

Chemical Characterization: the basics



Dr. David Moreels



22 MAY 2019

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Outline

1. Chemical Characterization: Introduction

2. Set-up of a chemical characterization study

2.1 Extract

2.2 Detect

2.3 Identify

2.4. Quantify

3. Why performing a chemical characterization study

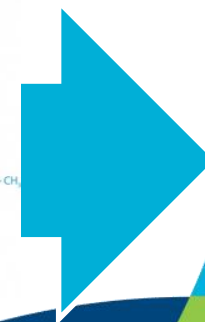
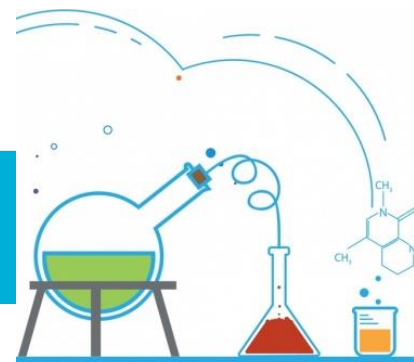
Introduction

BIOLOGICAL SAFETY EVALUATION

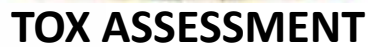


Introduction

ISO 10993-1 (2018): Risk Management Process



ISO 10993-1 (2018): Risk Management Process



Nelson Labs NV – Belgium

Center of Excellence for chemical characterization



Introduction



Extractables

Leachables

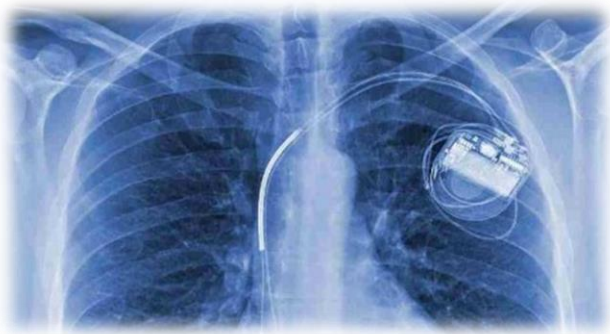
Introduction

EXTRACTABLES: What **CAN** come out of the **material**?



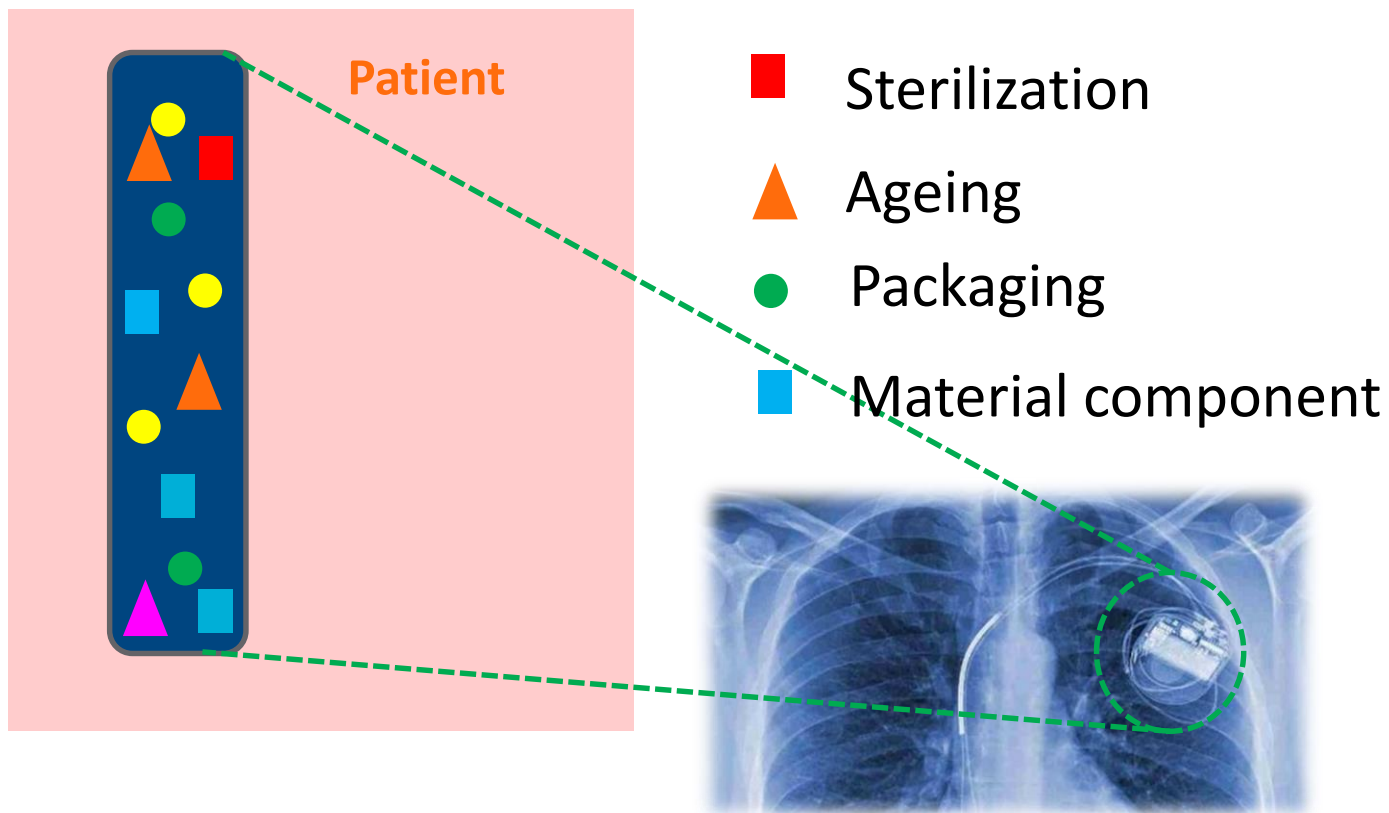
Extreme conditions!

LEACHABLES: What **DOES** come out (from the material) in the **patient/fluid** ?



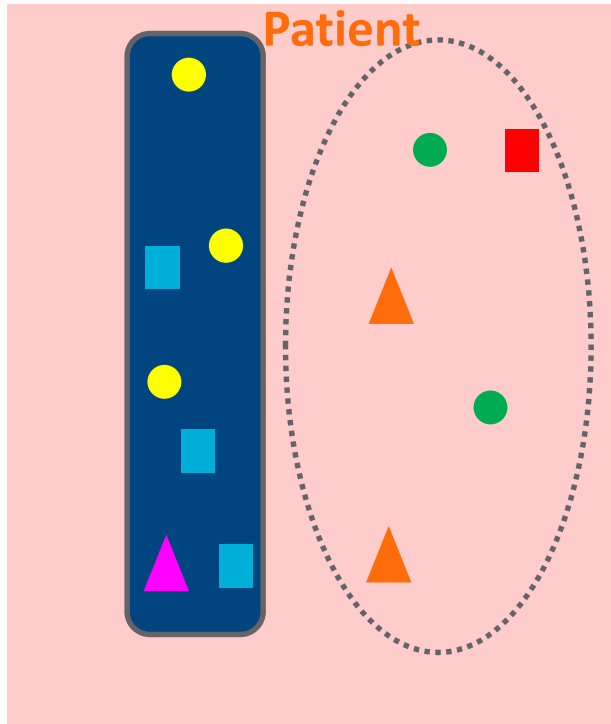
Normal conditions

Introduction



Introduction

ISO 10993-18



ISO 10993-17



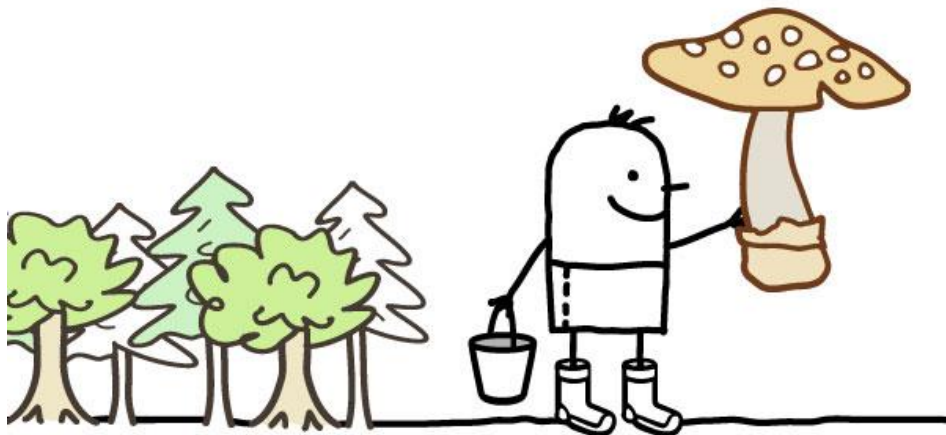
➡ Which compounds are migrating?

Introduction

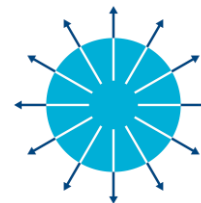
Extractables study: 4 steps

Introduction

Extractables study: 4 steps



1. Extract



Introduction



Extractables study: 4 steps

1. Extract



2. Detect



Introduction

Amanita muscaria



Source: Wikipedia

Extractables study: 4 steps

1. Extract



2. Detect



3. Identify



Introduction

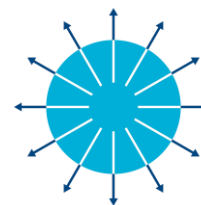
Amanita muscaria



Source: Wikipedia

Extractables study: 4 steps

1. Extract



2. Detect



3. Identify



4. Quantify



Introduction

Amanita muscaria



Source: Wikipedia



ISO 10993-17

Introduction



Extract, Detect and **Identify** the whole set of potentially hazardous compounds:

Missing a compound could be a **fatal error** for patient safety

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Past: ISO 10993-12



Now: ISO 10993-18





Type of Device

?

Analytical
Evaluation
Threshold



AnalYTical Evaluation Threshold (AET)



The AET is defined as the threshold below which the analyst need not to identify or quantify leachables or extractables or report them for potential toxicological assessment

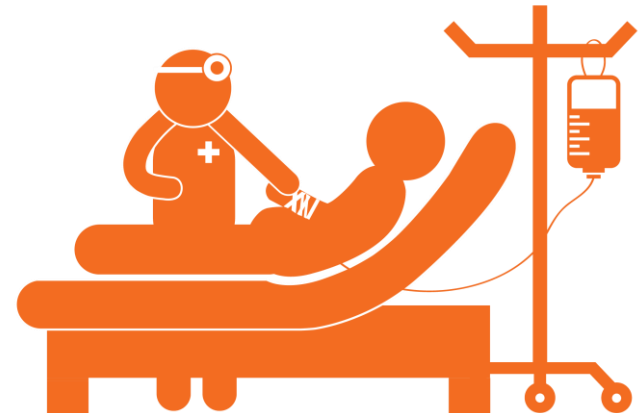
Extract



Extract



= Threshold of Toxicological
Concern (TTC)



Extract

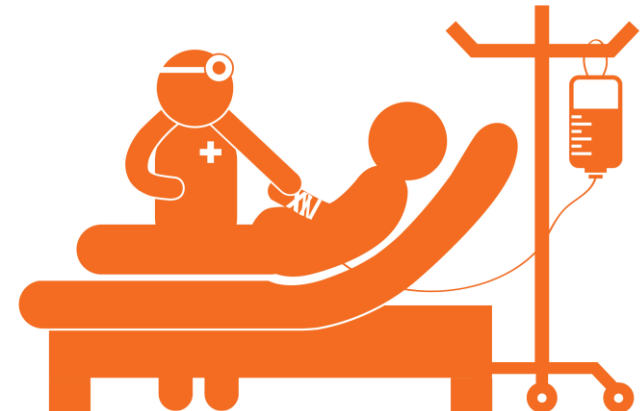


= Threshold of Toxicological
Concern (TTC)

< TTC



> TTC





- TTC: Reference guideline for drug products: ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (2014)

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [$\mu\text{g}/\text{day}$]	120	20	10	1.5



- TTC: Reference guideline
Control of DNA Reaction
Limit Potential C

Assessment and
pharmaceuticals to

Duration of treatment	Duration of use		
	1 - 10 years	>10 years to lifetime	
Daily intake [µg/day]	10	1.5	

BSI Standards Publication

ISO 21726

Biological evaluation of medical devices —
Application of the threshold of toxicological
concern (TTC) for assessing biocompatibility
of medical device constituents



Table 1 — Recommended ICH M7(R1) (2017) TTC values based on ISO 10993-1 medical device contact category

Medical device contact category	Limited (<24h)	Prolonged (24h to 30 d)	Long-term (>30 d)		
Duration of body contact	≤ 1 month		>1 month to 12 months	>1 year to 10 years	>10 years to lifetime
Daily intake ($\mu\text{g}/\text{d}$) of any one constituent	120		20	10	1,5

And:

“ when experimental data or model-derived predictions suggest that an identified constituent is not likely to have carcinogenic effects (e.g. Negative genotoxicity data or negative results in at least two computational models that operate using different approaches – expert system based and statistically based), then categorizing the constituent into its appropriate Cramer class and use of the corresponding TTC is recommended.”



Table 1 — Recommended ICH M7(R1) (2017) TTC values based on ISO 10993-1 medical device contact category

Medical device contact category	Limited (<24h)	Prolonged (24h to 30 d)	Long-term (>30 d)		
Duration of body contact	≤ 1 month		>1 month to 12 months	>1 year to 10 years	>10 years to lifetime
Daily intake ($\mu\text{g}/\text{d}$) of any one constituent	120		20	10	1,5

=> 1.5 $\mu\text{g}/\text{day}$ for long-term contacting devices

=> 5 $\mu\text{g}/\text{day}$ for short-term contacting devices

taking into account irritating and sensitizing compounds

**BUT: NO ARGUMENT FOR SKIPPING SENSITIZATION AND IRRITATION
ALLOWS CORRELATION RESULTS E&L testing & biocomp testing**



Example AET



Use: **1 device per patient per day**
> 30 days

➡ **TTC: 1.5 µg/day**

Device specific TTC: 1.5 µg/device



Example AET



Use: **1 device per patient per day**
> 30 days

➡ **TTC: 1.5 µg/day**

Device specific TTC: 1.5 µg/device

Extraction ratio:
4 devices in 400 mL

AET: 1.5 µg/100 mL
15 µg/L



UF = uncertainty factor that could be applied to account for the analytical uncertainty of the screening methods used to estimate extractables' concentrations in an extract



UF = uncertainty factor that could be applied to account for the analytical uncertainty of the screening methods used to estimate extractables' concentrations in an extract

PQRI
Nelson RRF evaluation
UF = 2

FDA
Jenke & Odufu, 2012
UF = 4

Extract



Example AET



Use: **1 device per patient per day**
> 30 days

➡ **TTC: 1.5 $\mu\text{g}/\text{day}$**

Device specific TTC: 1.5 $\mu\text{g}/\text{device}$

Extraction ratio:
4 devices in 400 mL

AET: 1.5 $\mu\text{g}/100\text{ mL}$
15 $\mu\text{g}/\text{L}$

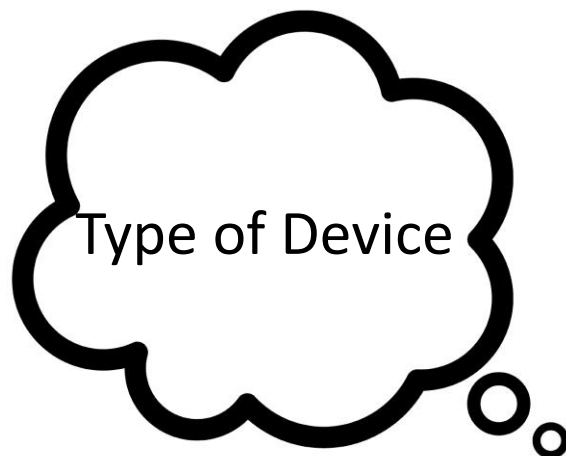


UF= 2

Final AET: 7 $\mu\text{g}/\text{L}$

Extract

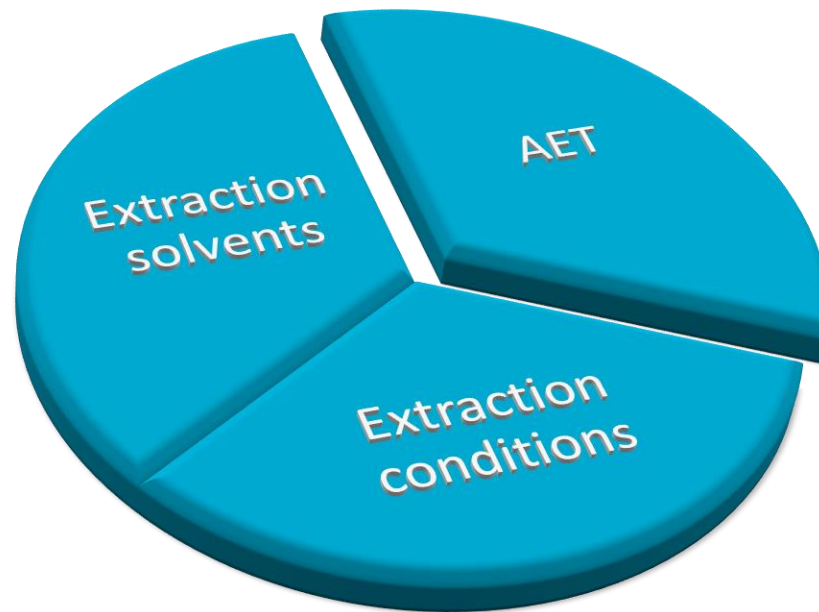




Extract



Extract



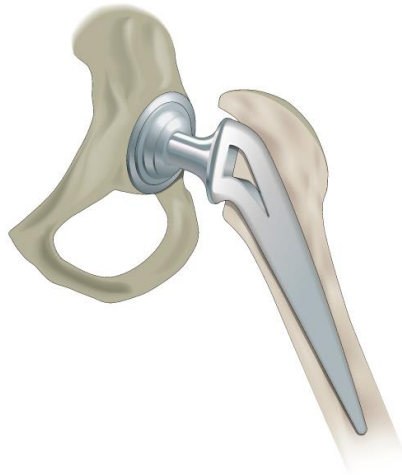


Type of Device:
examples



1. Long-term contact

> 30 days



- **Extraction solvents:**
 - Polar (UltraPureWater) & Non-polar (Hexane)
 - Semi-polar (e.g. Isopropanol)
- **Extraction technique:**
 - 50°C, XX h, shaking incubation
 - Exhaustive extraction (NVR **and alternatives**)
- **Extraction ratio:** AET to be reached,
based on TTC of 1.5 µg/day



2. Prolonged contact

24h – 30 days

Critical



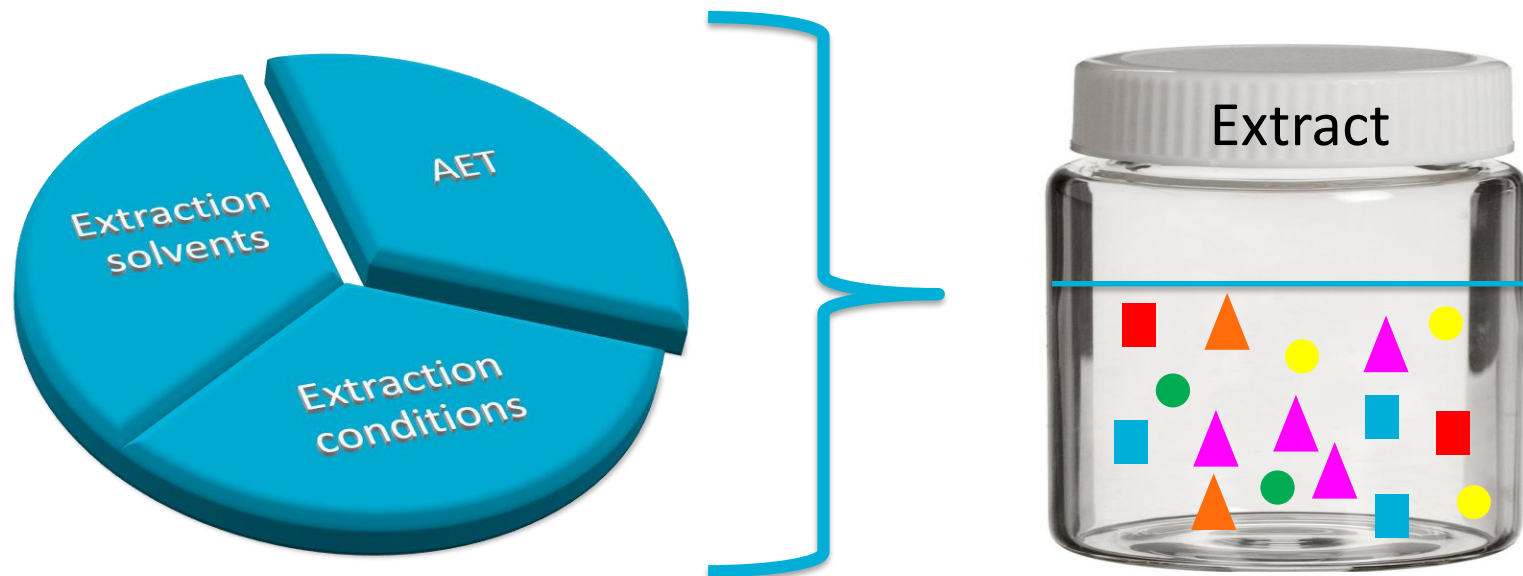
- **Extraction solvents:**
 - Polar (UltraPureWater) & Non-polar (Hexane)
 - Semi-polar (Isopropanol, 40% Ethanol): blood contact
- **Extraction technique:**
 - Exhaustive extraction (NVR **and alternatives**)
 - 50°C, xx h, shaking incubation
 - Exaggerated extraction:
 - High temp, > 24h, shaking incubation
- **Extraction ratio:** AET to be reached,
based on TTC of 5 µg/day



3. Fluid pathway



- **Extraction solvents:**
 - Biological fluid simulant
 - Device fluid simulant
- **Extraction technique:**
 - Simulate use: e.g. circulation
- **Extraction ratio:** AET to be reached,
based on TTC of 5 µg/day



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2.4 Quantify

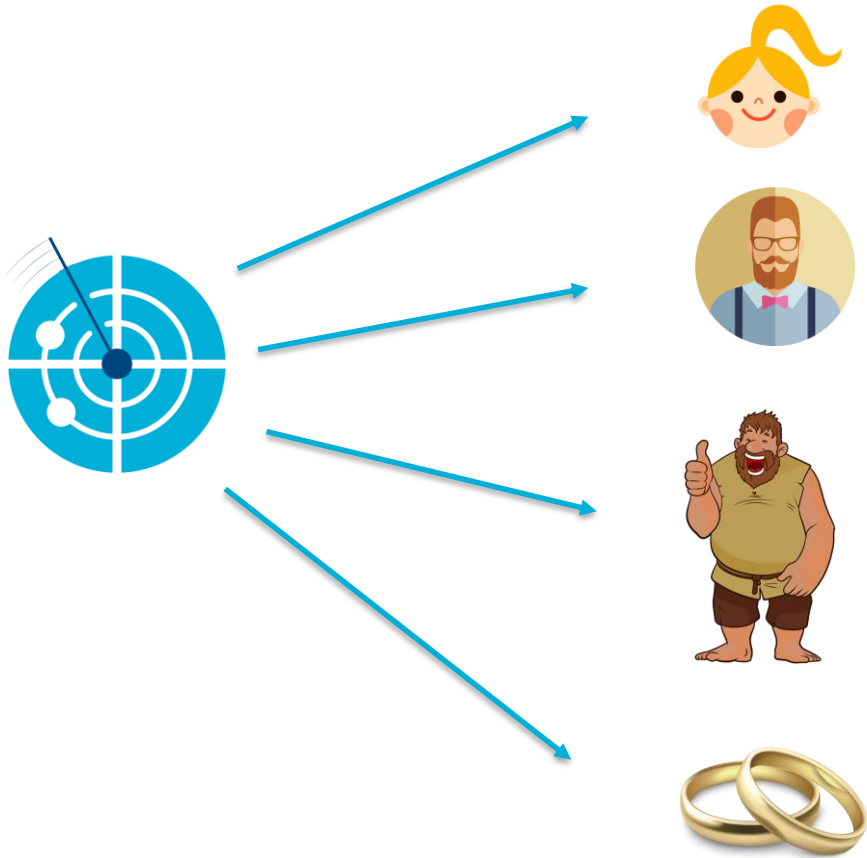
3. Why performing a chemical characterization study



Extract



Detect



Detect



Small

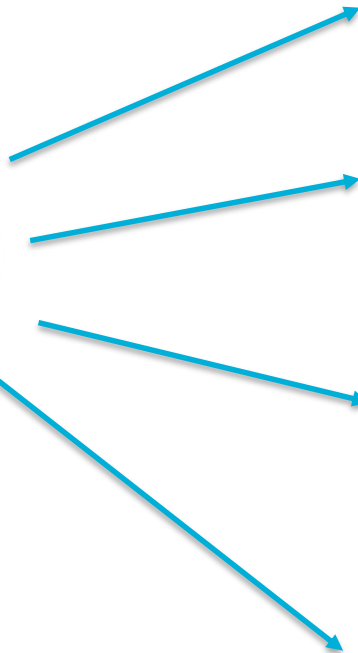
Medium-sized

Large

Metals



Detect



Volatile Organic
Compounds (VOC)



Semi-Volatile Organic
Compounds (SVOC)



Non-Volatile Organic
Compounds (NVOC)



Metals



VOC

HS-GC/MS
Screening

Volatile Organic Compounds (typically MW < 200)

- Monomer Residues
- Solvent Residues from Production steps
- Residues from polymer treatments (e.g. Washing)
- Small Polymer Breakdown products





VOC

HS-GC/MS
Screening

SVOC

GC/MS
Screening

Semi-Volatile Organic Compounds (MW < 650)

- **Lubricants**
- **Plasticizers**
- **Antioxidants**
- **Polymer degradation products**
- **Solvents with an elevated boiling point**





VOC

HS-GC/MS
Screening

SVOC

GC/MS
Screening

NVOC

UPLC/MS
Screening

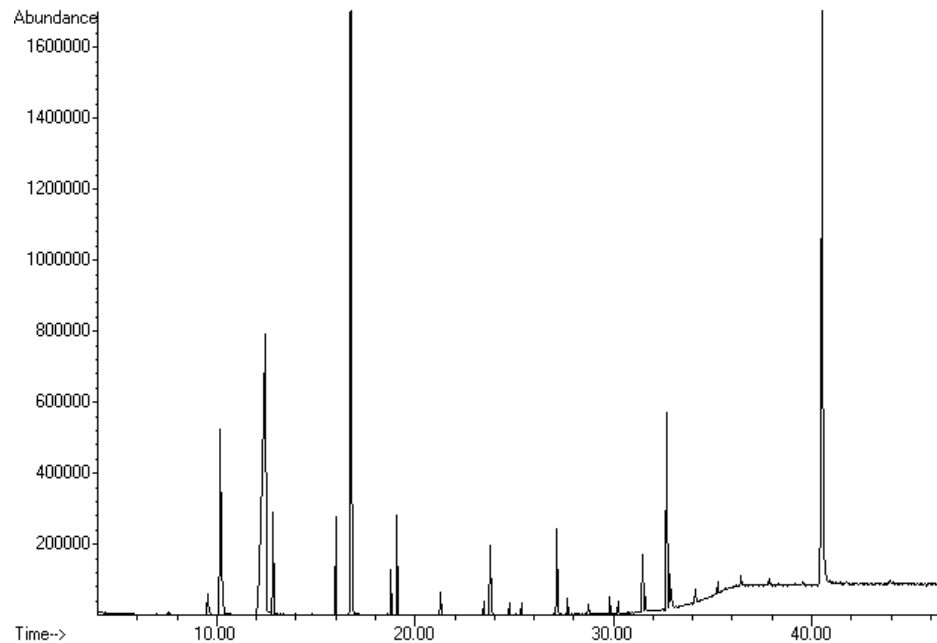
Non-Volatile Organic Compounds (MW < 1500)

- Fillers
- Plasticizers
- Antioxidants
- Anti-slip agents
- ...



Chromatogram

**Organic
(carbon based)**





VOC

HS-GC/MS
Screening

SVOC

GC/MS
Screening

NVOC

UPLC/MS
Screening



ICP/OES
ICP/MS

ELEMENTS

- Elements
- Heavy metals
- Quantitative

Outline

1. Chemical Characterization: Introduction

2. Set-up of chemical characterization

2.1 Extract

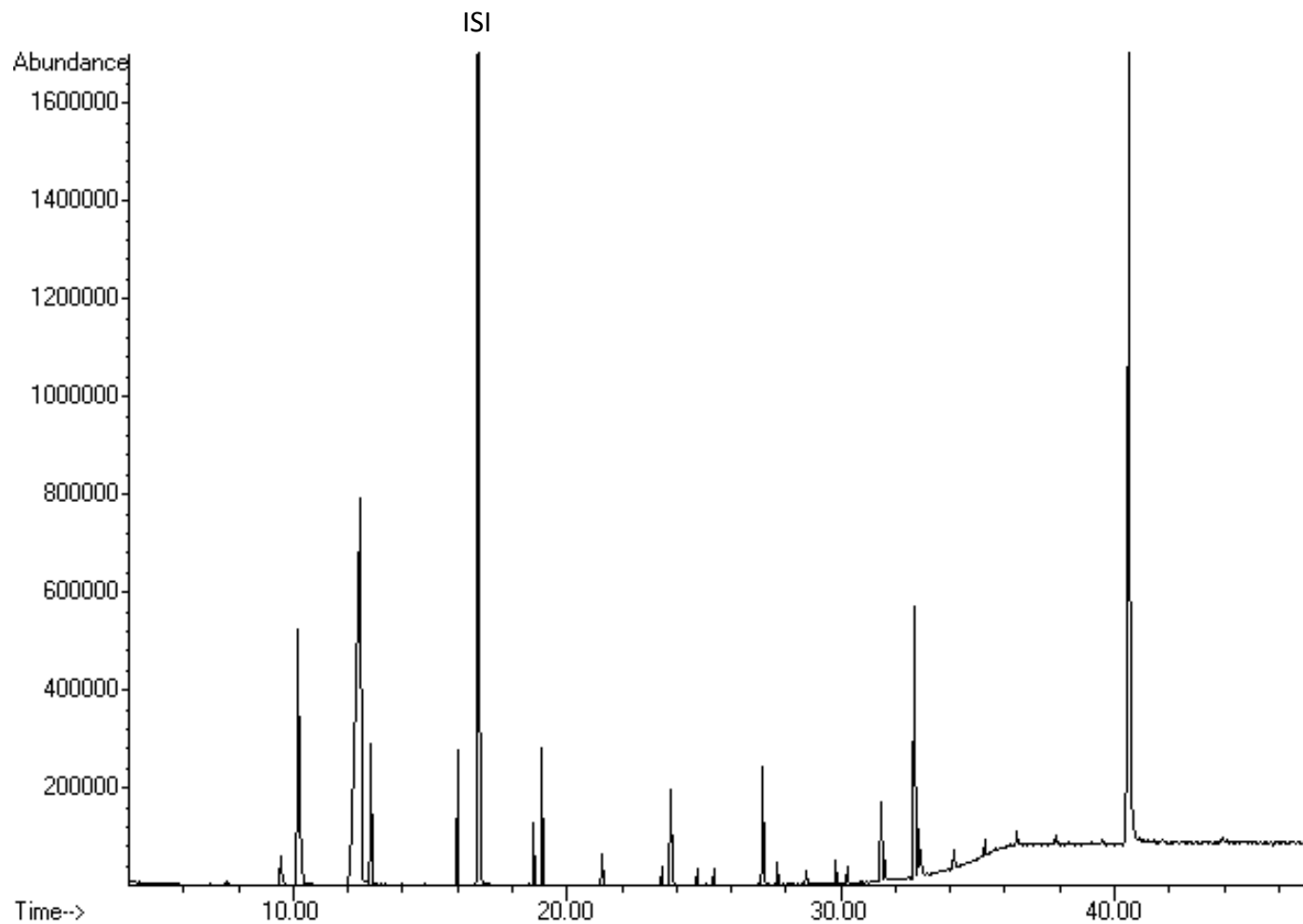
2.2 Detect

2.3 Identify

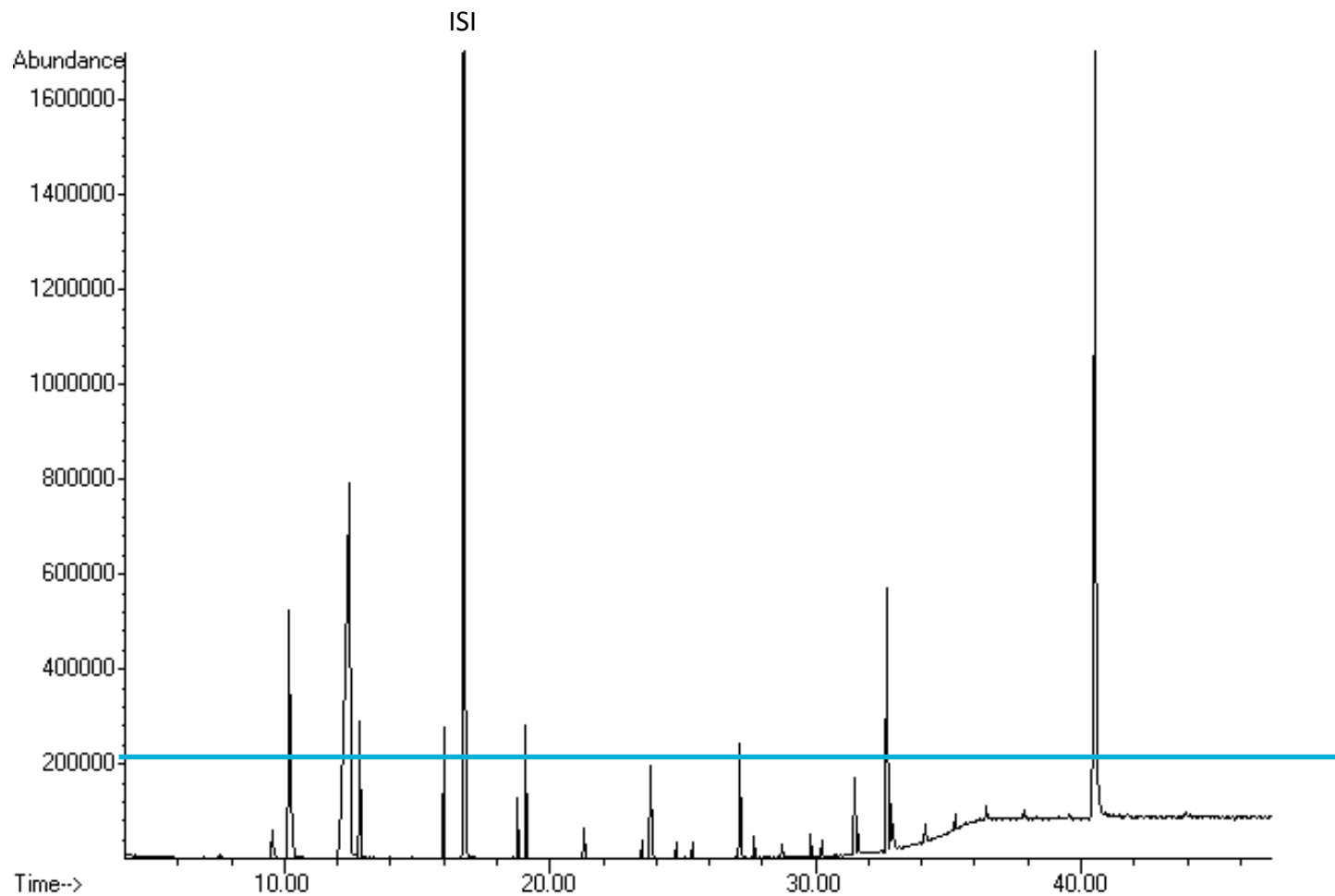
2.4 Quantify

3. Why performing a chemical characterization study

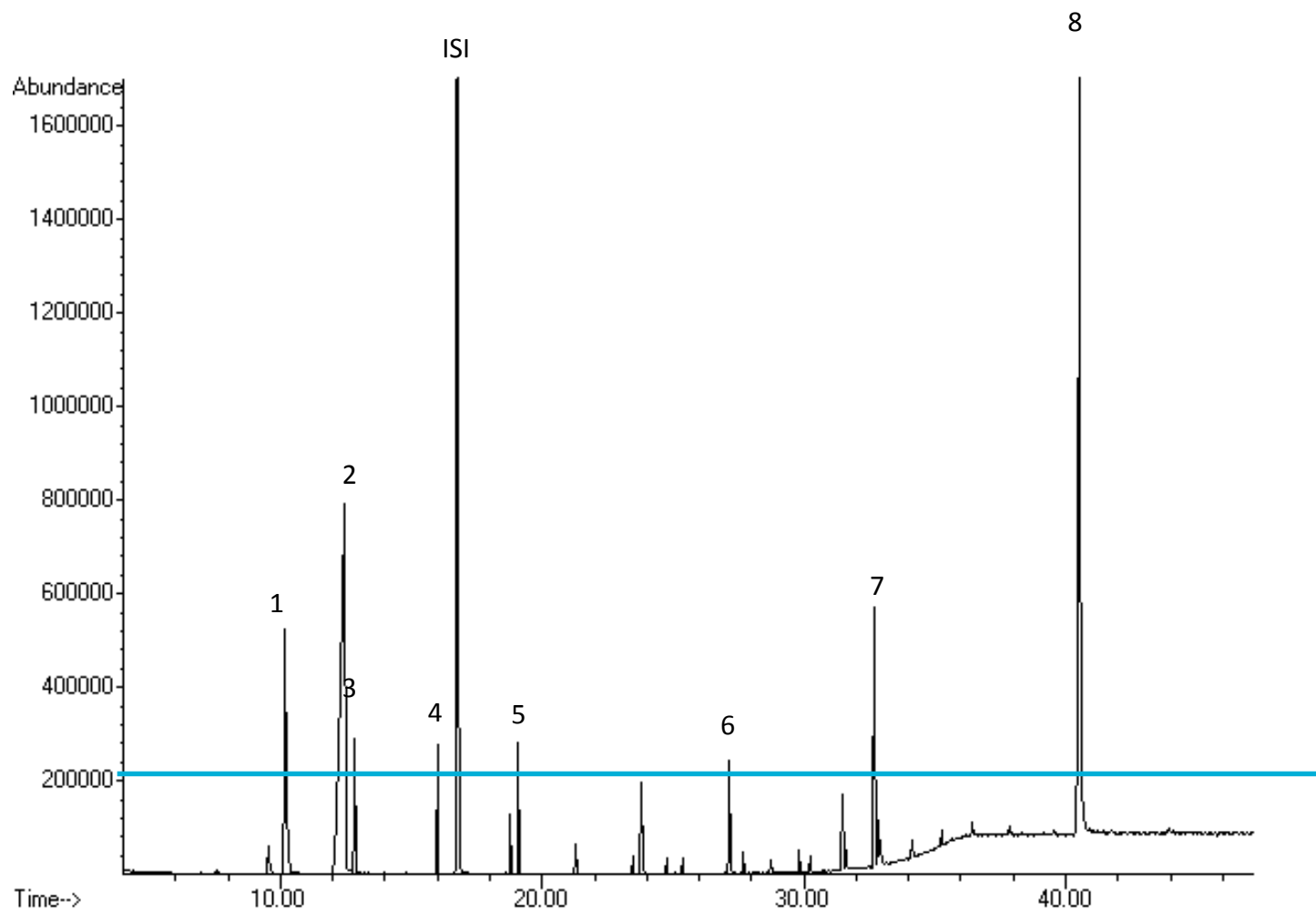
Organic
(carbon based)



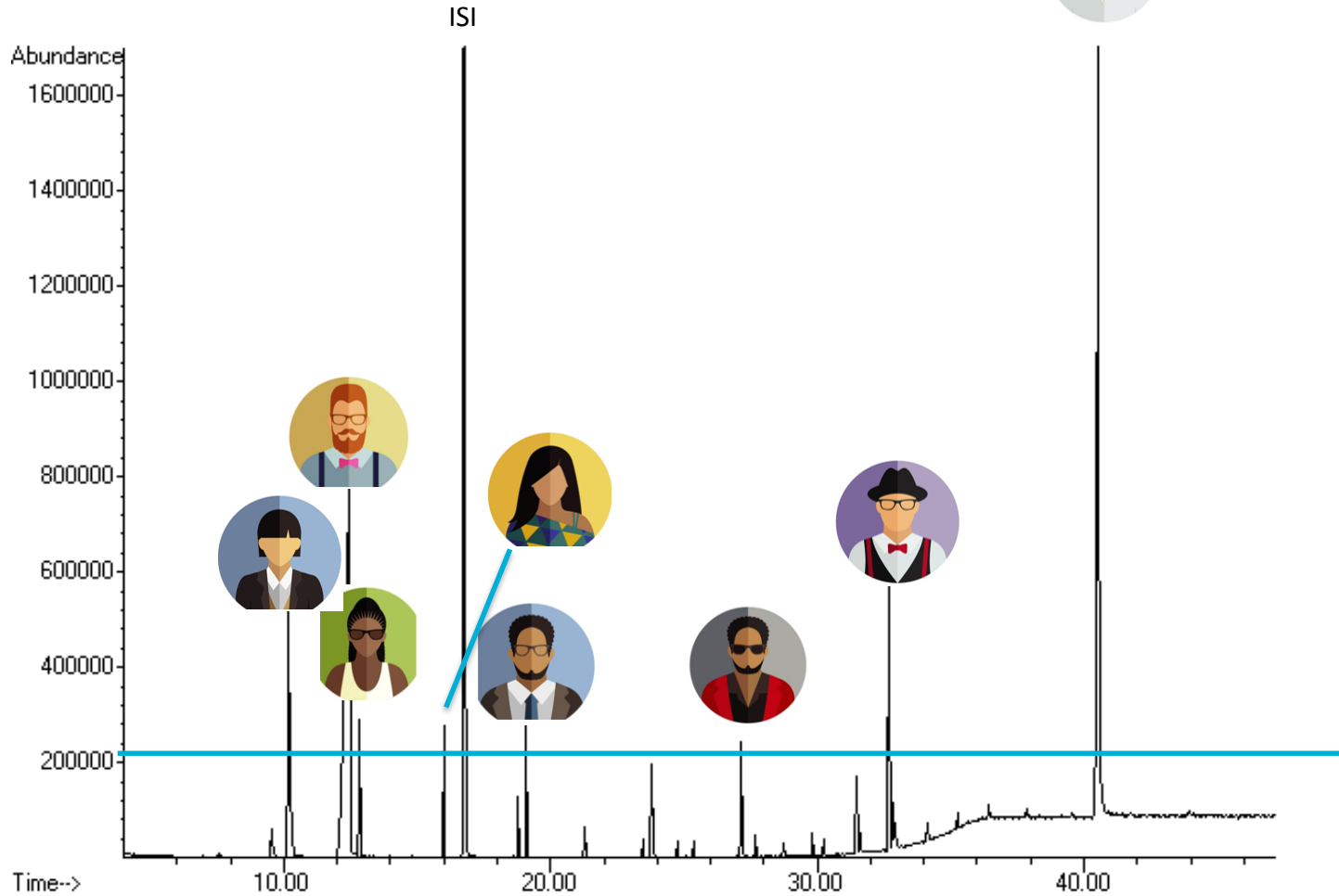
Organic
(carbon based)

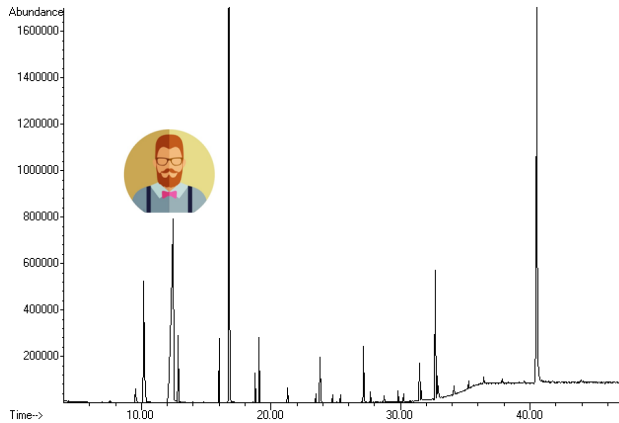


Organic
(carbon based)

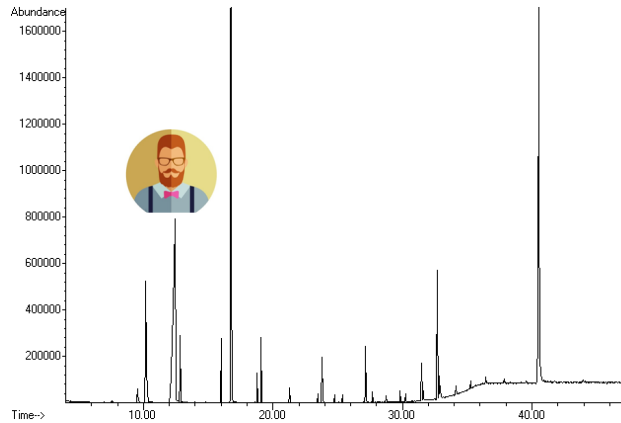


Final AET

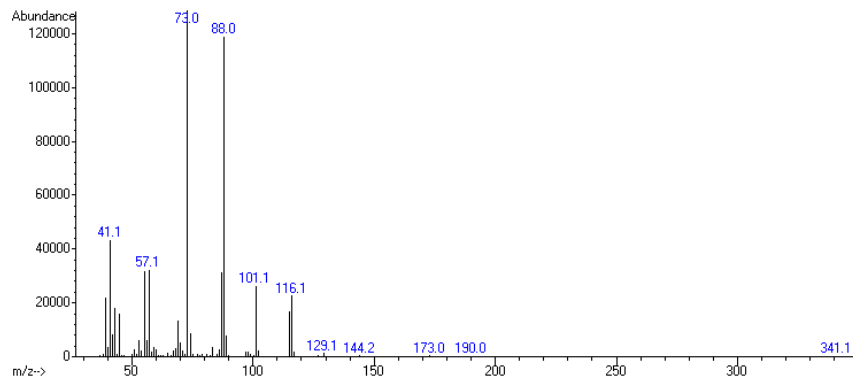


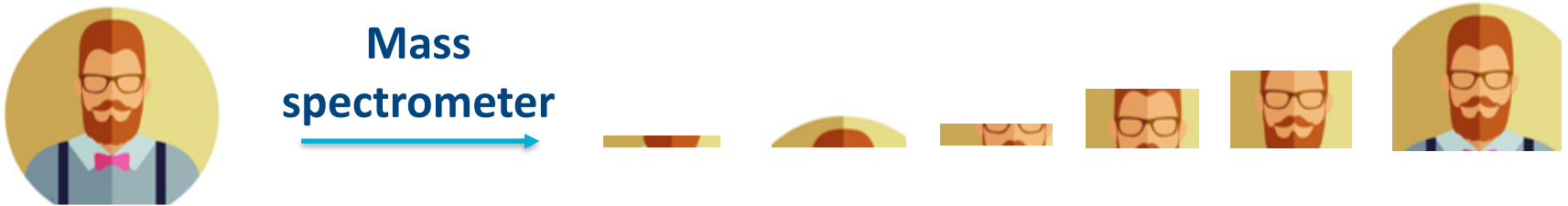


Identification with mass spectrometry

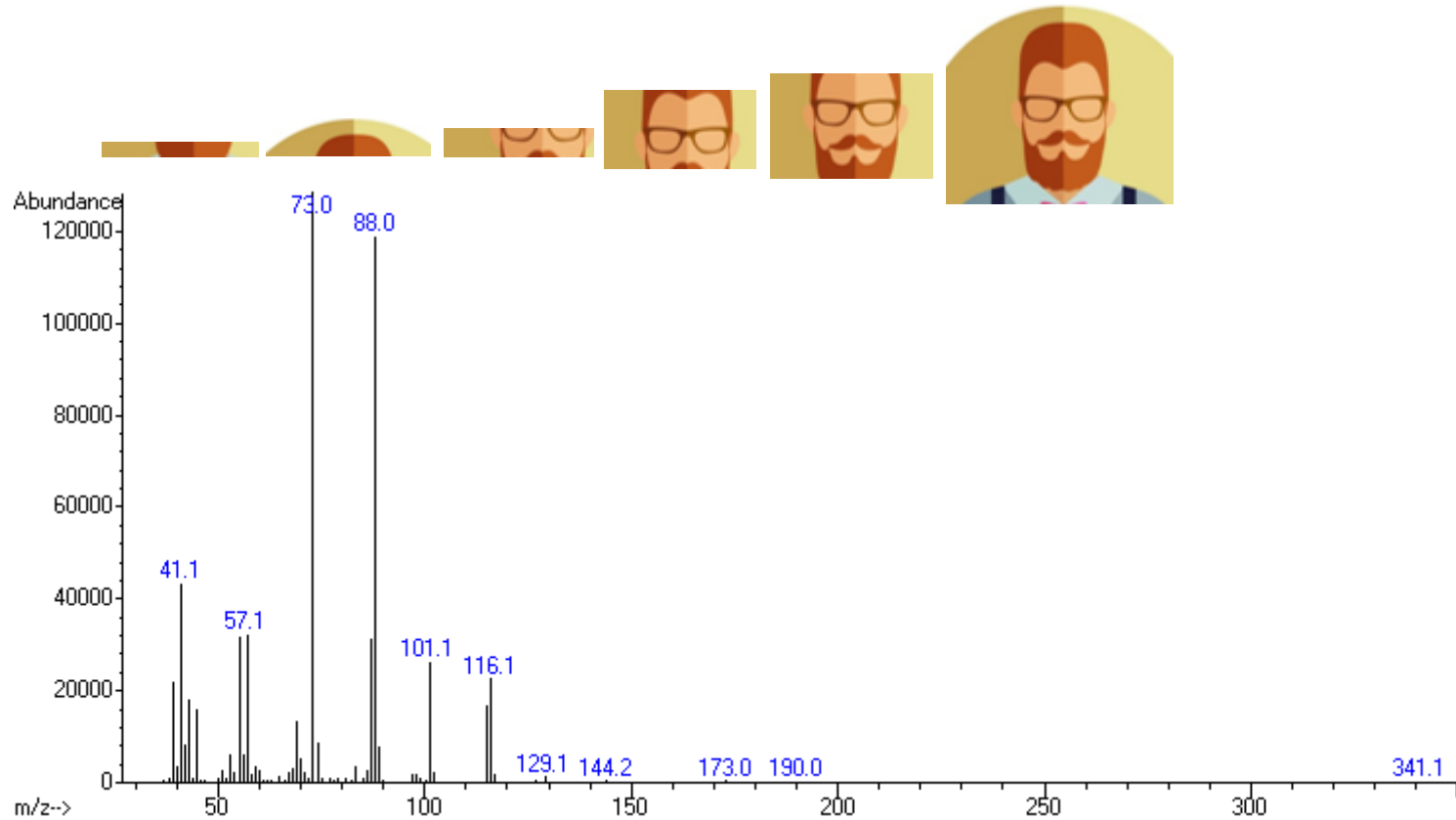


Identification with mass spectrometry





Chemical compound is fragmented in a unique combination of masses with specific abundance



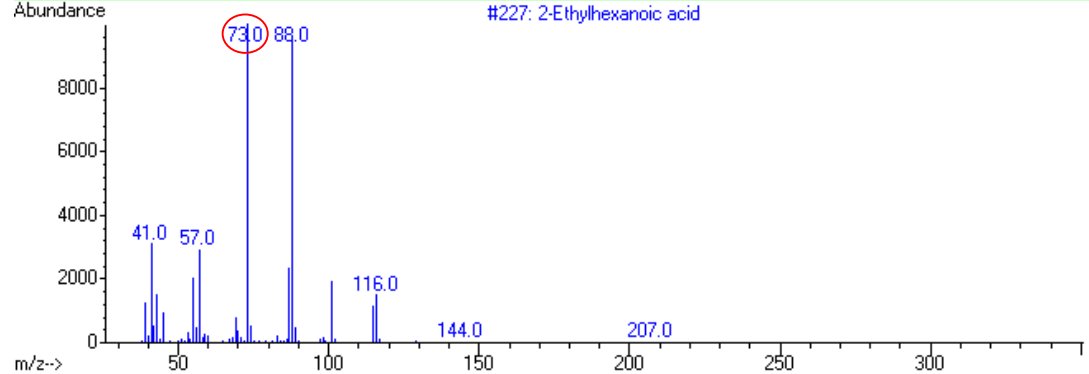
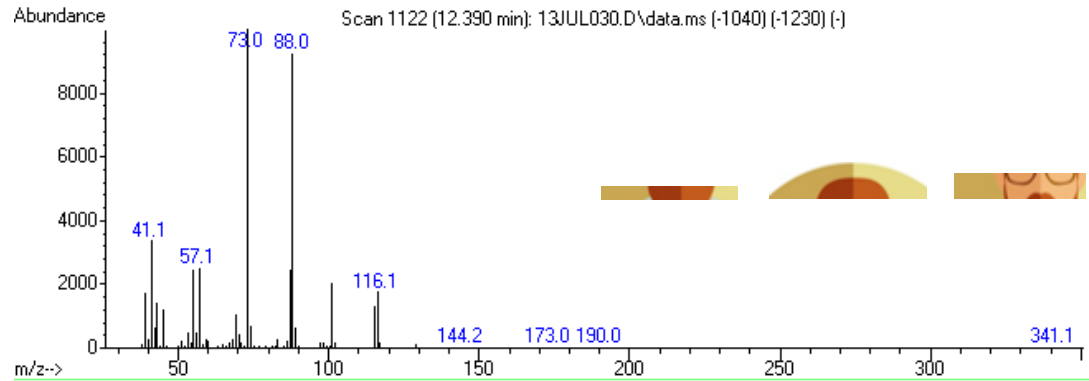


MAX

Unique
identification

Existing Library

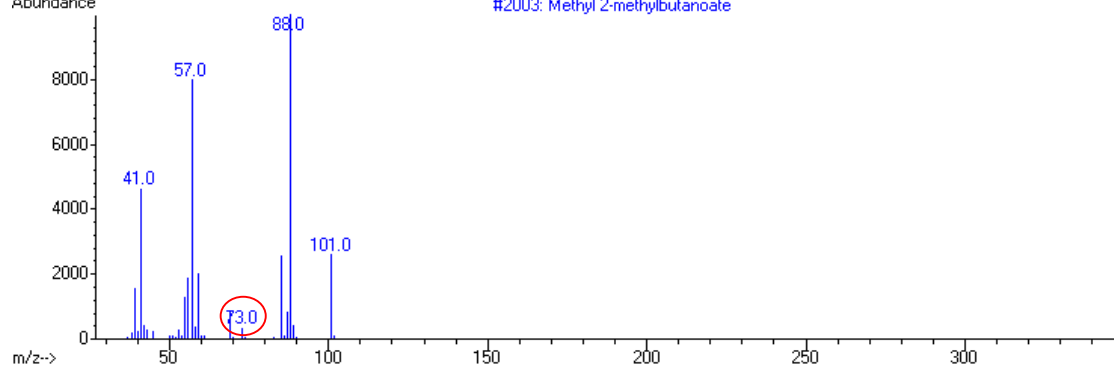
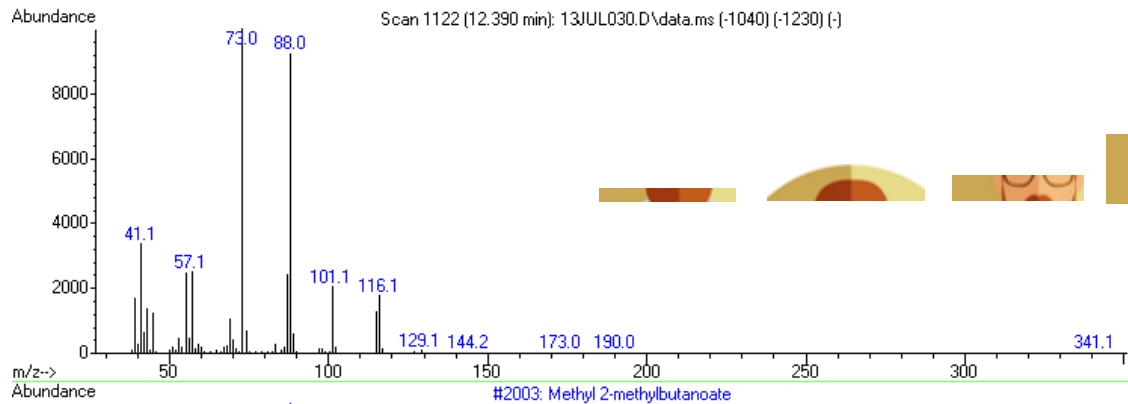




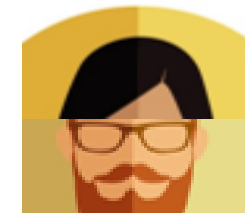
Compound = 2-Ethylhexanoic acid



MAX

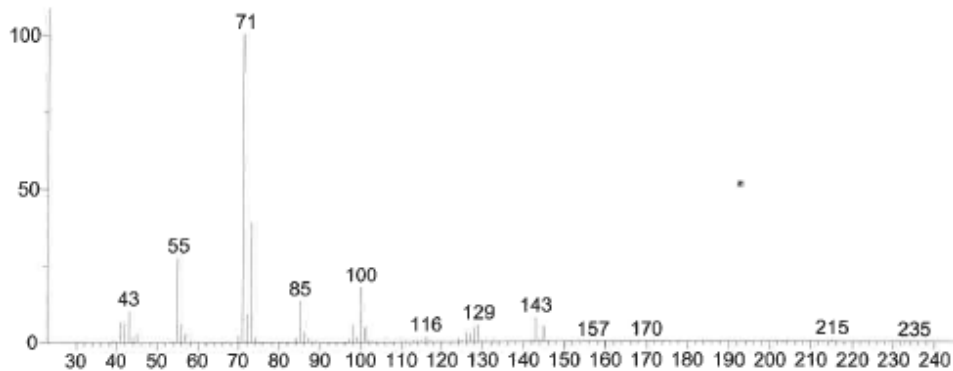


Compound = Methyl 2-methylbutanoate

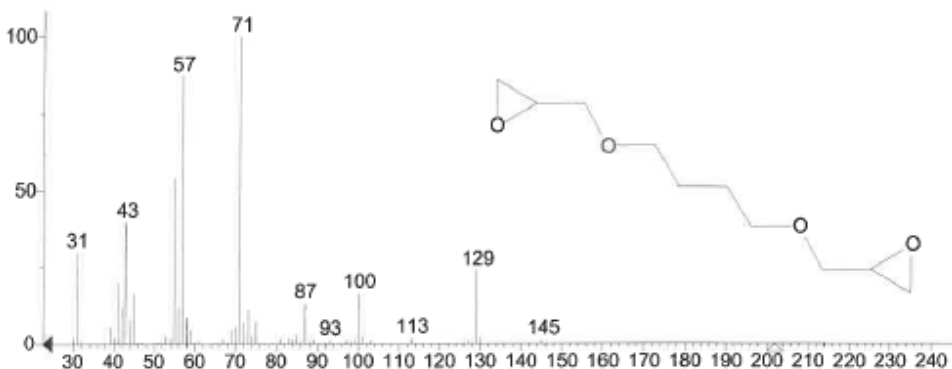


MAC

Unknown: Scan 4255 (35.831 min): 24NOV082.D\data.ms (-4250)
Compound in Library Factor = -1187



Hit 1 : Oxirane, 2,2'-[1,4-butanediylbis(oxymethylene)]bis-C10H18O4; MF: 620; RMF: 666; Pro **24.2%** CAS: 2425-79-8; Lib: replib; ID: 8646.

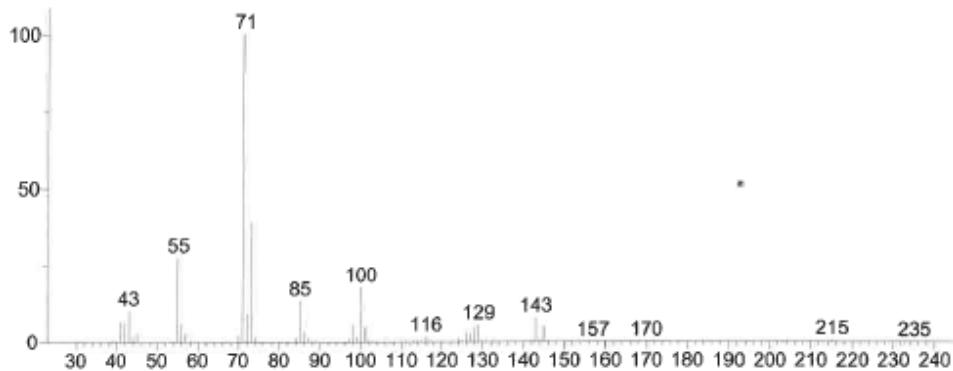


Look at match factor and similarities between your spectrum and library spectrum

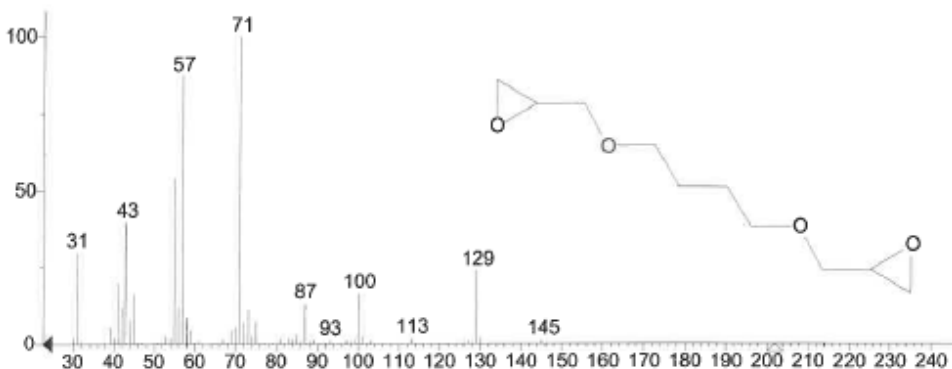


**Anonymous
Nonsense
Identification**

Unknown: Scan 4255 (35.831 min): 24NOV082.D\data.ms (-4250)
Compound in Library Factor = -1187



Hit 1 : Oxirane, 2,2'-[1,4-butanediylbis(oxymethylene)]bis-
C10H18O4; MF: 620; RMF: 666; Prot: **24.2%**; CAS: 2425-79-8; Lib: replib; ID: 8646.



Look at match factor and similarities between your spectrum and library spectrum



Unidentified

The world of medical devices

Identify

Non critical medical medical

exposure



Blood contacting

permanent exposure



Medical

exposure



Variety of Process parameters
Solvents, glue, sterilization,.....

Variety of materials
Metals, polymers, biodegradable

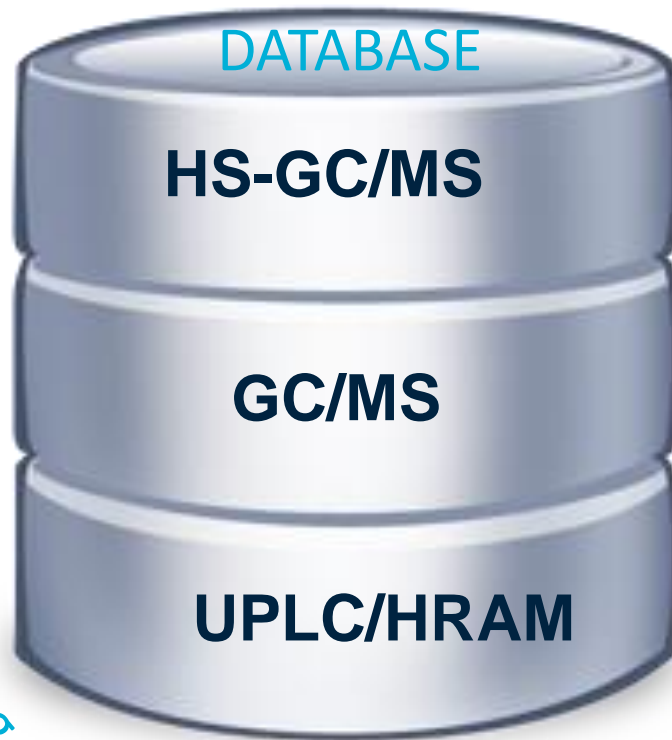
The world of medical devices NEEDS A

Identify 

Extensive

Reliable

Continuously growing



Clear Identification status

NELSON LABS' DATABASE: STATUS AS OF FEB 28, 2019

Headspace GC/MS - VOC

987 Compounds

Authentic Standards: 900 Compounds (250 with RRF in WFI)

T.I.C.'s: 1% Unknowns: 1%

GC/MS - SVOC

Approx. 3486 Compounds

Authentic Standards: 2650 (GC/MS + Deriv GC/MS)

I.C.'s: 75% M.P.C.'s: 5%

T.I.C.'s: 12% Unknowns: 8%

LC/MS APCI +/- NVOC

Approx. 1500 Cmpds

Authentic Standards: 1008 Compds

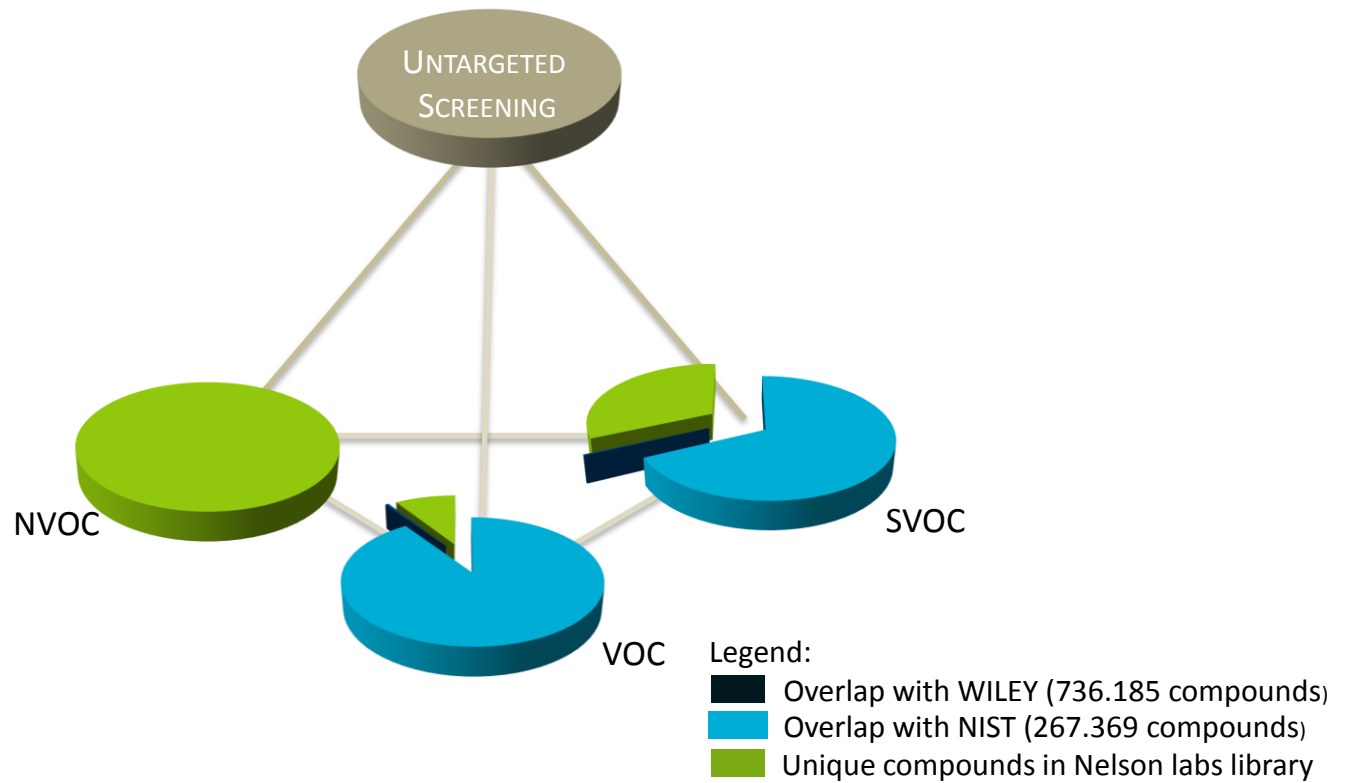
I.C.'s: 75% M.P.C.'s: 5%

T.I.C.'s: 12% Unknowns: 8%

LC/MS ESI +/-

Approx. 200 Cmpds

Authentic Standards: 150 Compds





IC

Identified Compound

- Analytical Standard Available
- MS and RT confirmed: 100% - in line with USP criteria

MPC

Most Probable Compound

- Analytical Standard NOT available
- Excellent fit with MS-library (>80%)

TIC

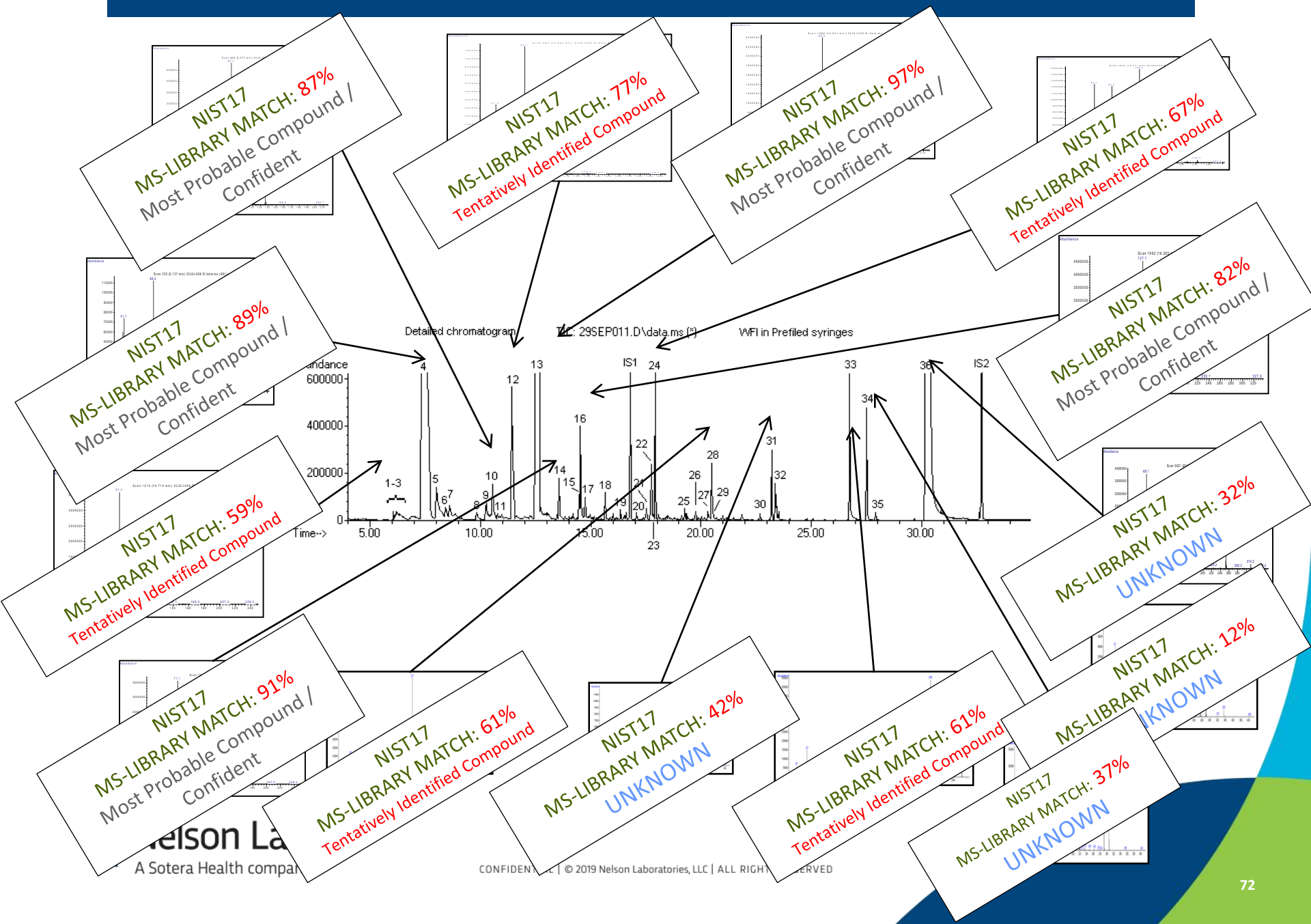
Tentatively Identified Compound

- Analytical Standard NOT available
- Lower fit with MS-library: only limited structural information/
molecular formula

U

Unidentified Compound

SCREENING WITHOUT THE NELSON LABS' DATABASE



Nelson Labs
A Sotera Health company

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SCREENING WITH THE NELSON LABS' DATABASE



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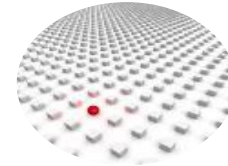
3. Why performing a chemical characterization study



TARGETED



SCREENING



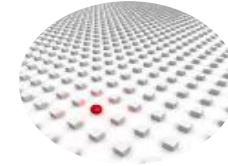
Quantify



TARGETED



SCREENING





TARGETED



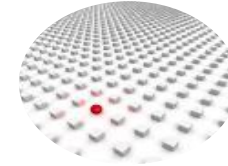
Carcinogenic
Mutagenic
Reproductive

Con

C

KNOWLEDGE OF MATERIALS

SCREENING



UNEXPECTED C

Less controlled parameters:
Ageing, packaging,
sterilization

TARGETED



MDR – Devices shall contain $< 0.1 \%$ (w/w) of

Carcinogenic
Mutagenic
Reproductive

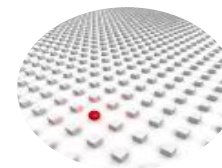
Compounds of Concern

Other....

Quantify



SCREENING



UNEXPECTED COMPOUNDS



TARGETED

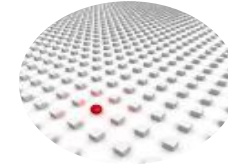


QUANTITATIVE:

- exact concentration – special method

Most accurate estimate of analyte's concentration by using a calibration curve generated specifically for the analyte using a reference standard

SCREENING



SEMI-QUANTITATIVE:

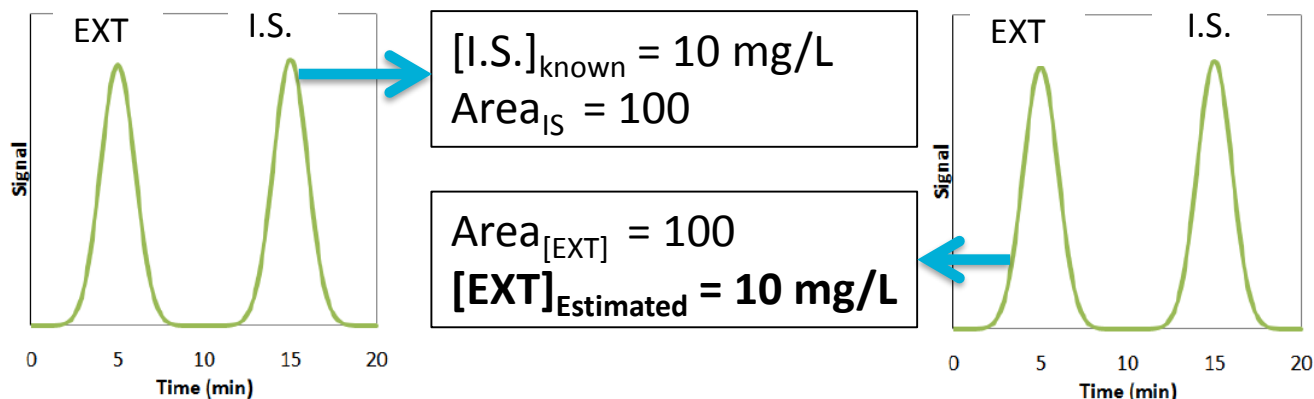
- Use internal standard/surrogate to estimate concentration

ESTIMATED QUANTIFICATION

Quantify



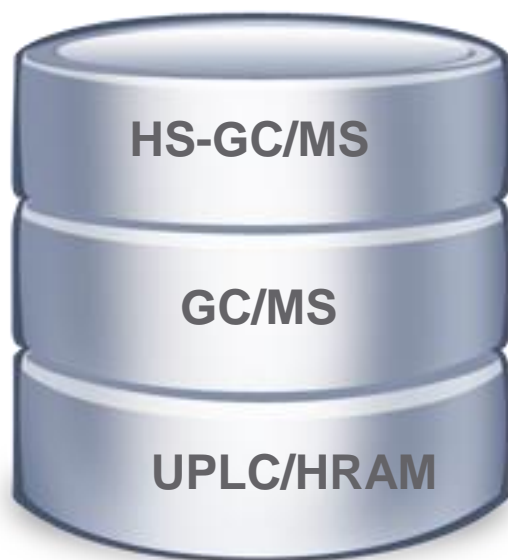
Assuming
 $RF_{IS} = RF_{[EXT]}$



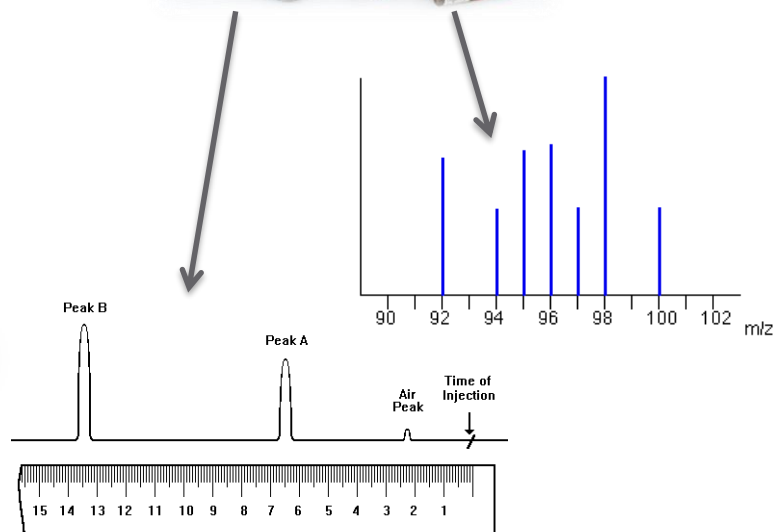
Chromatogram of Extract

Estimation of analyte's concentration by using response from a surrogate substance chosen without considering the relative responses of analyte and surrogate

NELSON LABS UNIQUE COMPOUNDS SCREENER
DATABASE

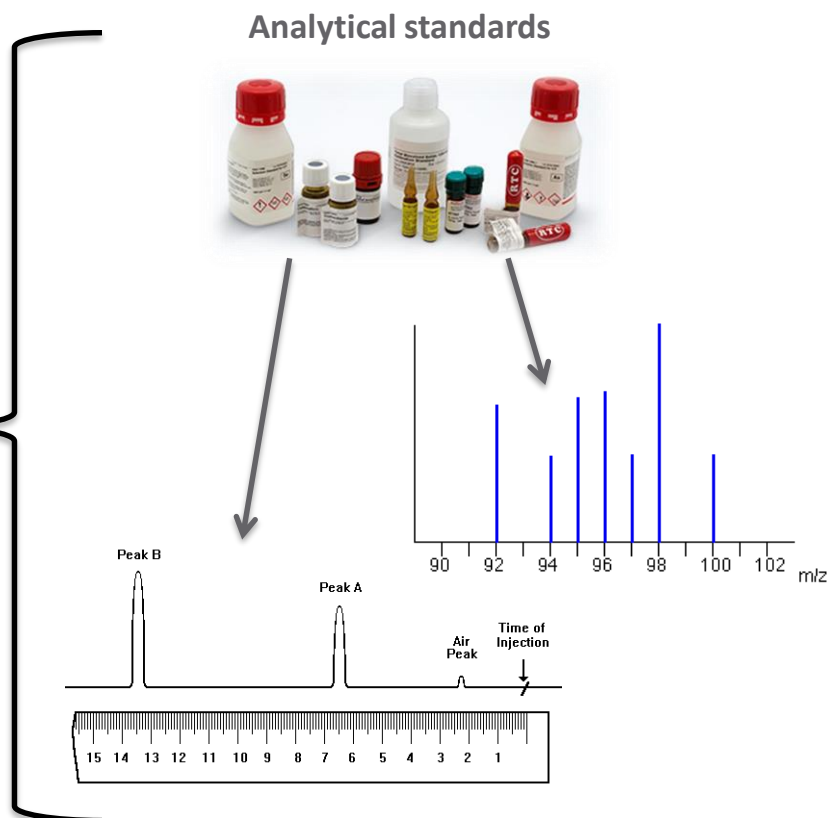


Analytical standards



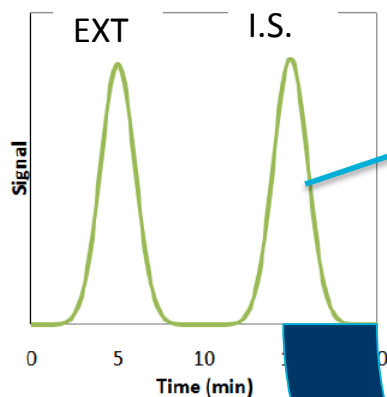
Analyte's concentration by using the response from a surrogate, accounting for the relative response of analyte and surrogate

Record Relative Response Factor (RRF)

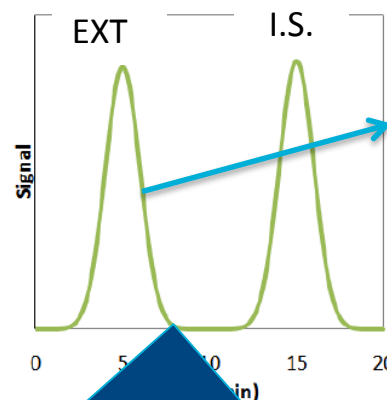


SEMI-QUANTIFICATION

Quantify

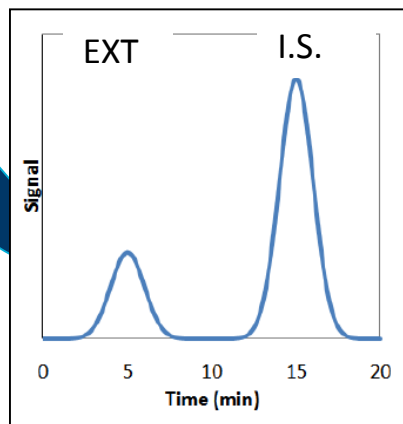


$\text{Area}_{\text{IS}} = 100$
 $[\text{I.S.}] = 10 \text{ mg/L}$



$\text{Area}_{[\text{EXT}]} = 100$
 $[\text{EXT}] = 30 \text{ mg/L}$

Chromatogram of Extract



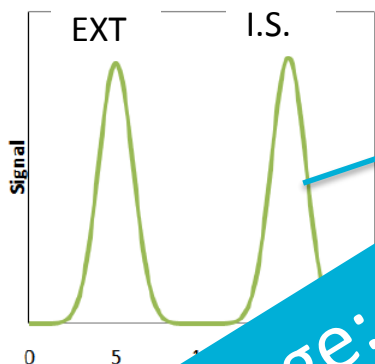
Authentic Standard Analysis of EXT

$[\text{EXT}] = 10 \text{ mg/L}$
 $\text{Area}_{[\text{EXT}]} = 30$

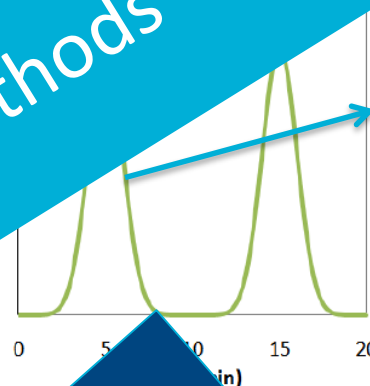
$[\text{I.S.}] = 10 \text{ mg/L}$
 $\text{Area}_{\text{IS}} = 100$

$\text{RRF}_{[\text{EXT}]} = 0,3$

SEMI-QUANTIFICATION

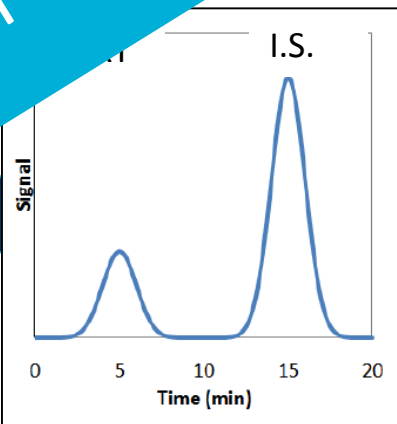


Area_{IS} = 100
[I.S.] = 10 mg/L



Area_[EXT] = 100
[EXT] = 30 mg/L

Advantage: No use of high UF or need for more quantitative methods



[EXT] = 10 mg/L
Area_[EXT] = 30

[I.S.] = 10 mg/L
Area_{IS} = 100

RRF_[EXT] = 0,3

Authentic Standard Analysis of EXT

Over 4000 RRF Values are included for EXT in the NELSON LABS' Database

Outline

1. Chemical Characterization: Introduction

2. Set-up of chemical characterization

2.1 Extract

2.2 Detect

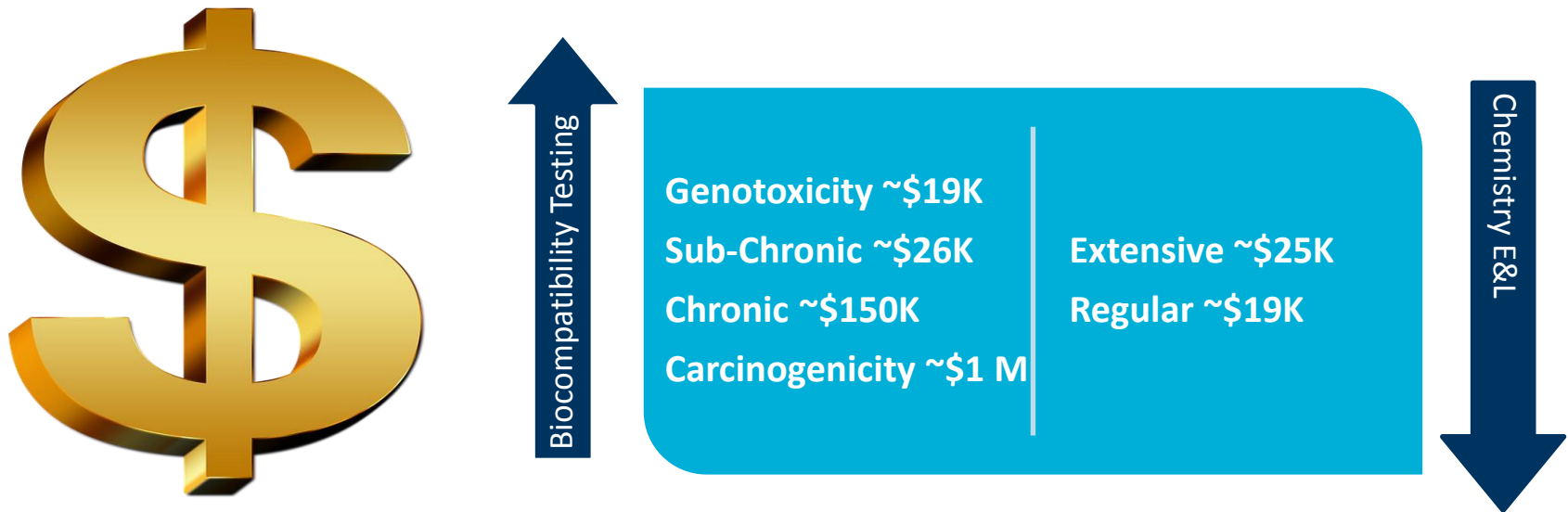
2.3 Identify

2.4 Quantify

3. Why performing a chemical characterization study

Why performing E&L testing?

Why performing E&L testing?



Why performing E&L testing?



Biocompatibility testing takes time

Sub-Chronic	~13 Weeks
Chronic	~26 Weeks
Carcinogenicity	~18 Months+

Chemistry E&L

Extensive	~8-14 Weeks
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Why performing E&L testing?

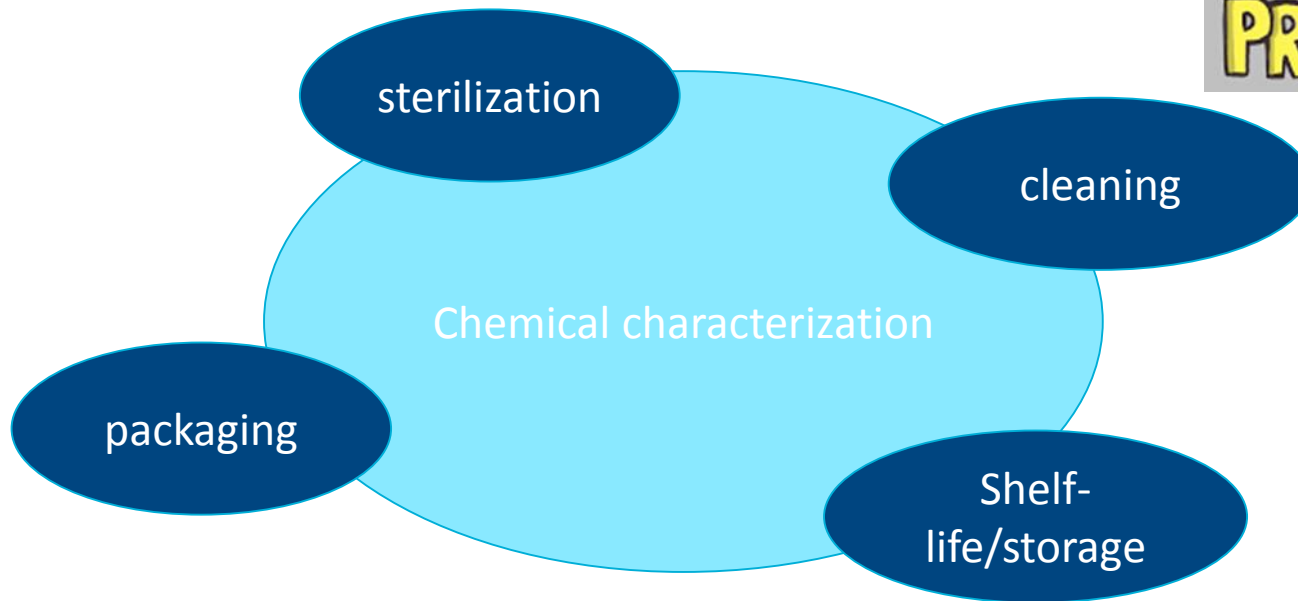


Biocompatibility results are pass/fail

Chemistry E&L results provide detailed results

- What does the device release?
- How much?
- Intention of reducing or eliminating animal testing

Why performing E&L testing?



Nelson Labs NV - Belgium

Ready when you are!

