Development and Application of the Analytical Evaluation Threshold

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Presentation Outline

- The Working Group’s hypothesis
- AET and SCT
- Process for determining AET
- MDI example
- Recommendation details

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.

Definition of the AET

"The AET is defined as the threshold at or above which an OINDP pharmaceutical development team should identify and quantify a particular extractable and/or leachable and report it for potential toxicological assessment."

Process

1. Convert the SCT (0.15 µg/day for an individual organic leachable) to an Estimated AET *(e.g. µ*g/canister for an individual organic leachable in an MDI) by considering the dosing and other parameters of the particular OINDP.
2. Convert the Estimated AET for leachables to an Estimated AET for extractables *(e.g. µ*g/g elastomer for an individual organic extractable) by considering the parameters of the particular OINDP container closure system (*e.g.* weight of elastomer per MDI valve).
3. Locate the Estimated AET on a particular leachables or extractables profile (*e.g.* a GC/MS Total Ion Chromatogram).
4. Evaluate the uncertainty of the particular analytical technique/method (*e.g.* GC/MS response factors for various potential extractables/leachables).
5. Convert the Estimated AET to a Final AET by considering this analytical uncertainty.

Recommendation - MDIs

"The Working Group recommends that AETs for MDI leachables profiles be based on the Safety Concern Threshold (SCT) of 0.15 µg/day for an individual organic leachable.

This recommendation includes potential organic leachables derived from critical components of the dose metering valve, canister inner surface, and inner surface coating if present."

Absolute Leachables Levels Assuming 0.15 µg/day

MDI Drug Product	Estimated Formulation Parameters from Product Labeling			Leachable Concentration Yielding 0.15 µg/day Intake	
	Formulation Net Weight (grams)	**Number of Actuations Per Can**	**Maximum Actuations Per Day**	(µg/g)	(µg/can)
Flovent 110	7.9	60	8	0.14	1.1
Alupent	7.0	100	12	0.18	1.3
Beconase *	6.7	80	8	0.22	1.5
QVAR	7.3	100	8	0.26	1.9
Nasacort *	9.3	100	8	0.20	1.9
Tilade	16.2	104	8	0.12	2.0
Azmacort	20.0	240	16	0.11	2.3
Proventil HFA	6.7	200	12	0.37	2.5
Ventolin HFA	18.0	200	12	0.14	2.5
Combivent	14.7	200	12	0.17	2.5
Atrovent	14.0	200	12	0.18	2.5
Serevent †	13.0	120	4	0.35	4.5
Maxair	14.0	400	12	0.36	5.0
median	13.0	120	12	0.18	2.3

Leachable concentrations corresponding to 0.15 µg/day intake are estimates calculated from formulation parameters as stated in the US product labeling. These estimates are for illustrative purposes only and should not be used for decision making because they may not reflect actual MDI formulation parameters.
Leachable µg/can at 0.15 µg/day = 0.15 µg/day × Actuations/can ÷ Actuations/day
Leachable µg/g at 0.15 µg/day = µg/can ÷ Net Formulation Weight
* Nasal inhalation drug product.
† No longer marketed in US.

Recommendation - MDIs

For example, consider an MDI with 200 labeled actuations per canister, a recommended dose of 12 actuations per day, and a critical component elastomer mass per valve of 200 mg. For an individual organic leachable derived from this elastomer, the estimated AET would be:

$$Estimated\ AET = \left(\frac{0.15\ \mu\text{g/day}}{8\ \text{actuations/day}} \times 200\ \textit{labeled}\ \text{actuations/canister} \right)$$

$$Estimated\quad AET\ \approx 3.75\ \mu\text{g/canister}$$

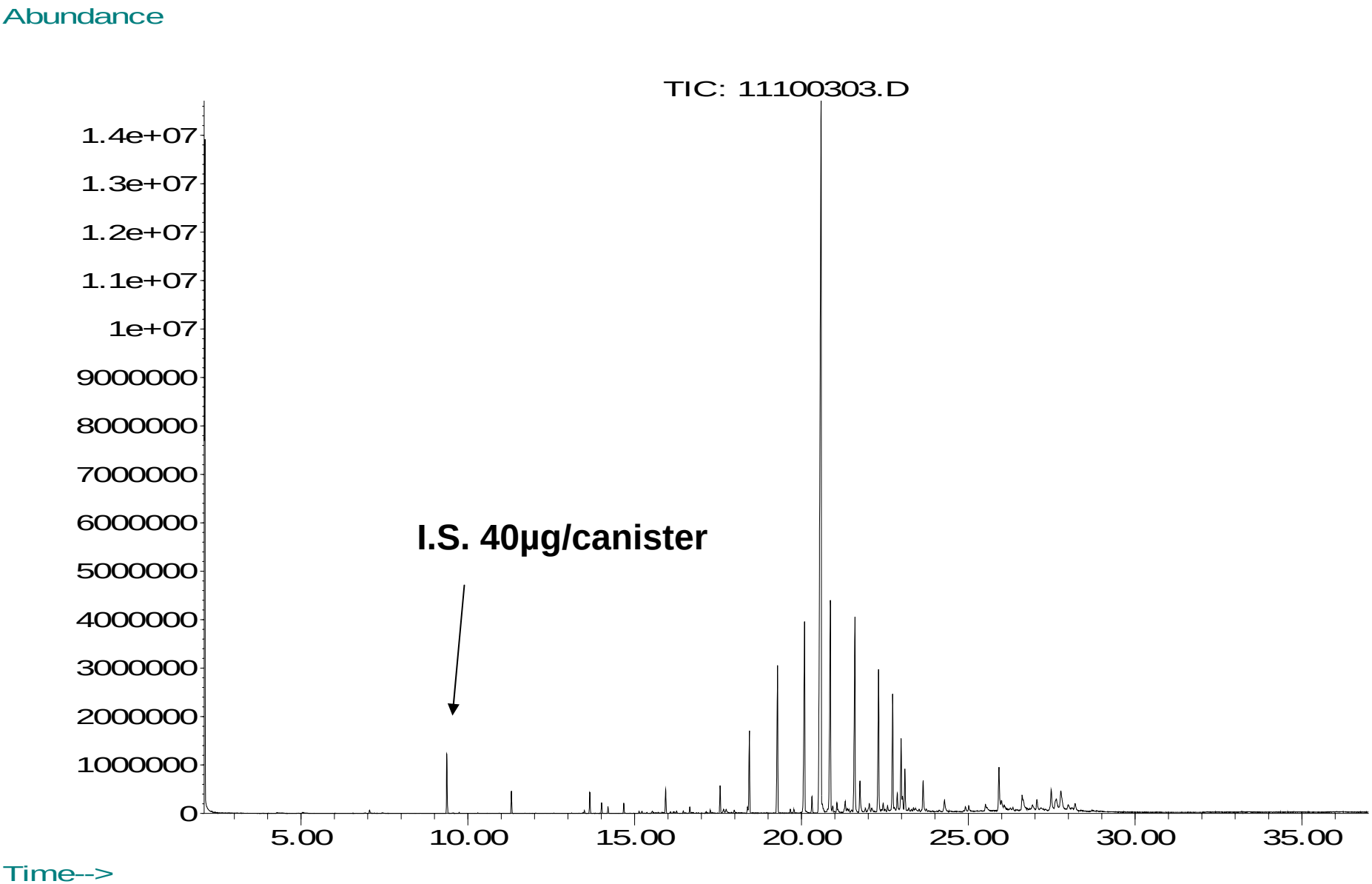
Recommendation - MDIs

Converting to an Estimated AET for individual extractables in an extractables profile of this particular elastomer:

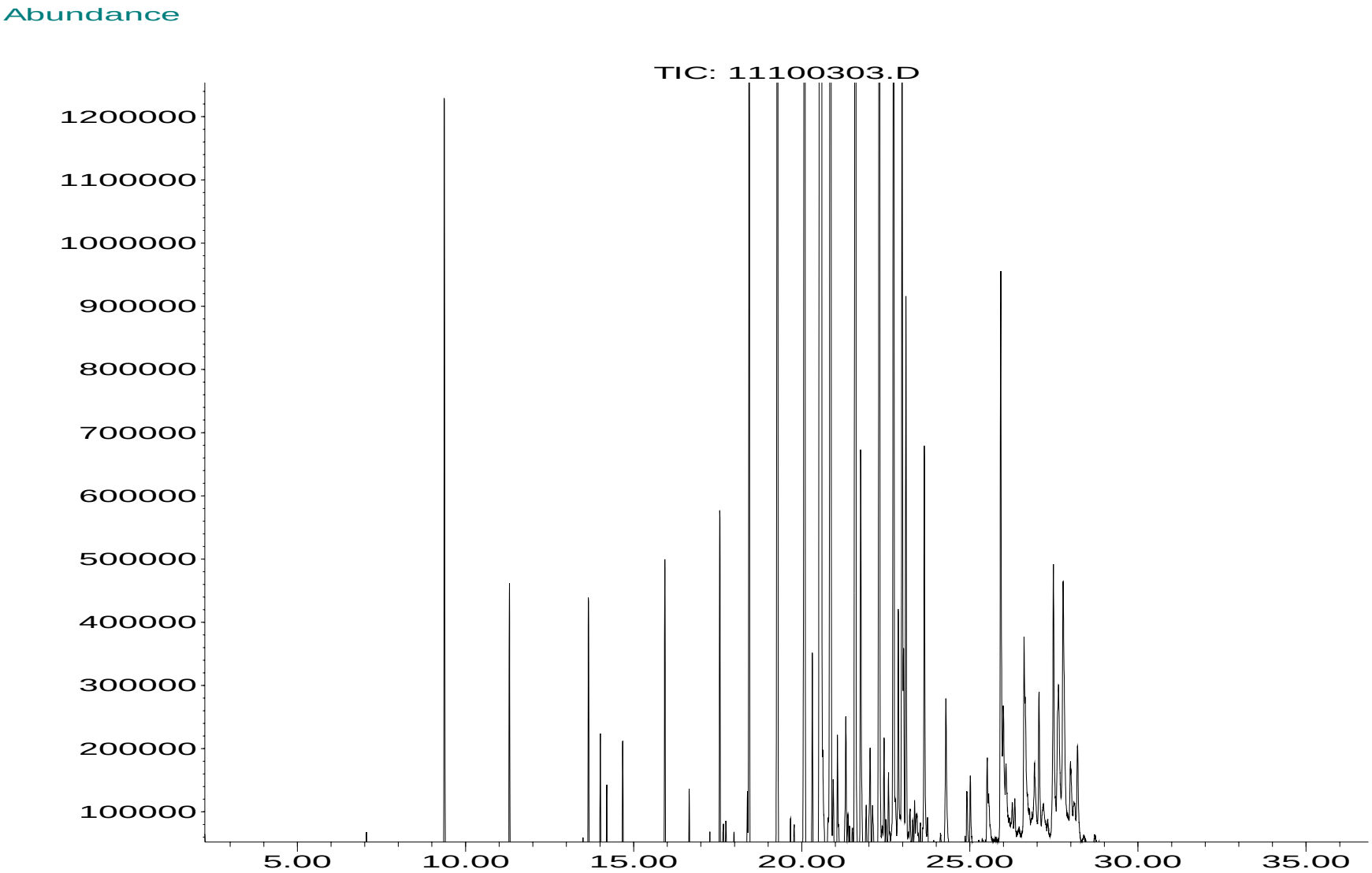
$$Estimated\ AET \approx \frac{(3.75\ \mu g/\text{canister}) \times (1\ \text{canister/valve})}{0.2\ \text{g elastomer/valve}}$$

$$Estimated\ AET \approx 18.8\ \mu g/g$$

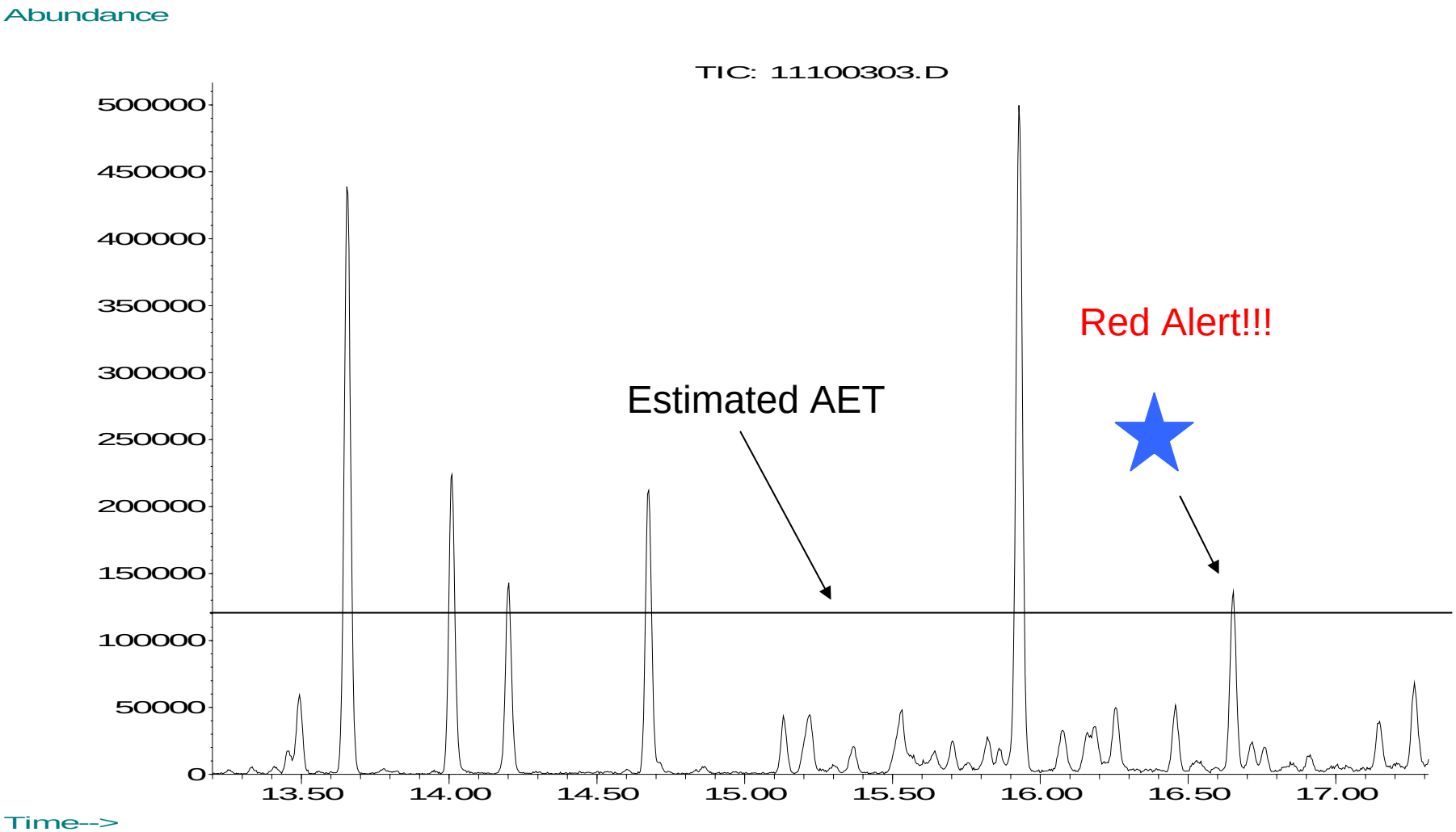
Leachables Profile – 1 Week Timepoint



Leachables Profile – 1 Week Timepoint Expanded



Leachables Profile – 1 Week Timepoint Expanded Section



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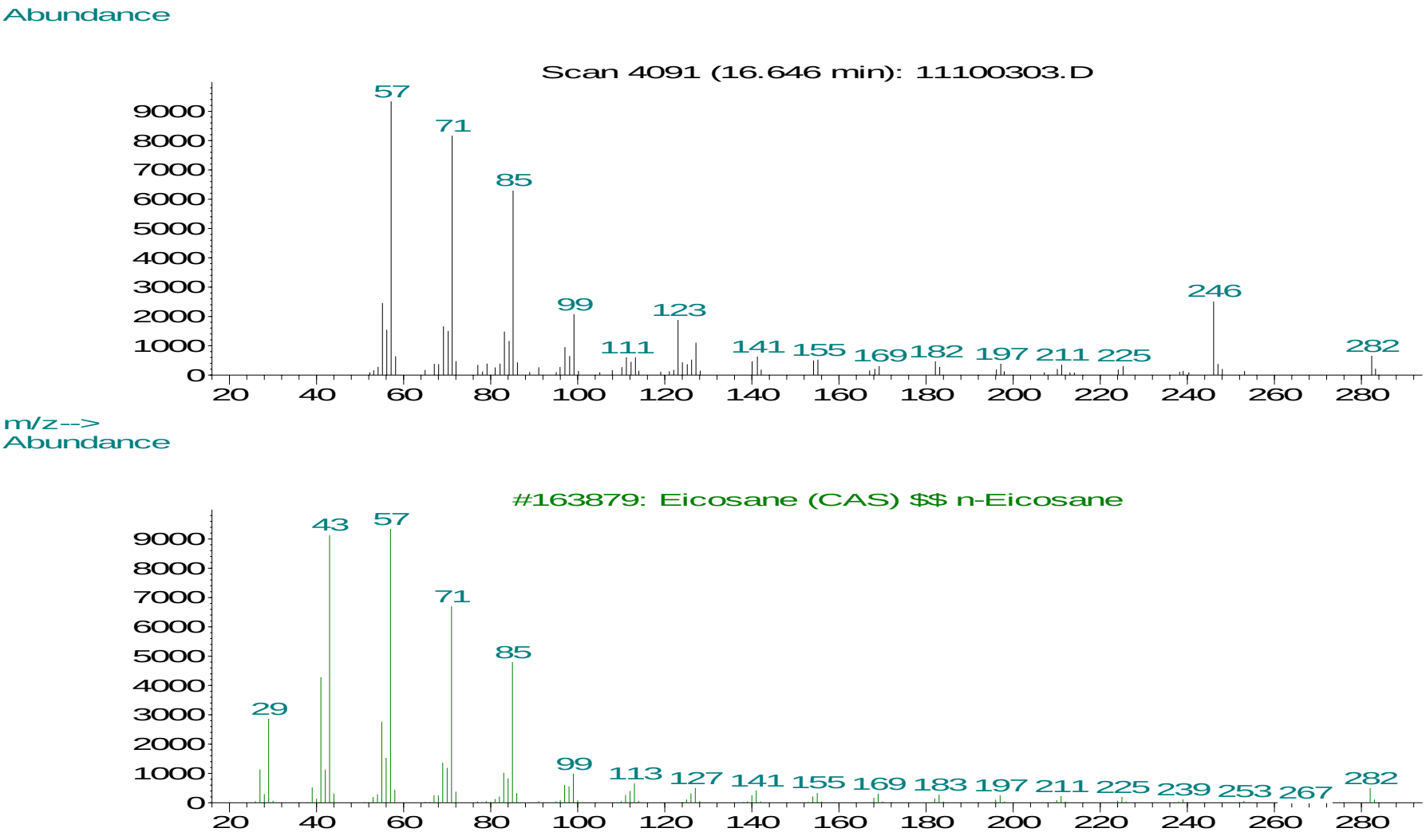
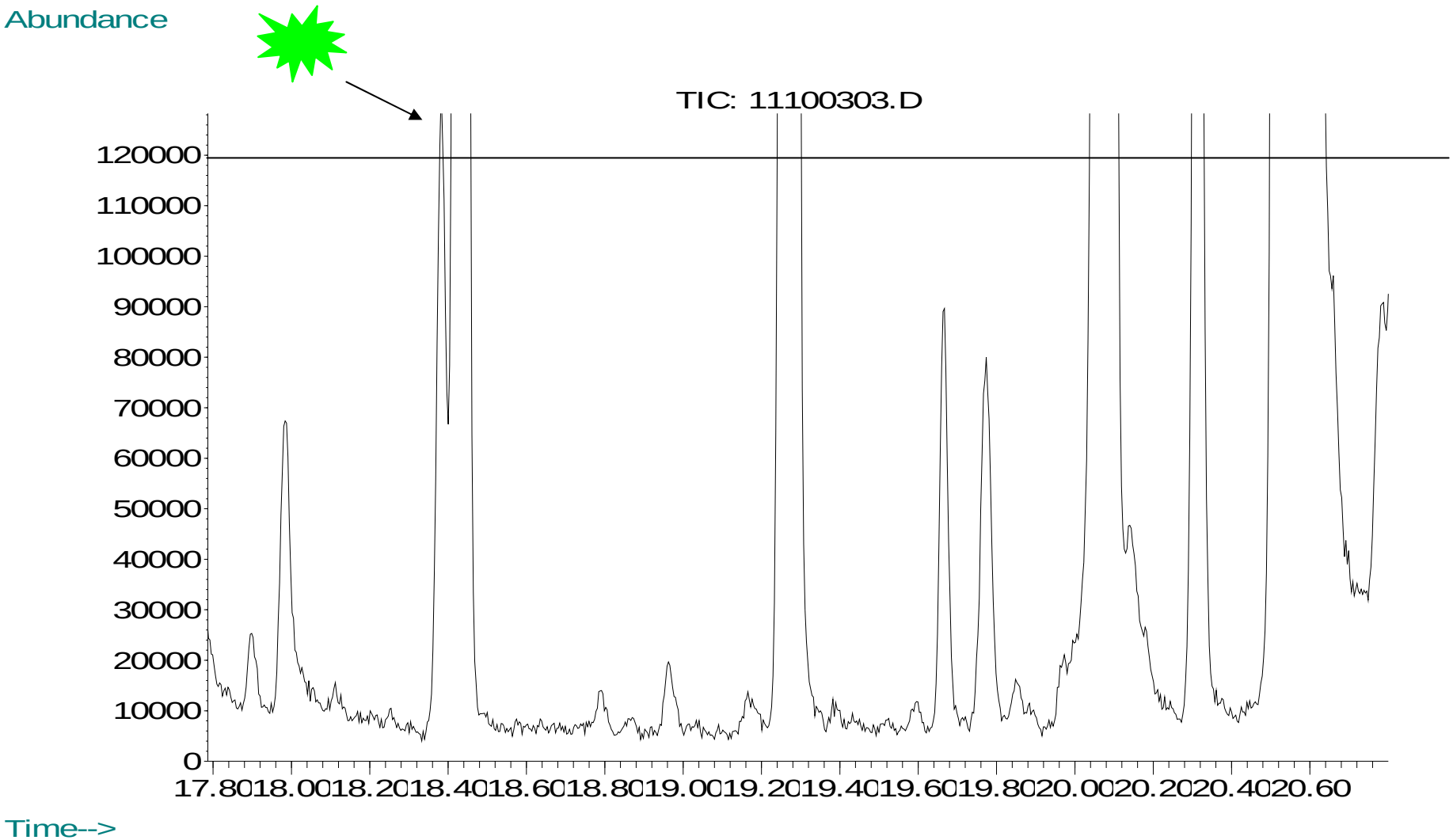


Leachables Profile – 1 Week Timepoint Expanded Section (2)



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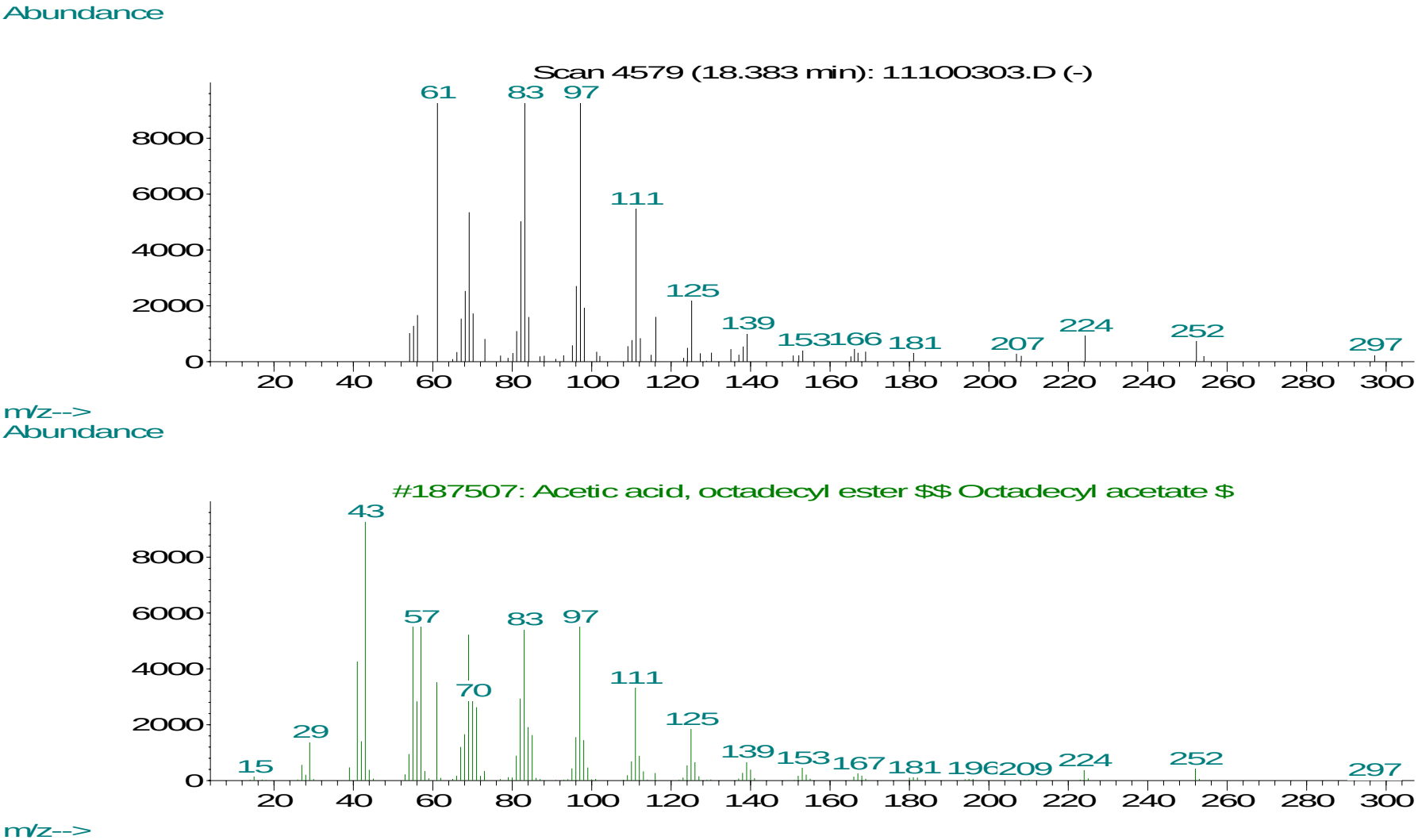


Recommendation - MDIs

"The above calculation assumes that all 200 mg of elastomer in this particular MDI valve has the same chemical composition and extractables profile, and takes no account of the number of individual valve components fabricated from this elastomer.

When accomplishing Controlled Extraction Studies and establishing acceptance criteria for unspecified (i.e. "new") extractables in Routine Extractables Testing programs, the pharmaceutical development team should consider the potential additive effect to the leachables profile of multiple elastomeric and/or plastic components fabricated from the same basic material."

Recommendation - MDIs

"The Working Group recommends that MDI actuator/mouthpieces have an extractables Estimated AET of 20 µg/g for an individual organic extractable."

Recommendation – Nasal Sprays and Inhalation Sprays

The Working Group recommends that AETs for Nasal Spray and Inhalation Spray leachables profiles be based on the Safety Concern Threshold (SCT) of 0.15 µg/day for an individual organic leachable. This recommendation includes potential organic leachables derived from the container and other critical components of the container closure system."

The Working Group recommends that critical components of Nasal Spray and Inhalation Spray drug product container closure systems that are not in continuous contact with the drug product formulation have an extractables Estimated AET of 20 µg/g for an individual organic extractable.

Recommendation - DPIs

The Working Group recommends that AETs for Dry Powder Inhaler leachables profiles be based on the Safety Concern Threshold (SCT) of 0.15 µg/day for an individual organic leachable. This recommendation includes organic leachables derived from the unit dose container closure system and other critical components of the device which may have continuous long term contact with the drug product formulation.

Leachables studies (either stability studies or “one-time” characterization studies) would only be required for DPIs if potential leachables (i.e. extractables) of safety concern were identified at the AET level during comprehensive Controlled Extraction Studies.

Recommendation - DPIs

"The Working Group recommends that critical components of DPI drug product container closure systems that are not in continuous contact with the drug product formulation have an extractables Estimated AET of 20 µg/g for an individual organic extractable."

Note that comprehensive Controlled Extraction Studies should always be performed on non-contact DPI critical components using the AET, even if they do not have continuous long term contact with the drug product formulation."

Recommendation – Inhalation Solutions

"The Working Group recommends that AETs for Inhalation Solution leachables profiles be based on the Safety Concern Threshold (SCT) of 0.15 µg/day for an individual organic leachable.

This recommendation includes potential organic leachables derived from the unit dose container closure system and other materials which may have continuous long term contact with the drug product formulation or unit dose container."

Recommendation – Inhalation Solutions

"The Working Group recommends that if it can be scientifically demonstrated that:

1. Aqueous and/or drug product formulation extracts of Inhalation Solution direct formulation contact container closure system material yield no extractables at Final AET levels, or no extractables above final AET levels with safety concern; AND
2. There is no evidence for migration of organic chemical entites through the unit dose container into the drug product formulation; THEN

Drug product leachables studies are not required."

Recommendation – Final AET

"The Working Group proposes and recommends that analytical uncertainty in the Estimated AET be defined as one (1) %Relative Standard Deviation in an appropriately constituted and acquired Response Factor database OR a factor of 50% of the Estimated AET, whichever is greater."

Recommendation – Final AET

Example Extractables RRF Database from GC/FID Method. 2-Fluorobiphenyl as internal standard		
Analyte ID	RF Value	RRF Value
BHT	19.28	0.95
Irganox 1076	7.4	0.35
p-terphenyl-D14	17.40	0.88
Bis (2-ethylhexyl) phthalate	14.38	0.71
2,6-d-tert-butylphenol	19.96	0.96
Eicosane	15.73	0.77
Diphenylamine	21.91	1.05
Dibutyl phthalate	12.54	0.61
Mean	**16.08**	**0.79**
Standard Deviation	**4.66**	**0.23**
%RSD	**28.98**	**29.00**

Recommendation – Final AET

Process for Determination of Estimated and Final AET

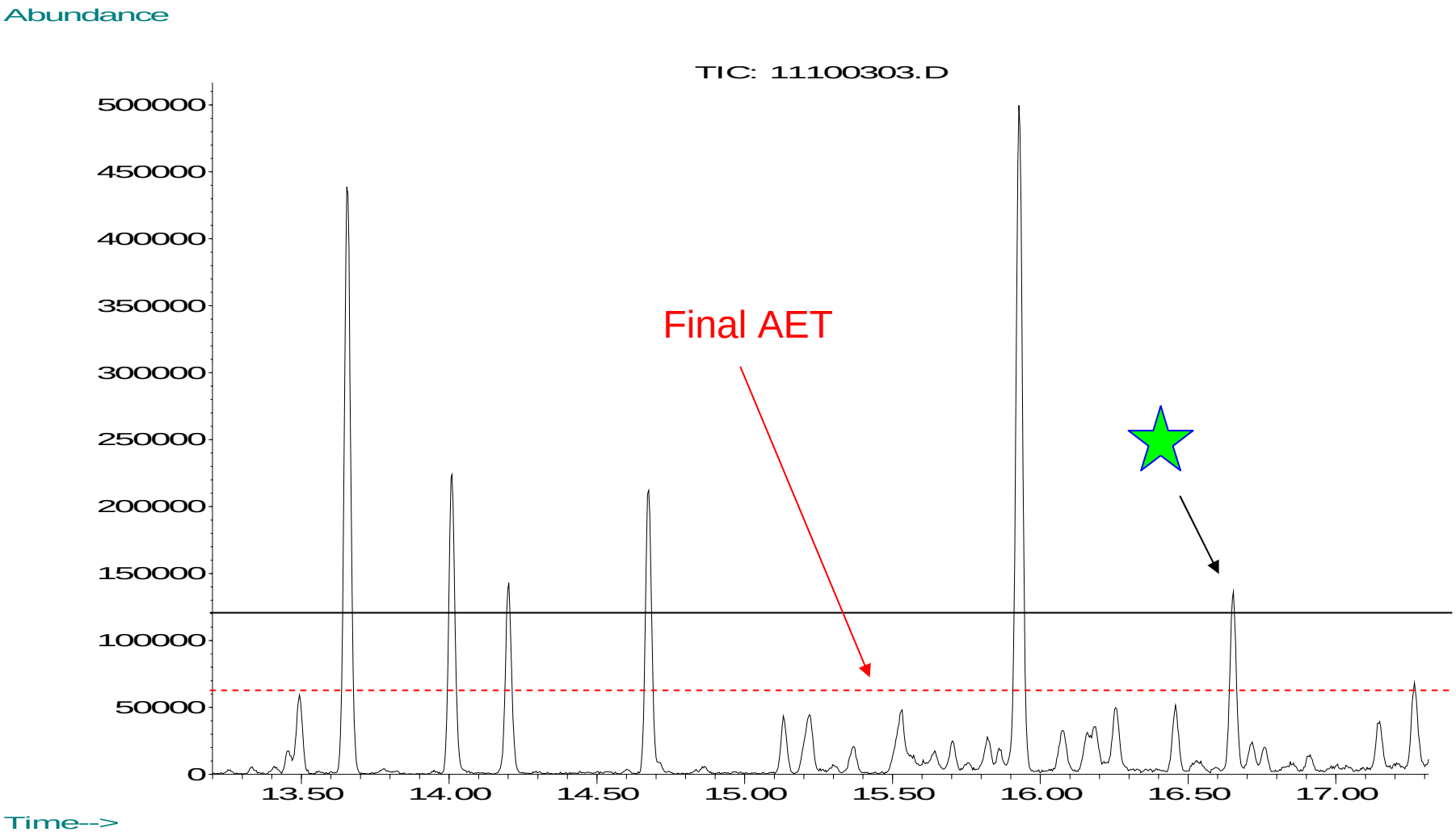
1. Determine estimated AET by converting SCT (0.15 µg/day) to units relative to an individual OINDP (e.g, µg/canister, µg/gram component, etc.).
2. Estimate position on the particular extractables/leachables profile of the SCT. This is the Estimated AET. The position should be based on:
    - The RF of an appropriate internal standard; or
    - The RF of an unambiguously identified major extractable/leachable.

Recommendation – Final AET

Process for Determination of Estimated and Final AET

3. Evaluate analytical uncertainty:
   - Create an appropriate RRF database.
   - Determine the Standard Deviation (SD) and %Relative Standard Deviation (%RSD) of RRFs in the database;
   - Use one (1) %RSD or a factor of 50% (of the Estimated AET), whichever is greater, to define the analytical uncertainty.
4. Establish the Final AET. The Final AET is defined as:
   - Final AET = Estimated AET – “uncertainty factor”

Leachables Profile – 1 Week Timepoint Expanded Section



Concluding Points

- The process described here for determining the Final AET is an example. Alternative processes could be proposed.
- We welcome your comments and suggestions.
- Additional details are in the poster presentation.