

Best Practices for Leachables and Extractables Testing

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Chair – PQRI Leachables and Extractables
Working Group

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Presentation Outline

- Why produce “Best Practice” recommendations?
- The Working Group’s hypothesis
- Laboratory work in support of recommendations
- Recommendation areas
- Introduction to recommendation specifics

Why Produce “Best Practice” Recommendations?

- To reduce uncertainty in the pharmaceutical development process for OINDP.
- To reduce or eliminate “Horror Stories” .
- To support Agency initiatives, such as Quality by Design and Risk Management.

Simulated Project Team Meeting



Can't we all just get along?

Simulated Encounter with Senior Management

Simulated
Project Team
Leader

But it was a
Project Team
decision!!!!

Simulated
VP

Simulated
NDA

Ultimapuff
MDI
(100% ETHANOL)
NDA
REJECTED!
!!!!!!!!!!!!



The Working Group's Hypothesis

1. Scientifically justifiable thresholds based on the best available data and industry practices can be developed for:
 - a. the reporting and safety qualification of leachables in orally inhaled and nasal drug products, and
 - b. reporting of extractables from the critical components used in corresponding container/closure systems.

Reporting thresholds for leachables and extractables will include associated identification and quantitation thresholds.

2. Safety qualification of extractables, would be scientifically justified on a case-by-case basis.

Laboratory Work

- Volunteer laboratories
- Custom made “Test Articles” (3 elastomers and one plastic, all with known formulations)
- Two Phases of extractables work (both protocol driven):
 - Phase 1 – Qualitative Controlled Extraction Studies
 - Phase 2 – Analytical Method Optimization/Validation
- Placebo leachables studies

Chemistry: Volunteer Laboratories

- Boehringer Ingelheim Pharmaceuticals, Inc.
- Cardinal Health (Magellan Laboratories)
- CIBA Expert Services
- Merck and Company, Inc
- West Monarch Analytical Laboratories
- PPD
- Valois, Inc
- West Pharmaceutical Services
- FDA
- Owens Illinois
- Chevron Phillips

Rubber Formulation A (Sulfur Cured)

<u>Ingredient</u>	<u>%</u>
CALCINED CLAY	8.96
BLANC FIXE (barium sulfate)	25.80
CREPE	38.22
BROWN SUB MB	16.84
1722 MB	2.11
ZINC OXIDE	4.04
2, 2' METHYLENE-BIS (6-TERTIARY BUTYL-4-ETHYL PHENOL)	0.56
COUMARONE-INDENE RESIN	1.12
PARAFFIN	1.12
TETRAMETHYLTHIURAM MONOSULFIDE	0.11
ZINC 2-MERCAPTOBENZOTHAZOLE	0.29
SULFUR	0.84

Polypropylene Formulation

Ingredient

wt %

- **Primary Stabilizers**

Tetrakis (methylene(3,5-di-t-butyl-4-hydroxyhydrocinnamate)) methane

Irganox 1010 (Ciba)

0.08 wt%

Anox 20 (Great Lakes)

- **Secondary Stabilizers**

Bis(2,4-di-t-butylphenyl)pentaerythritol diphosphite

Ultranox 626 (GE)

0.05 wt%

Polypropylene Formulation

Ingredient

wt %

- **Corrosion Inhibitors**

Calcium Stearate 114-50 (Ferro)

0.03 - 0.4 wt%

- **Antistatic**

Vegetable oil derived

90% alpha monoglycerides (soybean)

Pationic 901 (Patco)

0.3 wt%

Dimodan HS-KA (Danisco)

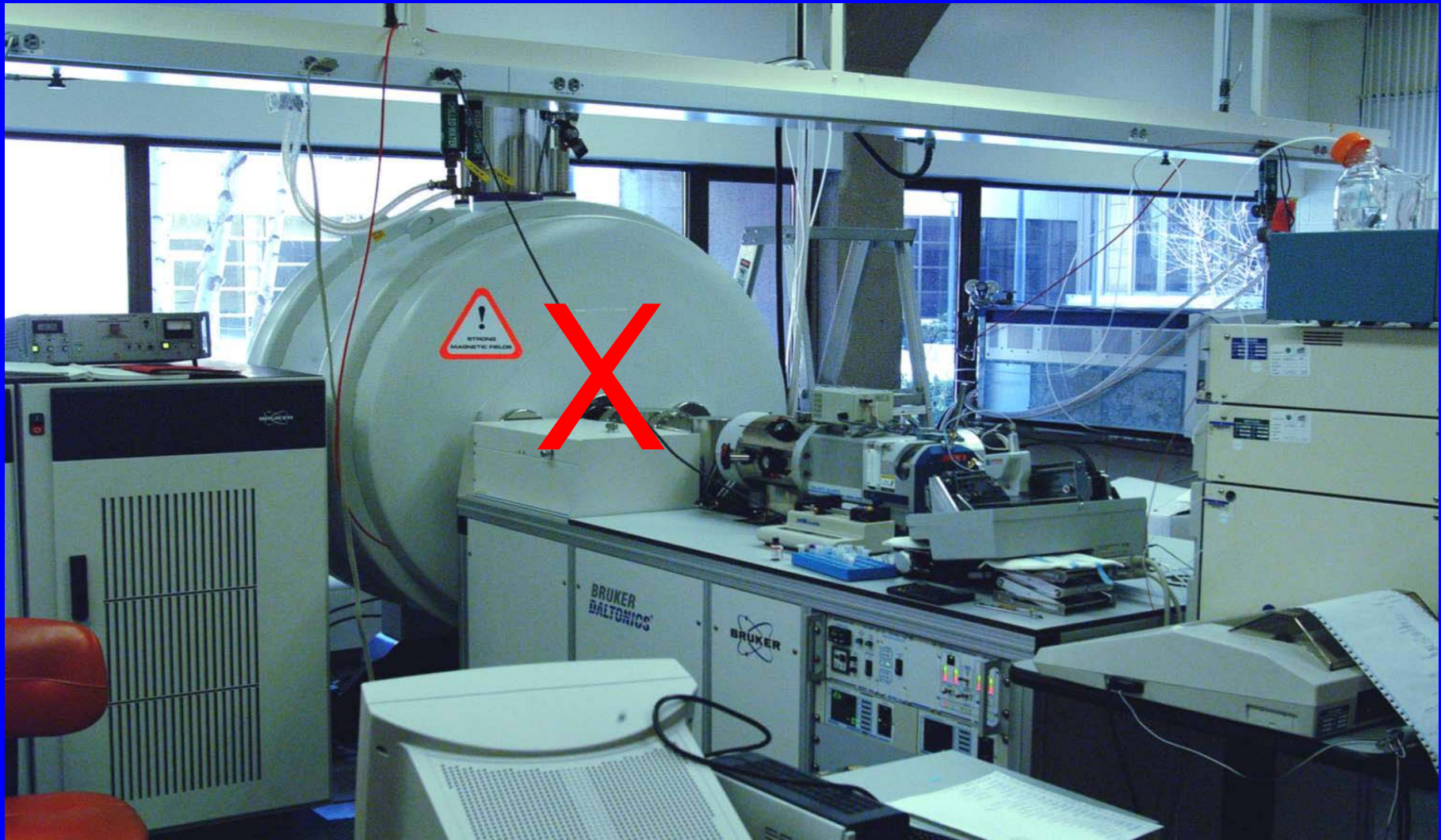
- **Nucleating Agents**

3,4 -dimethyl dibenzylidene sorbitol

Millad 3988 (Milliken)

0.2 wt%

State-of –the-Art Instrumentation



A "Modern" LC/MS System



Chemistry: Phase 1 Studies

- Controlled Extraction Studies
- Multiple solvents with differing polarities:
 - Dichloromethane, 2-propanol, hexane
- Multiple extraction techniques
 - Sonication, Soxhlet, reflux
- Multiple analytical techniques
 - GC/MS, LC/UV (DAD), LC/MS

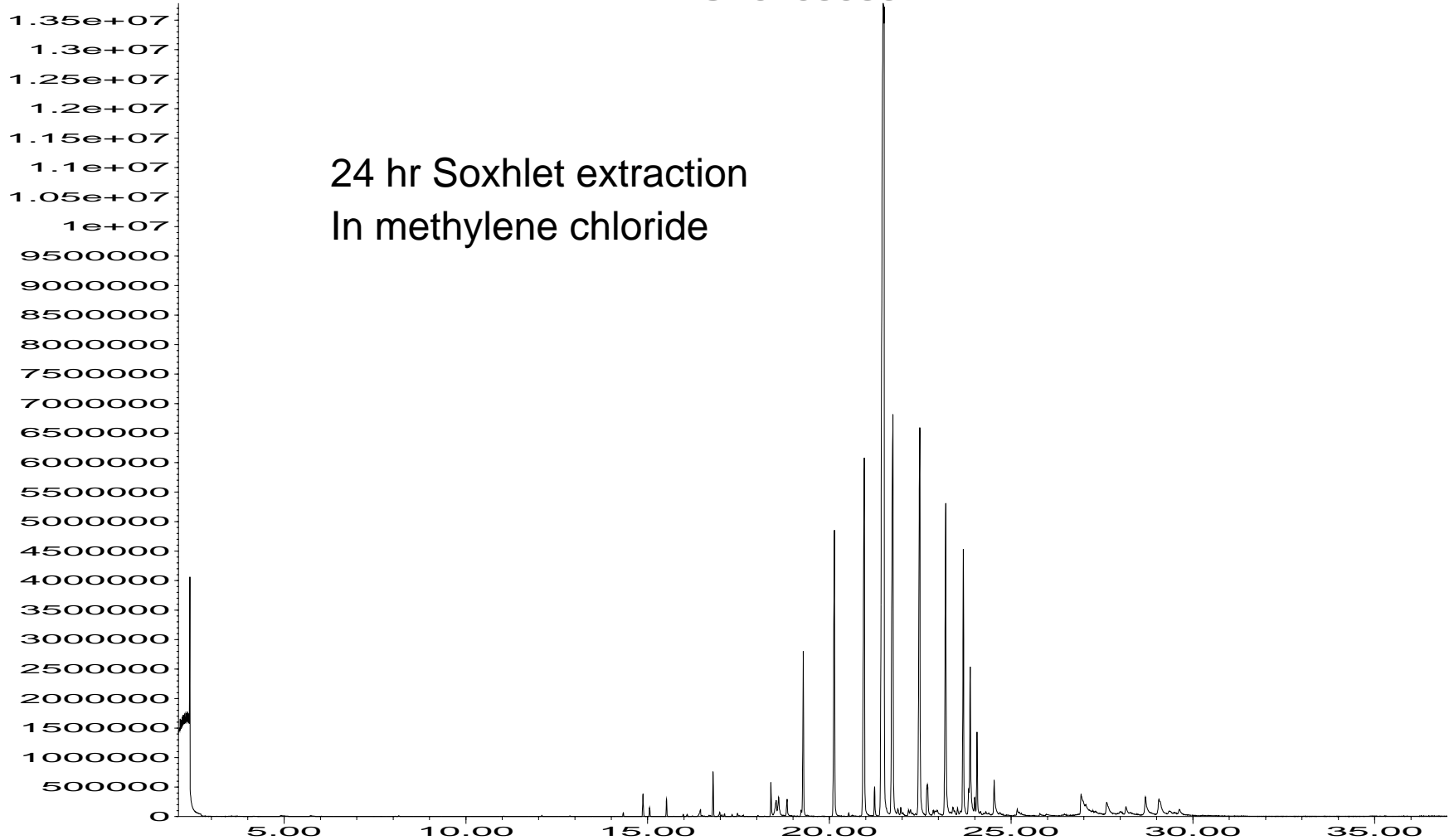
Representative Extraction Apparatus



GC/MS Extractables Profile of the Sulfur-Cured Elastomer

Abundance

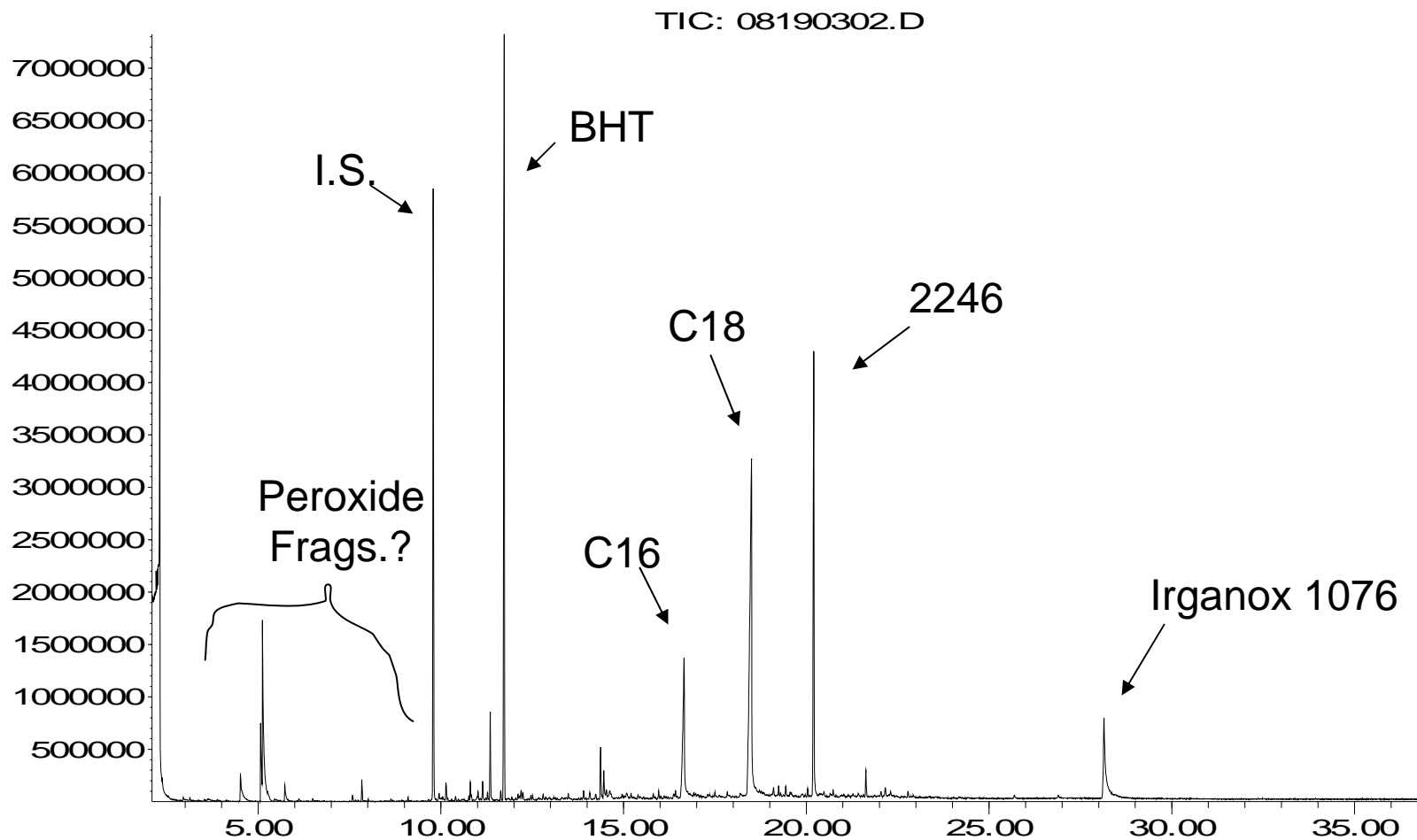
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GC/MS Extractables Profile of Valois Elastomer Methylene Chloride Soxhlet Extract

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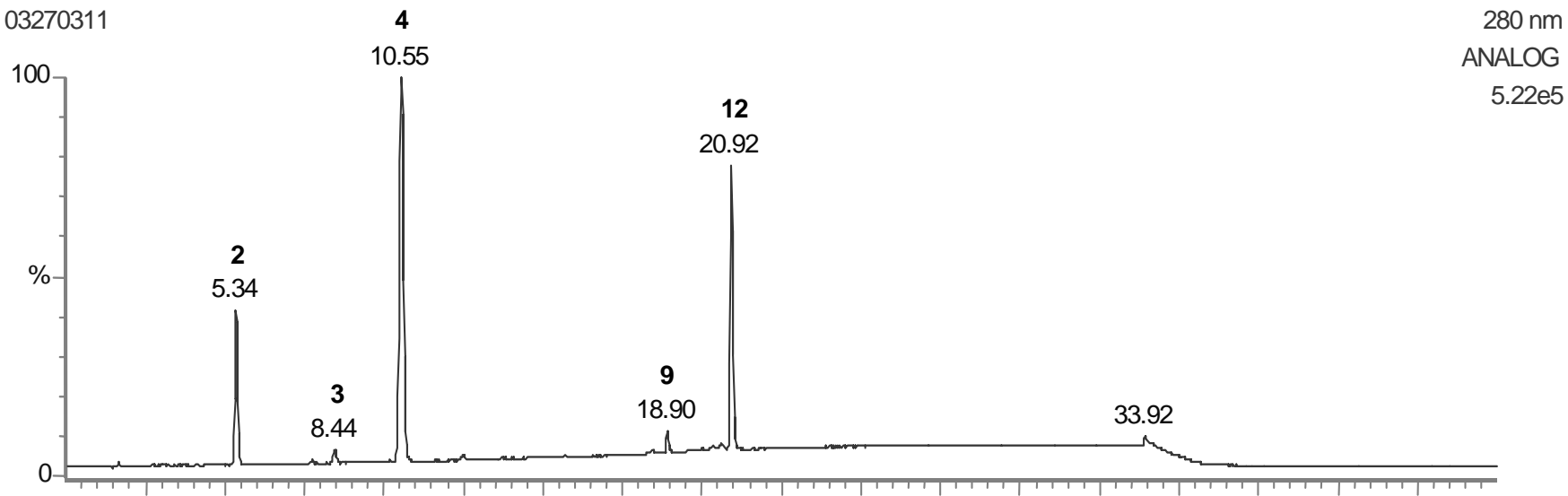


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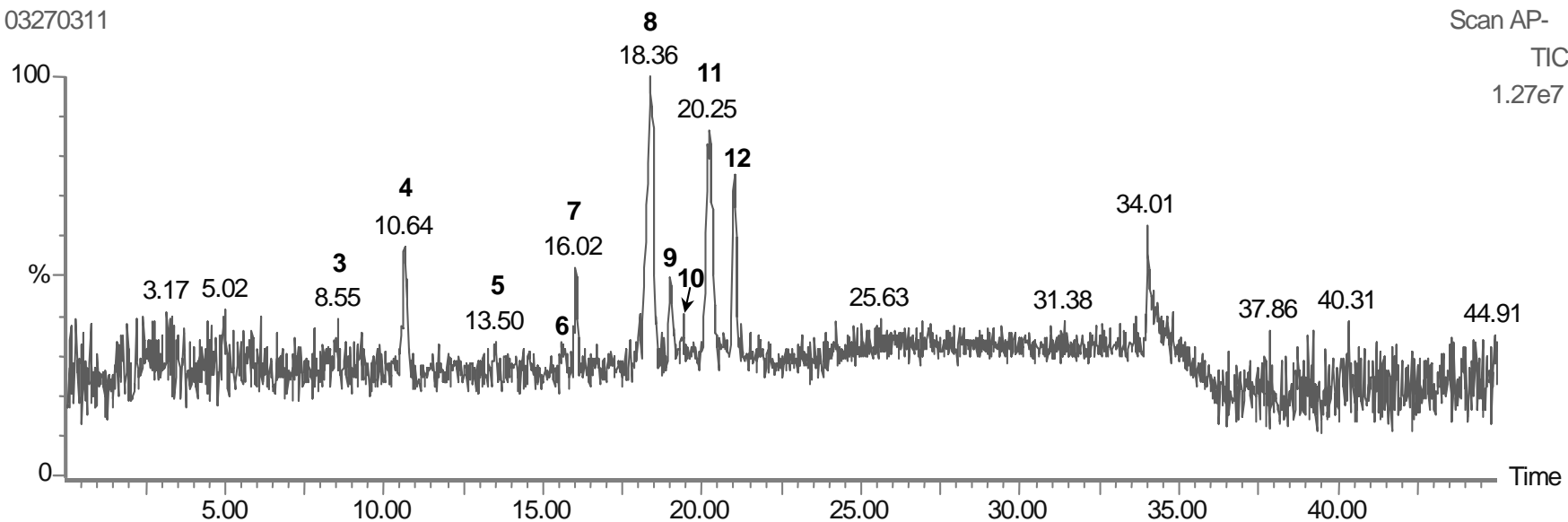
LC/MS Extractables Profile of Polypropylene Methylene Chloride Reflux Extract

Reflux PP Disc/CH₂Cl₂

03270311



03270311



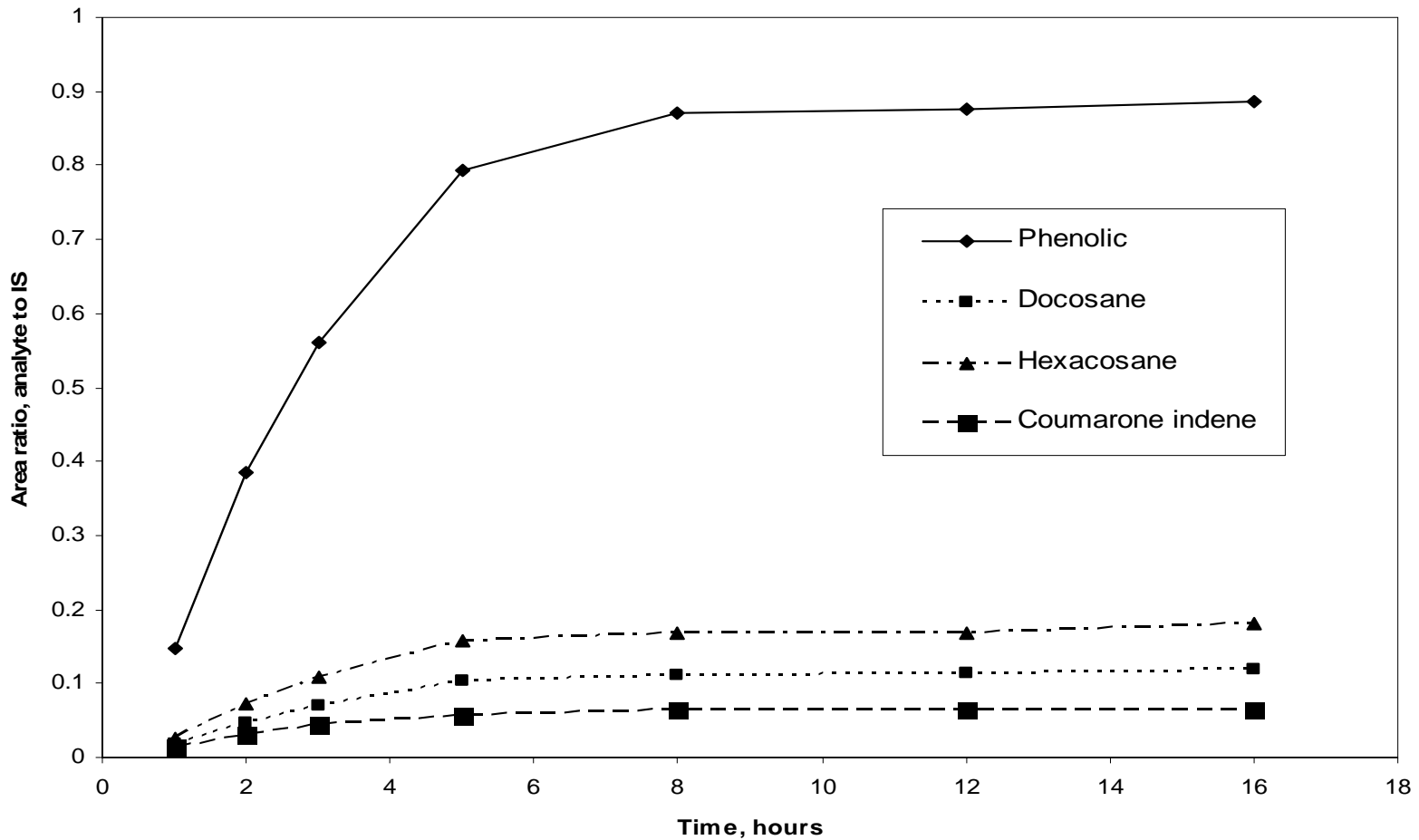
Chemistry: Phase 2 Studies

- **Sulfur-cured elastomer (Ciba)**
 - Completed optimization of extractions using Soxhlet extraction with methylene chloride
 - Completed validation on GC/FID method
 - Details available in poster presentation

- **Polypropylene (West Monarch)**
 - Completed optimization of extractions using reflux in isopropanol and THF
 - Completed validation of LC/UV method
 - Details available in poster presentation

SULFUR-CURED ELASTOMER EXTRACTABLES

PQRI Extractives Phase II Exp. 2



Placebo Leachables Study

- Samples contained in formulation development bottles (plastic coated)
- CFC-11
- Sulfur-cured elastomer



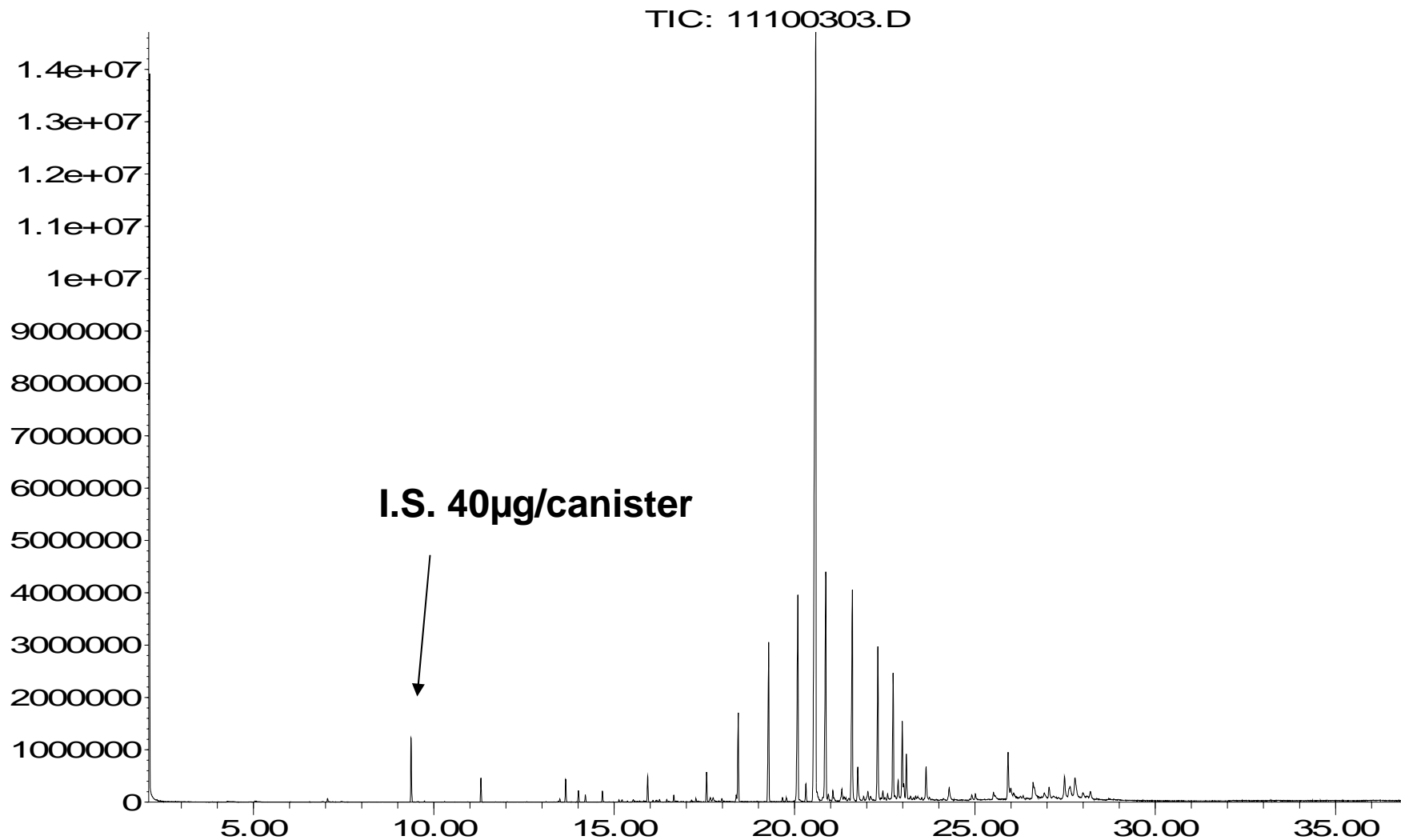
Laboratory Scale Stability Chamber

- Note inner door
- Note placebo leachables study in storage
- 40°C/75%RH
- 3 months storage anticipated



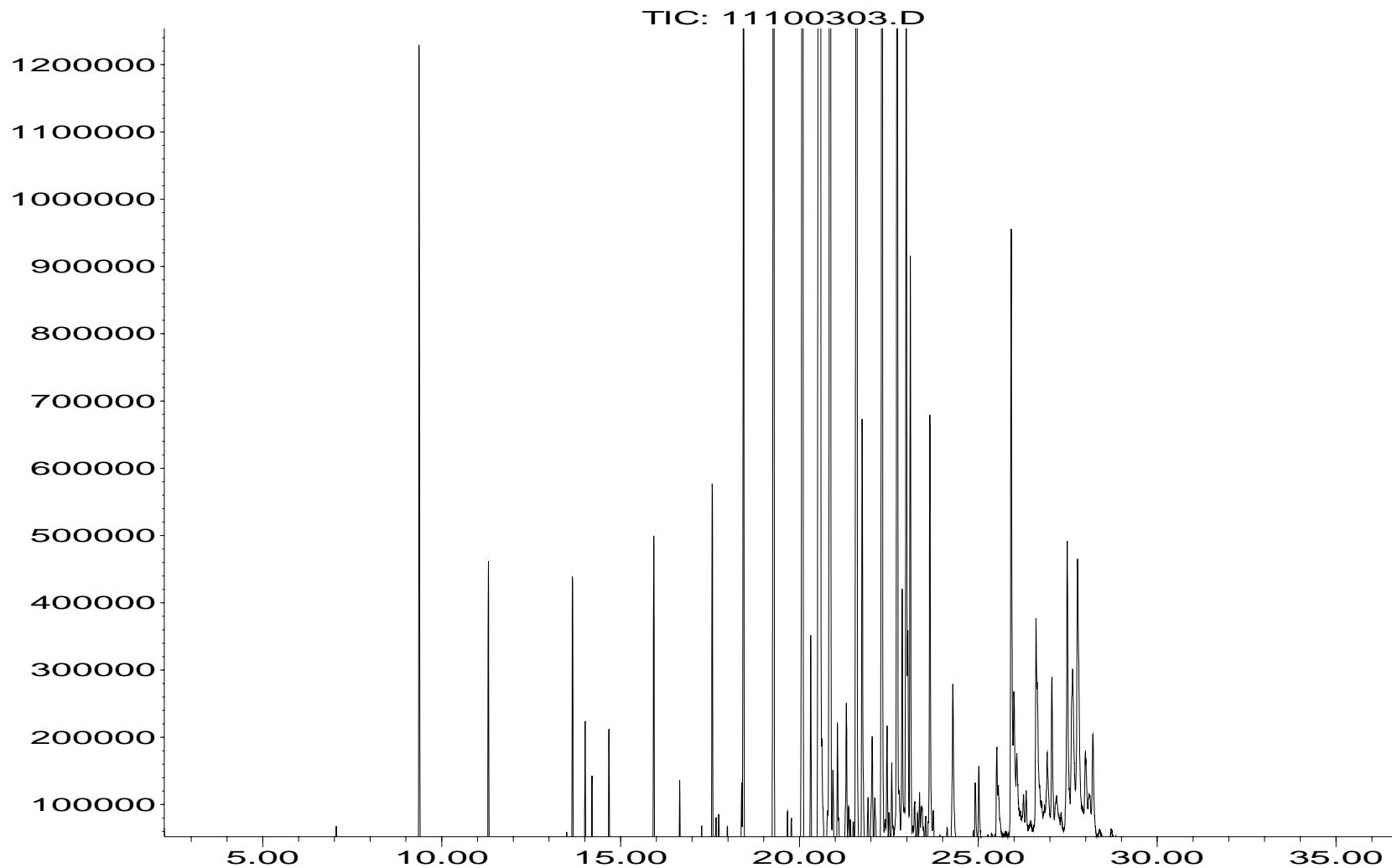
Leachables Profile – 1 Week Timepoint

Abundance



Leachables Profile – 1 Week Timepoint Expanded

Abundance



Time-->

Recommendation Areas

- Container/Closure System Components – Composition and Selection
- Controlled Extraction Studies
- Leachables Studies and Routine Extractables Testing
- The Analytical Evaluation Threshold (AET)

Specific Questions Addressed

1. What does it mean to “identify” a leachable or extractable?
2. How do you “correlate” extractables and leachables profiles? What does the term “correlate” mean?
3. How do you optimize extractables methods? What are “asymptotic” levels?

Introduction to Recommendation Specifics

1. Component Selection – Fran DeGrazio
2. Controlled Extraction Studies – Tom
Feinberg
3. Leachables Studies and Routine
Extractables Testing – Diane Paskiet
4. Analytical Evaluation Threshold – Dan
Norwood

Final Points

- The “Best Practice” recommendations are designed to be comprehensive.
- We welcome your comments and suggestions.
- I did not personally create the issue of leachables/extractables in OINDP.