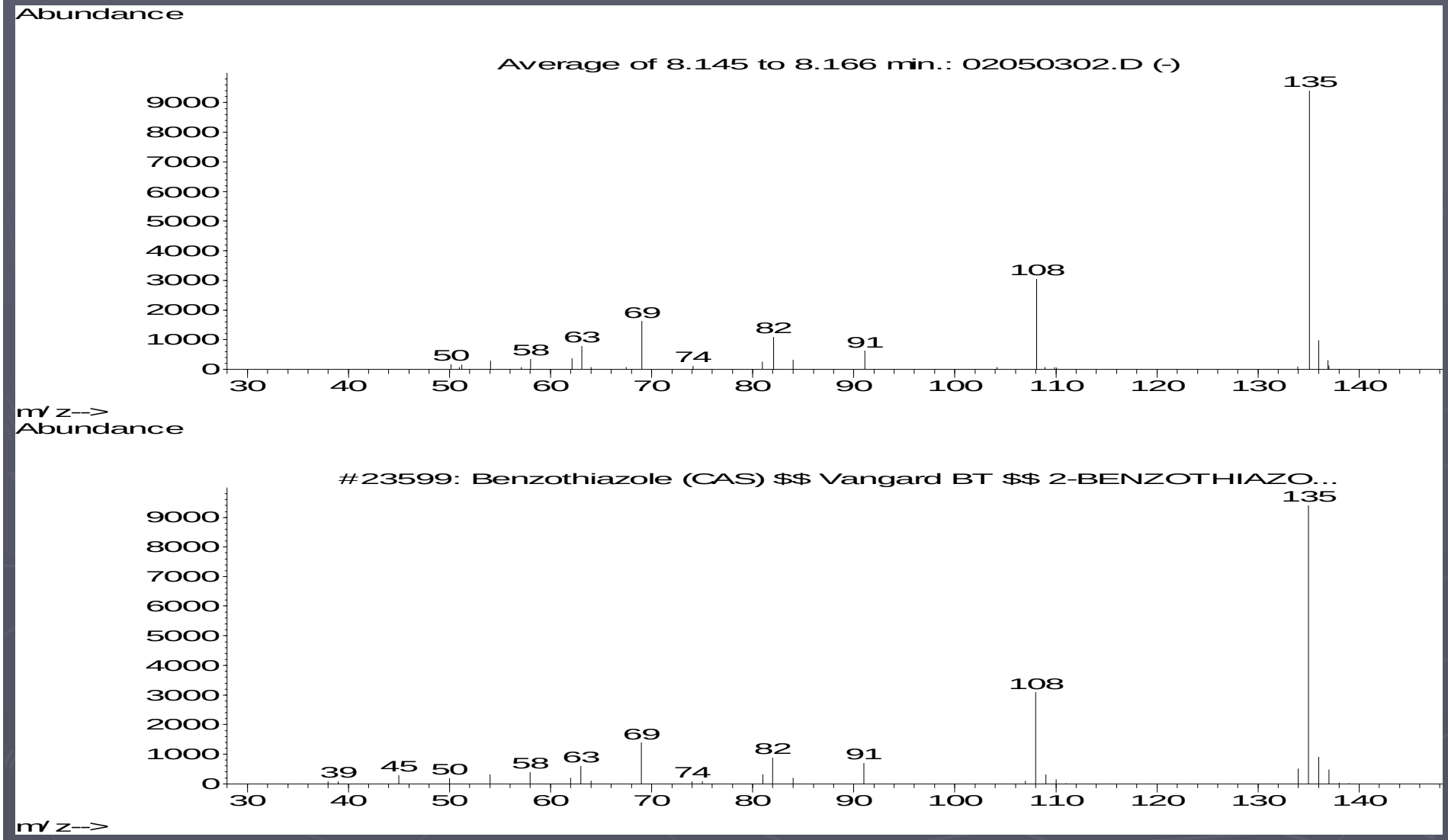
Benzothiazole

Mass Spectrometric Fragmentation Behavior; Mass Spectrum Matches Automated Library Search



Confident Peak 8.15 min

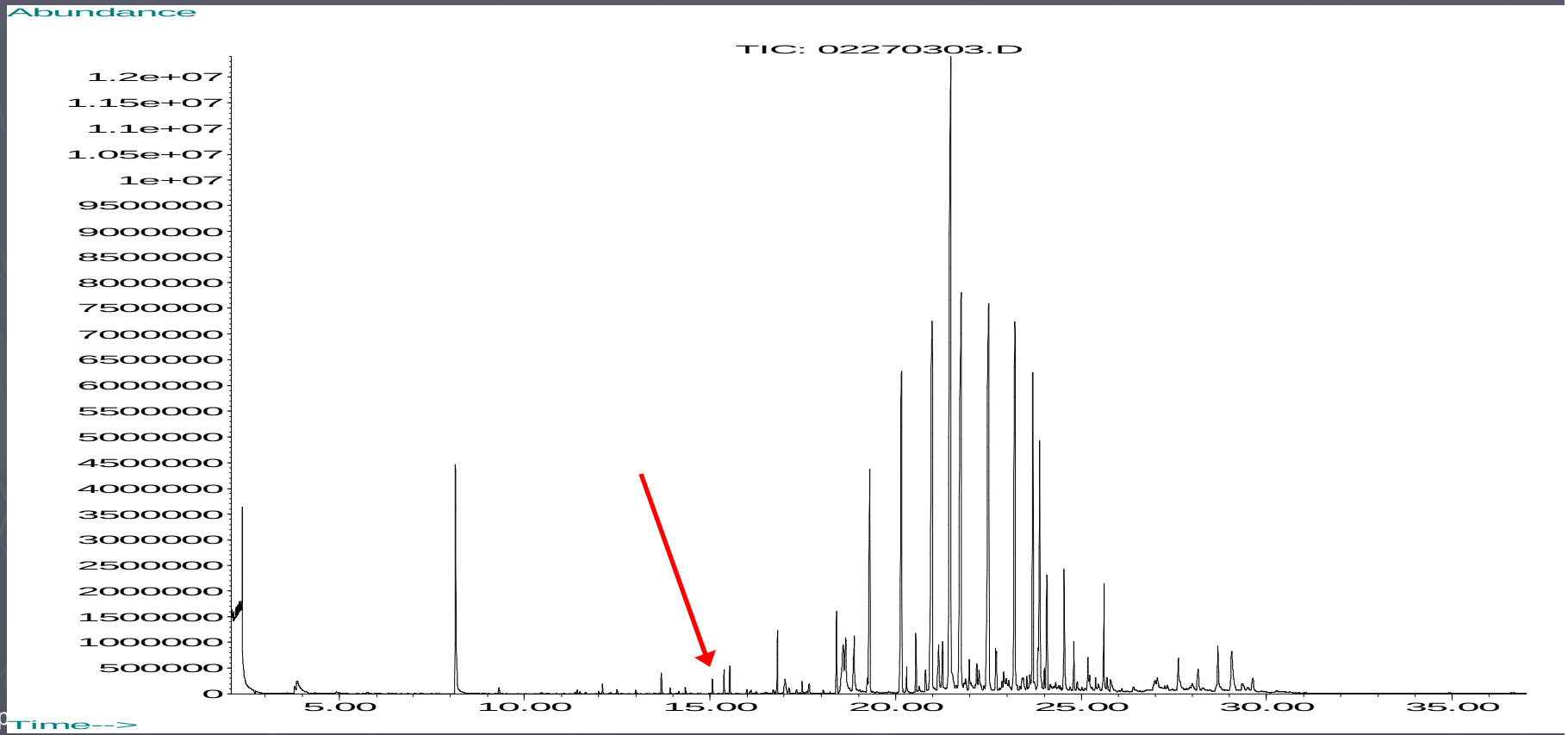
Benzothiazole



Tentative Peak 15.05 min

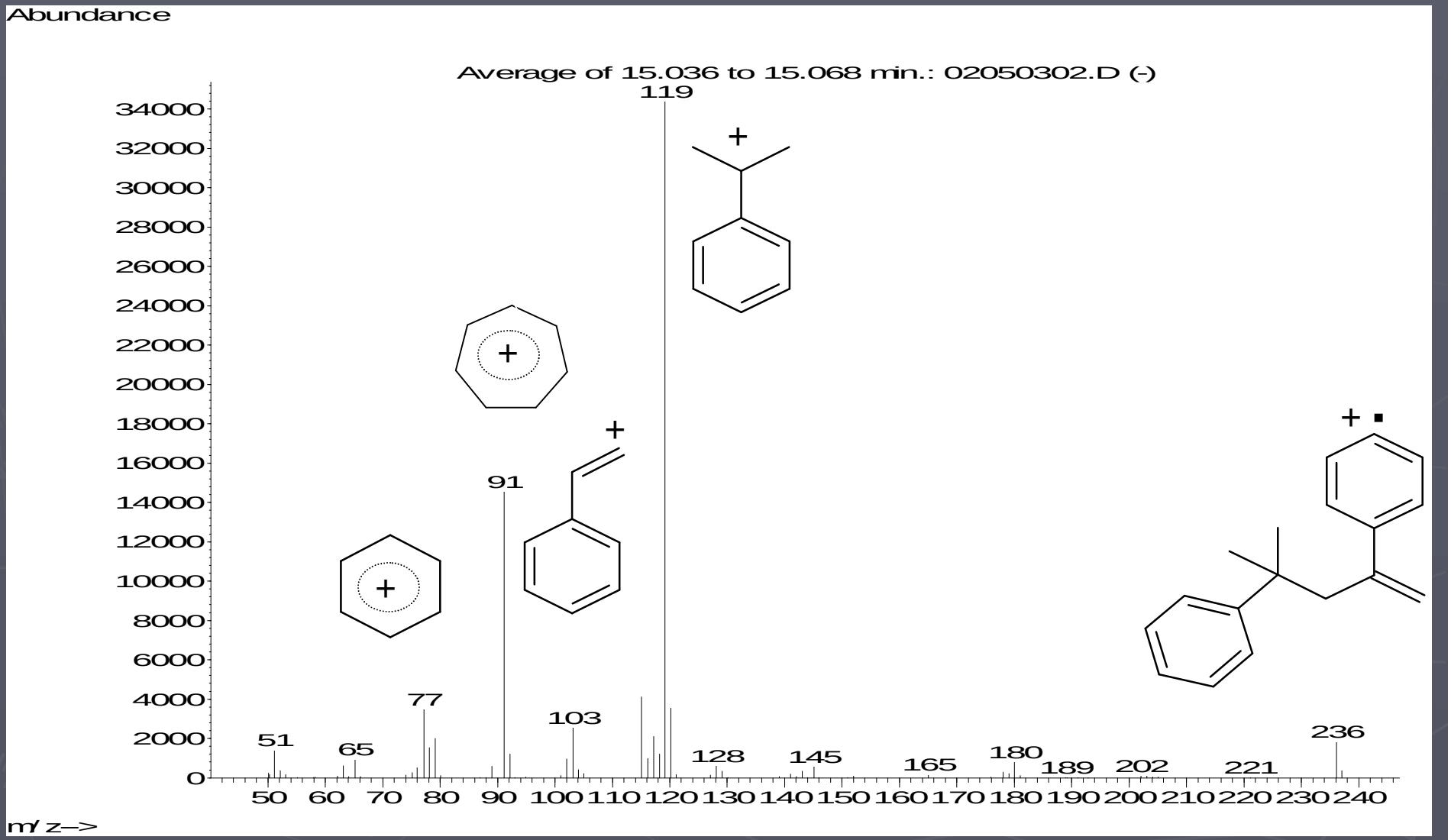
Coumarone-indene resin related

Confirmation of Elemental Composition; Mass Spectrometric Fragmentation Behavior



Tentative Peak 15.05 min

Coumarone-indene resin related



#6 Controlled Extraction Study "definitive" extraction methods should be optimized.

- Asymptotic Levels
- Represent at Least Worst Case Leachables
  - Qualitative
  - Quantitative
- Verification of Quantitative Results
- Basis for Development and Validation of Routine Extractable Control Methods

Sulfur Cured Rubber

Analysis: GC/MS

Extraction: Soxhlet

Optimization:

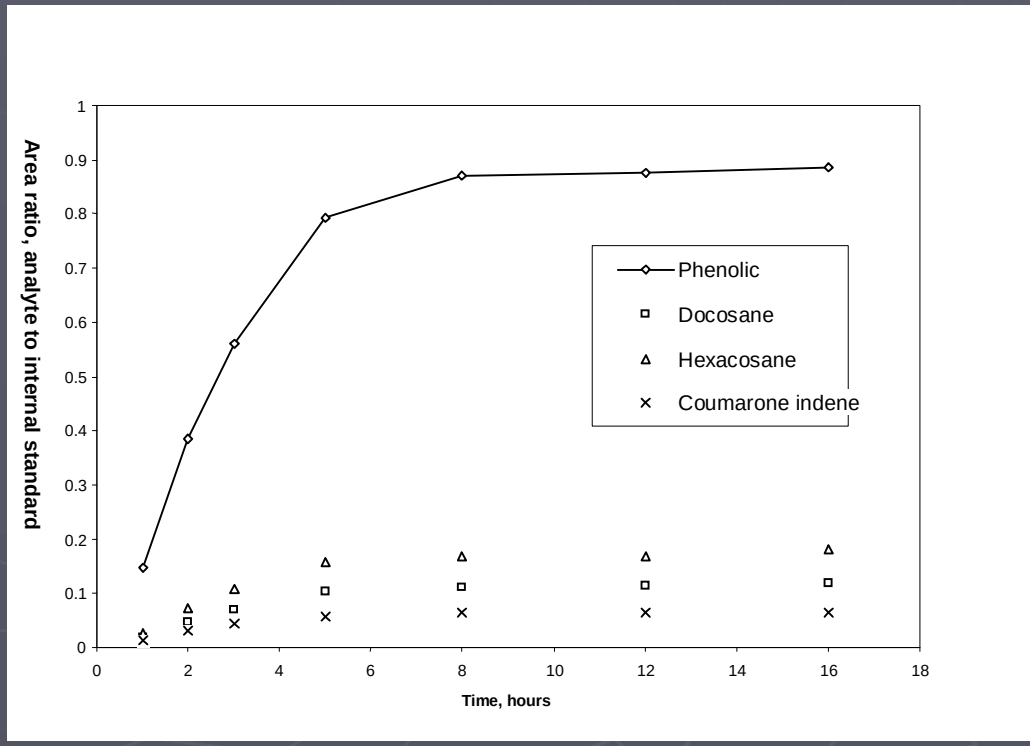
7g/200ml

Methylene Chloride

10:1 Dilution

Internal Standard

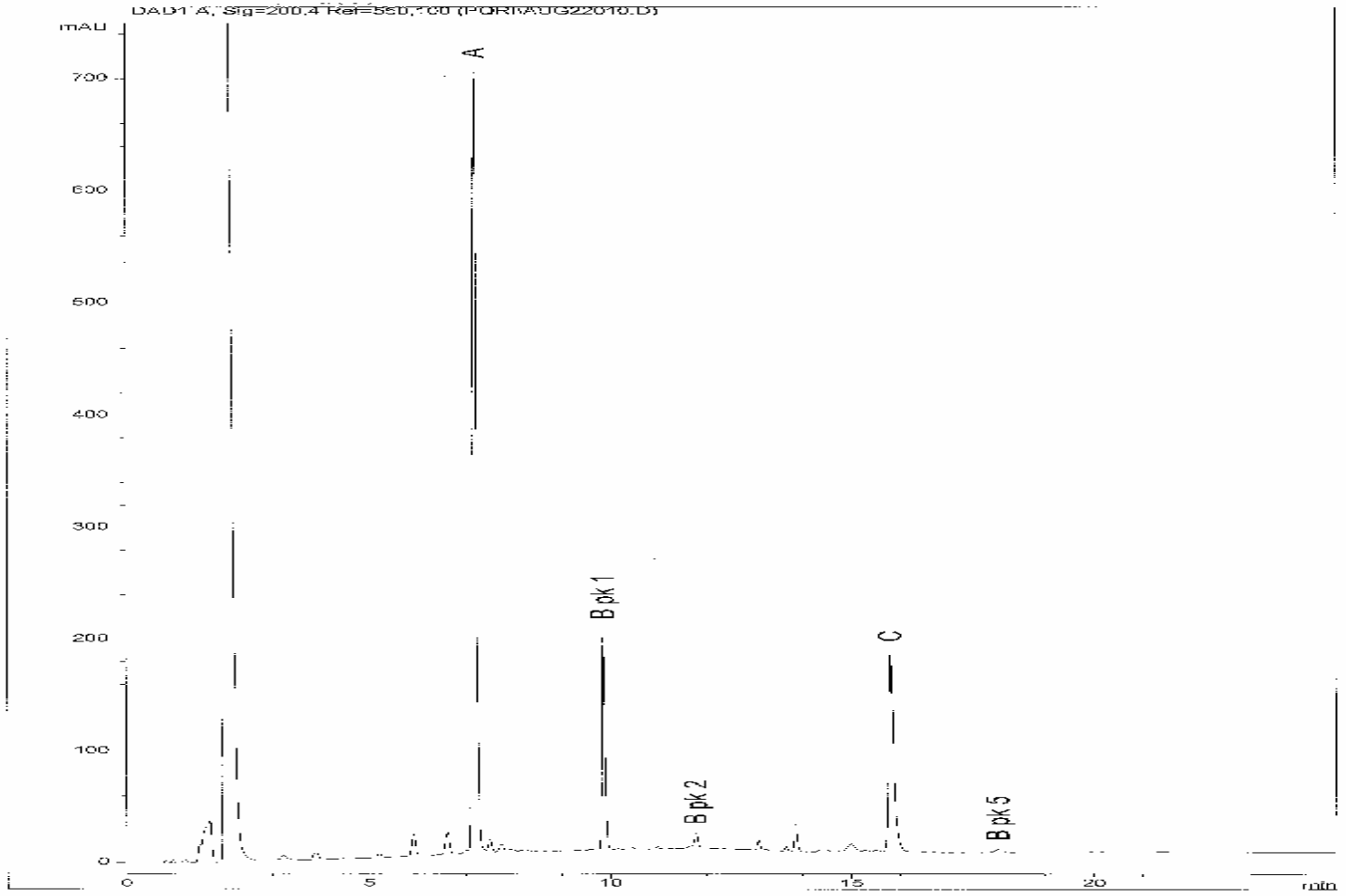
16 Hours Extraction



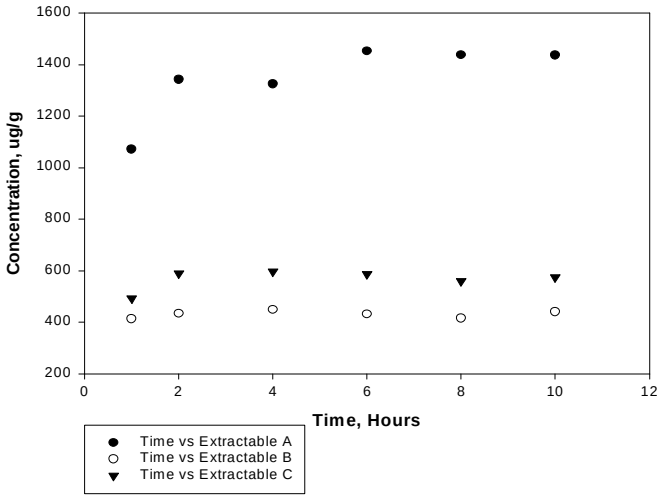
Polypropylene

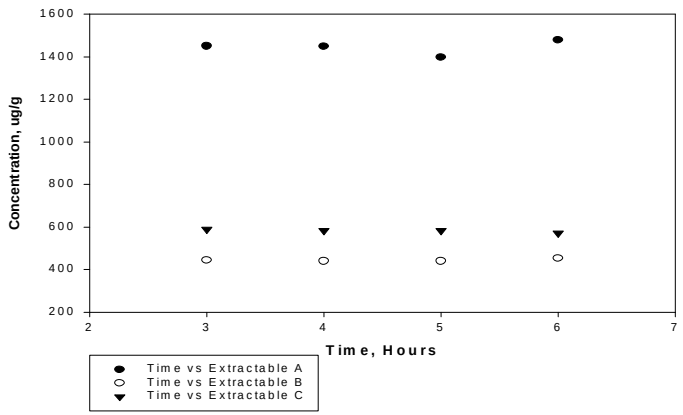
Extraction:	**Reflux**
Analysis:	**HPLC/UV**
Optimization:	**Solvent to Sample Ratio** **Analyte Solubility/Standardization** **Asymptotic Extraction** **Chromatography Conditions**
Results:	**1g:25ml (50/50 THF/IPA)** **3 Hr Extraction**

Polypropylene



Polypropylene





Example Chromatography Conditions

- Qualitative

LC/MS

Column: C18, 4.6mmx25cm, 5u
Injection Vol: 10ul (1/mL/min)
Mobile Phase: <A> 75:25 (ACN:H20)
<B> 50:50 (ACN:THF)
Gradient: 30 min. gradient at 100% A to 100% B hold 12 min
Ionization: APCI
Scan: m/z 50-1350 ,5 sec/scan

- Quantitative

HPLC/DAD

Column: C18, 4.6mmx25cm, 5u @ 60C
Injection Vol: 10ul (1/mL/min)
Mobile Phase: <A> ACN
<B> H2O
Gradient: 25 min. linear gradient at 30:70 A:B to 100% A hold 5min
Detector: Diode Array Detector 200nm, 220nm, bw/4nm; ref.sig 550nm, bw/100nm

Quantitation

Internal Standard

$RRF = (A_a C_i) / (A_i C_a)$

- A_a = Area of Analyte Peak
- C_i = Concentration of Internal Standard
- A_i = Area of Internal Standard Peak
- C_a = Concentration of Analyte

- Concentration in Sample Extract
  $C_a = A_a x\ C_i / A_i x\ RRF$

  Total mass = $C_a$ug/ml x Vol of extract

- Extractable in Component
  µg/g Extractable =
  Total mass (µg)/g Component

External Standard

$RF = C_s / A_s$

- C_s = Concentration of External Standard
- A_s = Area of External Standard

- Concentration in Sample Extract
  $C_a = A_a x\ RF$

  Total mass = $C_a$ug/ml x Vol of extract

- Extractable in Component
  µg/g Extractable =
  Total mass (µg)/g Component

System Suitability Example

Instrument Precision (%RSD)	≤ 10
Resolution (n=6)	≥ 2
Tailing Factor (n=6)	≤ 2
Sensitivity (S/N of MQL)	≥ 10
Method Repeatability (%RSD)	≤ 10%
Intermediate Precision (%RSD)	≤ 10%
Recovery	80-120%

Method Validation

- Acceptance Criteria
  - System Suitability
  - Instrument Precision
  - Chromatographic Resolution
  - Chromatographic Tailing Factor
  - Linearity/Range
  - Precision
    - Method Repeatability
    - Standard Sample Stability
  - Intermediate Precision
  - Specificity
  - Accuracy
  - Limit of Quantitation/Limit of Detection
  - Robustness/Ruggedness

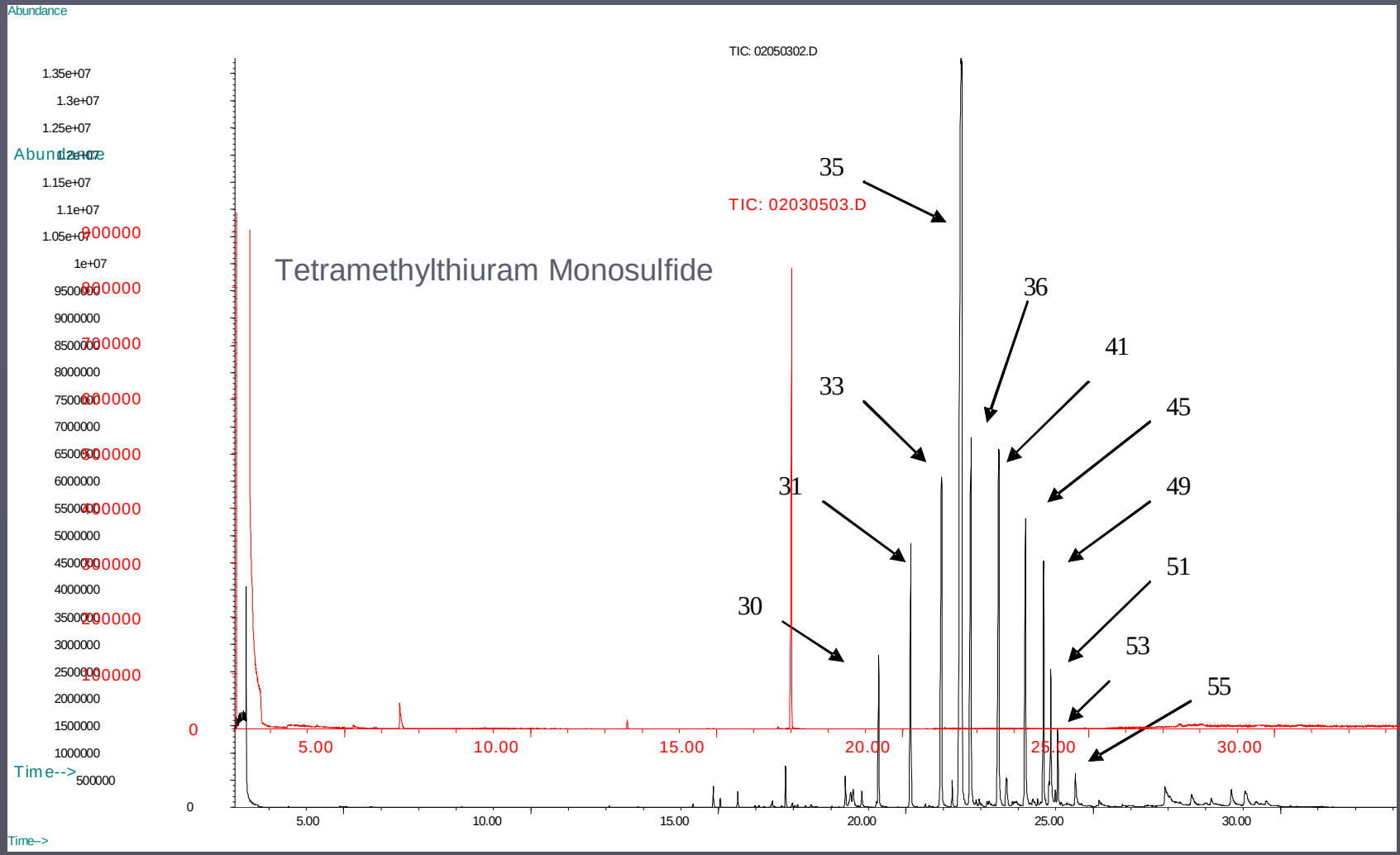
#7 During the Controlled Extraction Study process, sponsors should revisit supplier information

- Investigate
  - Chemical entities found in the extractable data not included in supplier information
  - Known chemical entities not detected in the extractable

Extractable Data

Code Letter	Qualitative Results	Supplier Information	Quantitative Results
C	Tetrakis (methylene(3,5-di-t-butyl-4-hydroxyhyrocinnate)) methane	Phenolic Antioxidants 0.08 %	0.059%
B	Bis(2,4-di-t-butylphenyl)pentaerythritol disphosphite and di-tert butylphenol	Phosphite Antioxidant 0.05%	0.045%
	Calcium Stearate	Stearate Mould Release 0.03 – 0.4%	Not Detected
	Glycerol monopalmitate/monostearate	Vegetable oil 0.2 - 0.3 %	Not Detected
	Tetradeconoic, Hexadecanoic and Octadecanoic Acids	N/A	N/A
A	3,4-dimethyldibenzylidene sorbitol	Clarifier 0.2 - 0.3 %	0.14

Known Accelerator



GC-MS of Methylene Chloride Soxhlet Extract

#8 Controlled Extraction Studies should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety evaluation threshold

- How low to go to identify and evaluate individual extractable

AET Extractables

- A leachable dose less than or equal to the SCT is a dose so low that there would be negligible safety concerns from toxic effects.
  - Internal or External Standards can be employed to Measure the SCT level.
  - The sensitivity needed for the extractable and leachable methods can be postulated.
  - Comprehensive extractable studies can be predictive of end of shelf life leachable studies

1st Application of the Analytical Evaluation Threshold (AET)

- Example Nasal Spray Component #1:

  4 doses per day

  120 doses per container

  0.15g tube

- Estimate AET: (Tox Assessment Value)

  Convert SCT (0.15 µgTDI) to µg/container

  $$\frac{0.15\ \mu g/day}{4\ doses/day} \times 120\ doses/container = \mathbf{4.5\ \mu g/tube}$$

  $$\frac{4.5 \mu g/tube}{0.15g\ tube} = \mathbf{30 \mu g/g}$$

How are unknowns measured?

- Estimated
  - Based on Response of
    - Internal Standard
    - Significant Identified Extractable Peak
- Final
  - Incorporate Uncertainty
    - RRF Data Base
    - One %RSD or 50% of Estimated AET

Uncertainty Factor

- **Final AET**

  Tube (30 ug/g)

  50% correction of the estimated AET = 15ug/g

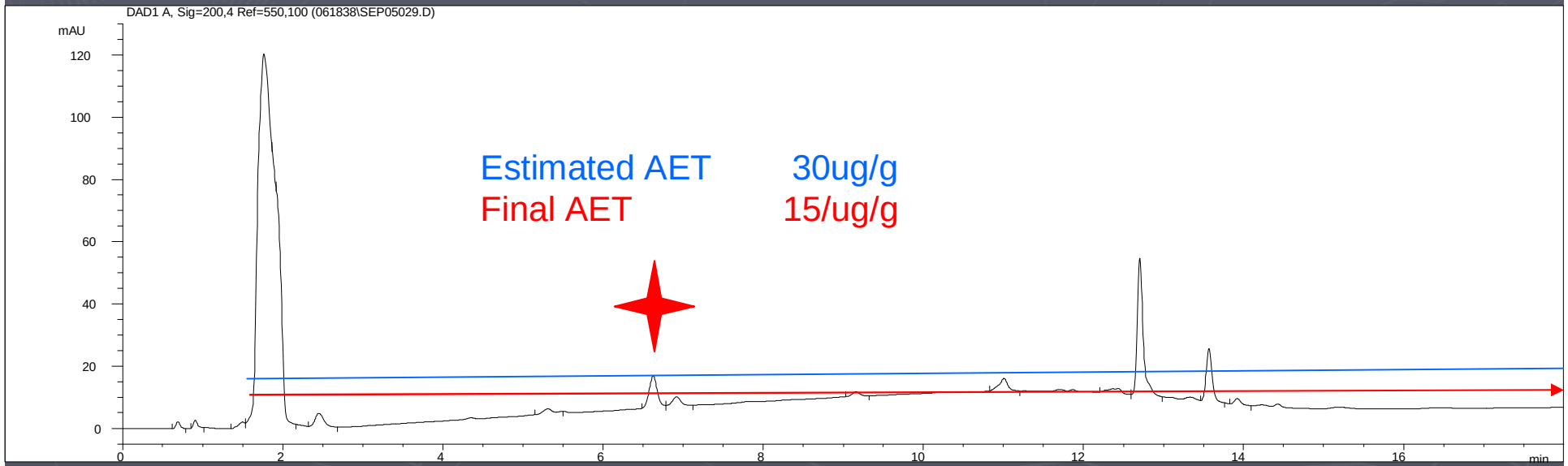
  Estimated AET corrected for one %RSD (i.e., 35%) =20ug/g

What does that mean?

Extractables ≥ The Estimated AET should be Identified to the Extent Possible

Location of the AET (Extractables)

- Extraction
  - 2 grams (100 cm^2) extracted in 100mL of 2-propanol
- AET
  - AET response typical of UV antioxidant species
- Final AET
  - 50% Factor



#9 Polyaromatic Hydrocarbons (PAH's; or Polynuclear Aromatics, PNA's), N-nitrosamines, and 2-mercaptobenzothiazole (MBT) are considered to be "special case" compounds, requiring evaluation by specific analytical techniques and technology defined threshold

#10 Qualitative and quantitative extractables profiles should be discussed with and reviewed by pharmaceutical development team toxicologists so that any potential safety concerns regarding individual extractables, i.e. potential leachables, are identified early in the pharmaceutical development process

Component Profiles

Qualitative

- Sampling and Preparation
- Multiple Solvents
- Sample to Surface Ratio
- Guided by the AET
  - Standard Reference Materials
- Multiple Extraction Techniques
- Multiple Analytical Techniques
  - System Suitabilities

Quantitative

- Evaluate Qualitative Profiles
- Optimize Method
  - Extraction
    - Asymptotic Levels
  - Analysis Conditions/Calibrations
  - Method Accuracy/Precision
- Uncertainty
  - Finalize AET
- Correlation
  - Supplier Information
  - Leachable Studies

Controlled Extraction Study
Summary of Steps

- **Qualitative Profile**
- **Determine Extractable AET**
  - Convert SCT total daily intake to drug product relative units then associate to the mass of the component
- **Quantitative Profile**
  - Selection of Analytes
  - Asymptotic Extractions
  - Linear Dynamic Range
  - Consider Special Case Compounds
- **Optimize Method and Determine Range and Limits**
  - Recovery/Repeatability
  - Based on Techniques used in Controlled Extraction Study
- **Validate Methods**
- **What Next?**

Routine Extractable Testing

- Test Multiple Component Lots
- Correlate to Leachables
- Establish Specification and Acceptance Criteria
- Component Control

Science Based Approach

- Define expectation early
- Understand and apply the science involved
- Select appropriate CCS materials and components
- Apply appropriate upstream controls
- Communicate and Collaborate starting in early stages of drug development
  - With-In company
  - With suppliers
  - With regulatory bodies
- PQRI WG proposal seems to support similar approach

Guirag Poochikian PhD.
PQRI Safety Thresholds and Best Practices for Extractables and Leachables in OINDP
November 2005

Summary of PQRI Recommendations

- Controlled Extraction Studies should:
  - employ vigorous extraction with multiple solvents
  - incorporate multiple extraction techniques
  - include careful sample preparation based on knowledge of analytical techniques to be used
  - employ multiple analytical techniques
  - define a systematic process for identification of individual extractables
  - optimize definitive extraction techniques/methods
  - be evaluated relative to supplier information describing formulation
  - consider special case (PNA, MBT and nitrosoamines) separately
  - review profiles with development team toxicologists to be alerted to safety concerns regarding individual extractables

Conclusion

- Extraction techniques/methods used for Controlled Extraction Studies must be technically justified and optimized to produced extractable profiles at least equivalent to leachable profiles obtained under worst case conditions of drug product use, allowing both qualitative and quantitative extractable leachable correlations
- Properly conducted Controlled Extraction Studies, when accomplished early in the pharmaceutical development process, permit a pharmaceutical development team to begin early evaluation of potential drug product leachables. This evaluation can alert the pharmaceutical development team to potential leachables with toxicological concern, allowing adequate time to begin appropriate safety qualification studies, or modification of CCS system.

Conclusion

- The Best Practices recommendations for Controlled Extraction studies are not meant to be prescriptive or to exclude other scientifically valid approaches, the analytical techniques/methods, or control strategies
- These recommendations represent a consensus with-in the Working Group on current best practices with-in the pharmaceutical industry and are designed to reduce the level of uncertainty with-in the pharmaceutical development process for OINDP

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