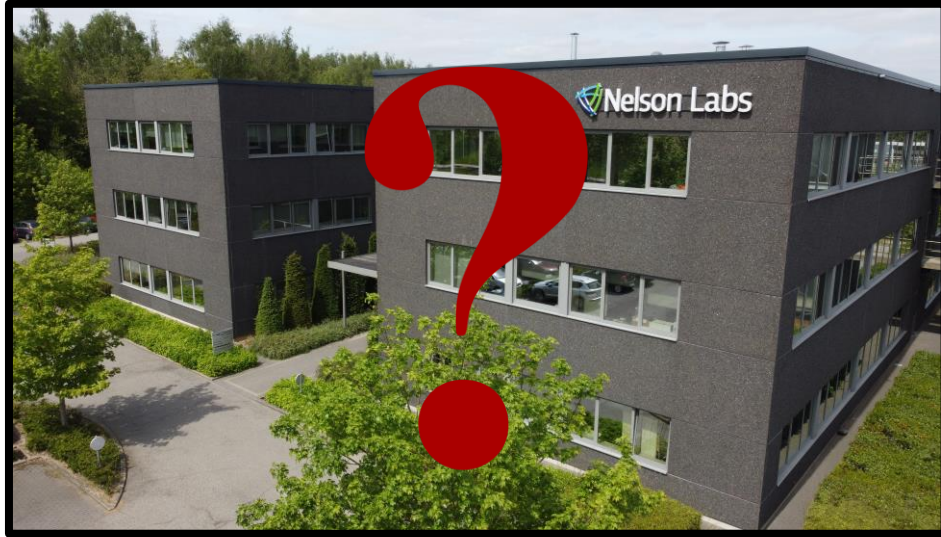




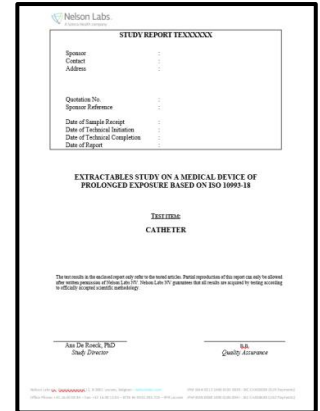


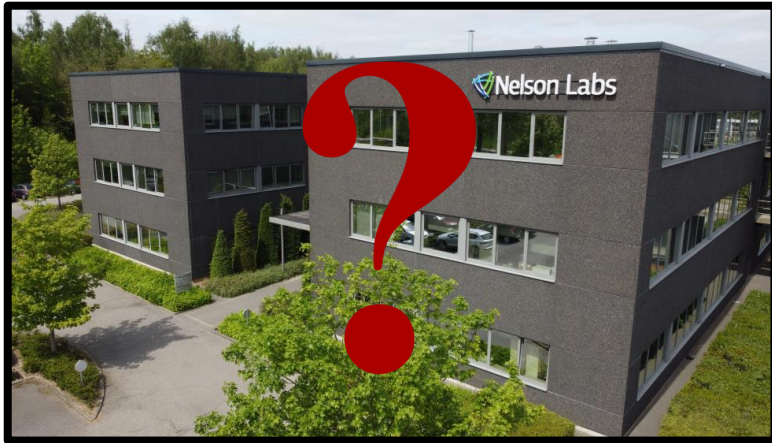


Input



Output





# ISO 10993-18

## Introduction to Extractables and Leachables testing for medical devices

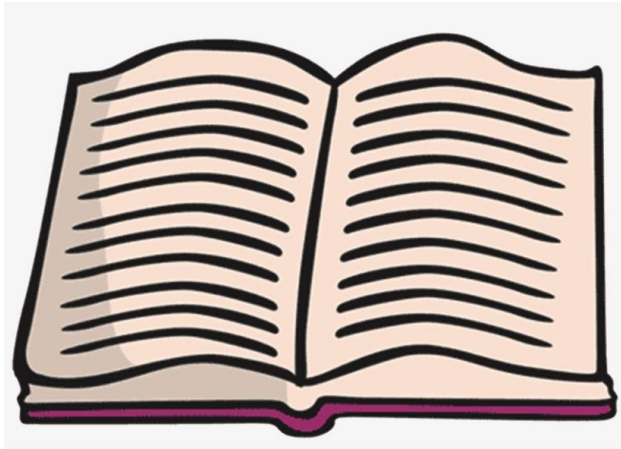
*From device to chromatogram*



Ans De Roeck

26 April 2023



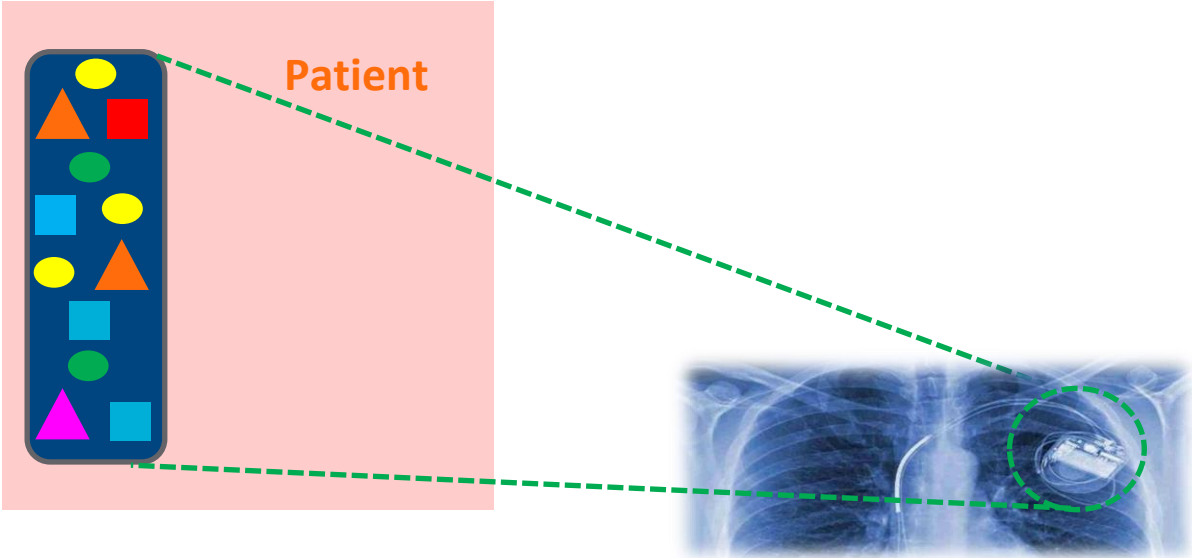


**ISO 10993-1**

**E&L testing according  
ISO 10993-18 needed**

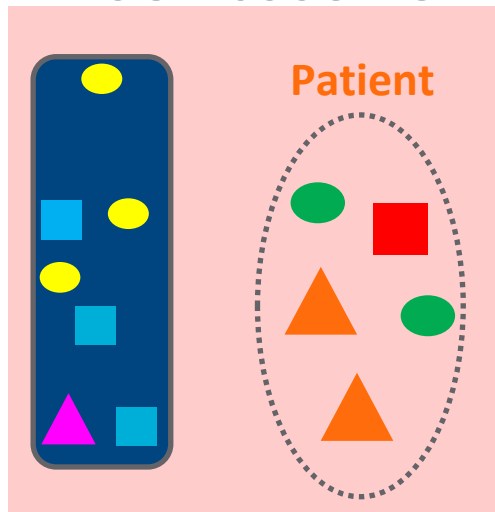


# Extractables & Leachables testing – What?



# Extractables & Leachables testing – What?

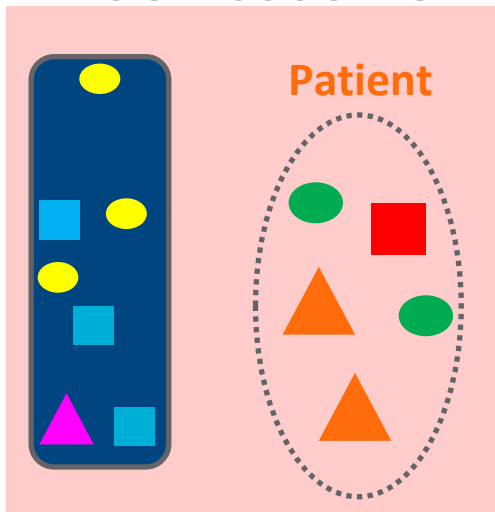
ISO 10993-18



➔ Which compounds are migrating?

# Extractables & Leachables testing – What?

ISO 10993-18



ISO 10993-17



# Extractables testing



→ What CAN come out of the material?

# Extractables testing



# Leachables testing



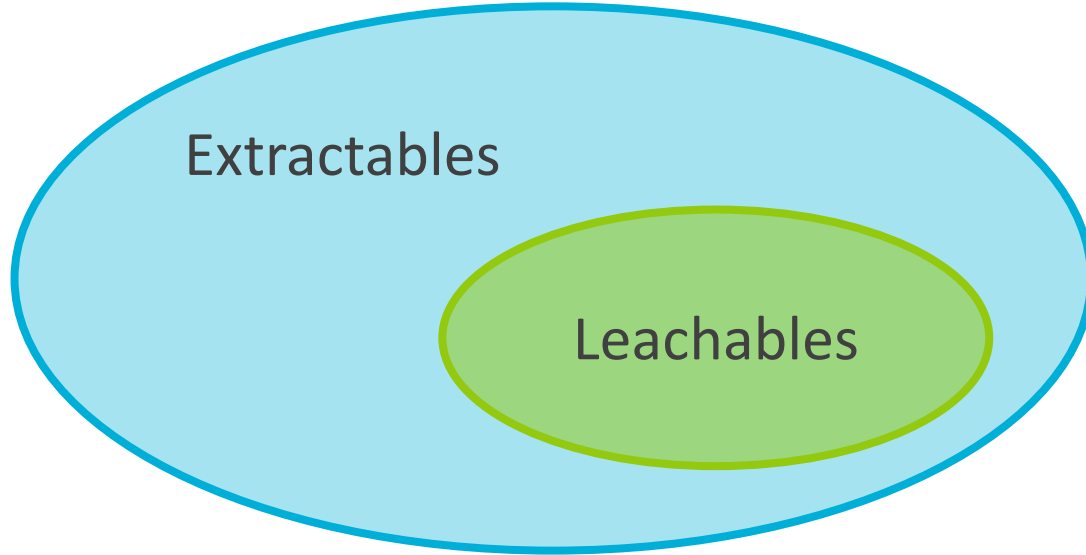
→ What CAN come out of the material?

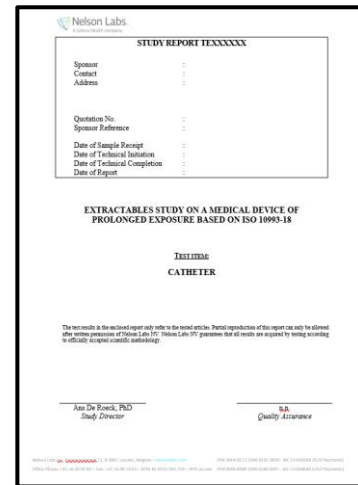
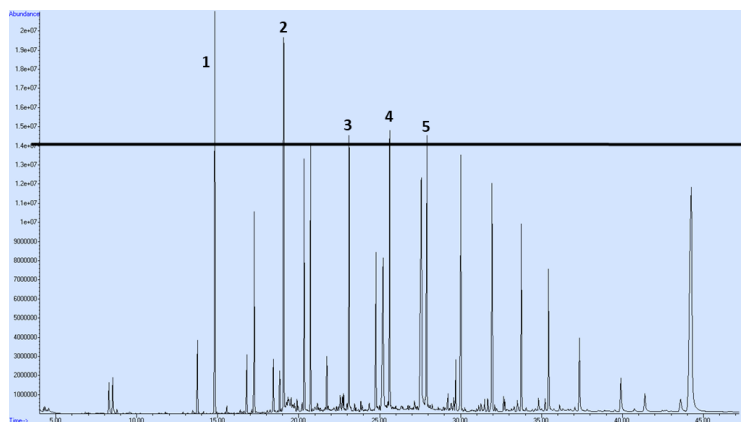
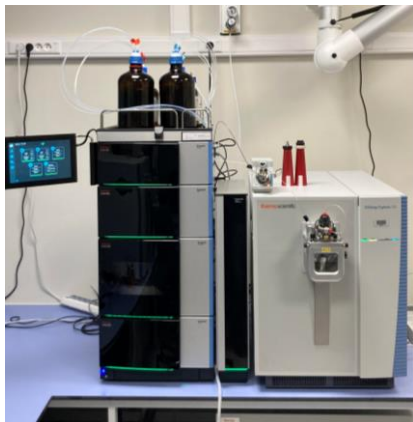
→ What DOES come out from the material in the patient?

Extractables testing



Leachables testing







## Sample Preparation

1. Test item
2. Extraction solvents
3. Extraction ratio
4. Extraction conditions





# 1. Test item

- Finished medical device



# 1. Test item

- Finished medical device
- Only patient contacting parts (direct, indirect)



## 2. Extraction solvents



## 2. Extraction solvents

**Table D.1 — Parameters of solvents commonly used for extraction of polymeric medical devices/materials**

	Solvent <sup>a</sup>	Polarity index <sup>[50]</sup>	Boiling point (°C) <sup>b</sup>
<b>Polar</b>	Water <sup>c</sup>	10,2	100
<b>Semi Polar</b>	Dimethyl sulfoxide	7,2	189
	Acetonitrile	5,8	82
	Methanol	5,1	65
	Acetone	5,1	56
	Ethanol <sup>d</sup>	4,3	78
	Tetrahydrofuran	4,0	65
	<i>n</i> -Propyl alcohol	4,0	97
	<i>i</i> -Propyl alcohol	3,9	82
<b>Non-Polar</b>	Dichloromethane	3,1	41
	Toluene	2,4	111
	Cyclohexane	0,2	81
	Heptane	0,1 <sup>e</sup>	98
	<i>n</i> -Hexane	0,1	69

Source: ISO 10993-18 (2020)

## 2. Extraction solvents

- Consider the use
  - Interactions with specific solutions / drug products?
  - Indirect patient contact?



## 2. Extraction solvents

- Avoid solvents that cause swelling and/or degradation

HEX

IPA



UPW

IPA

HEX



### 3. Extraction ratio



### 3. Extraction ratio

**Table 1 — Standard surface areas and extract liquid volumes**

<b>Thickness<sup>a</sup> mm</b>	<b>Extraction ratio (surface area or mass/volume) ±10 %</b>	<b>Examples of forms of materials</b>
<0,5	6 cm <sup>2</sup> /ml	film, sheet, tubing wall
0,5 to 1,0	3 cm <sup>2</sup> /ml	tubing wall, slab, small moulded items
>1,0	3 cm <sup>2</sup> /ml	larger moulded items
irregularly shaped solid devices	0,2 g/ml	powder, pellets, foam, non-absorbent moulded items, porous high-density materials
irregularly shaped porous devices (low-density materials)	0,1 g/ml	membranes, textiles

Source: ISO 10993-12 (2021)



## 4. Extraction conditions

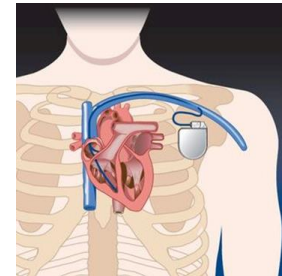


## 4. Extraction conditions

**Table 2 — Recommended extraction conditions**

Contact category	Recommended extraction conditions	Credible alternatives
Limited contact devices	Simulated use conditions <sup>a</sup>	Exaggerated conditions
Prolonged contact devices	Exhaustive conditions	Exaggerated conditions <sup>b,c</sup>
Long-term contact devices	Exhaustive conditions	Exaggerated conditions <sup>b,c,d</sup>

Source: ISO 10993-18 (2020)



## 4. Extraction conditions

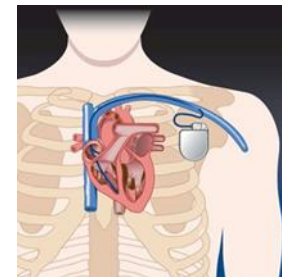
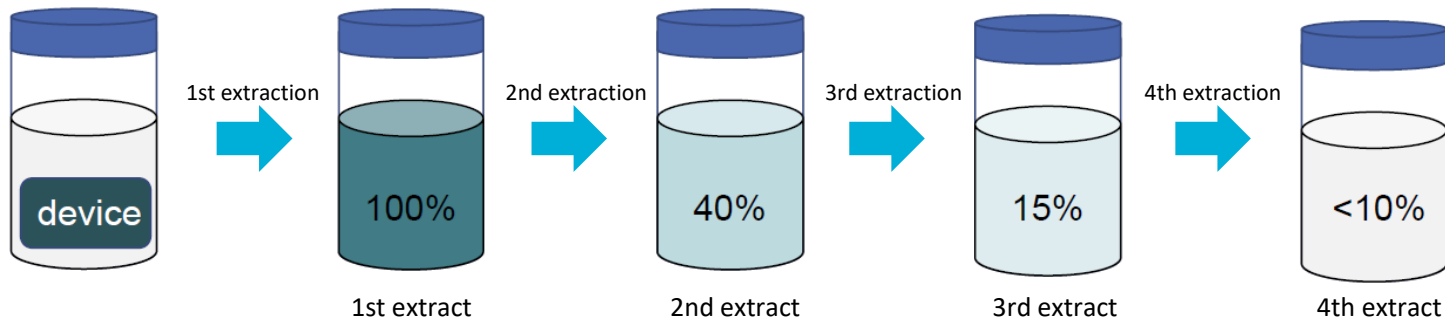


Table 2 — Recommended extraction conditions

Contact category	Recommended extraction conditions	Credible alternatives
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Prolonged contact devices	Exhaustive conditions	Exaggerated conditions <sup>b,c</sup>
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Source: ISO 10993-18 (2020)

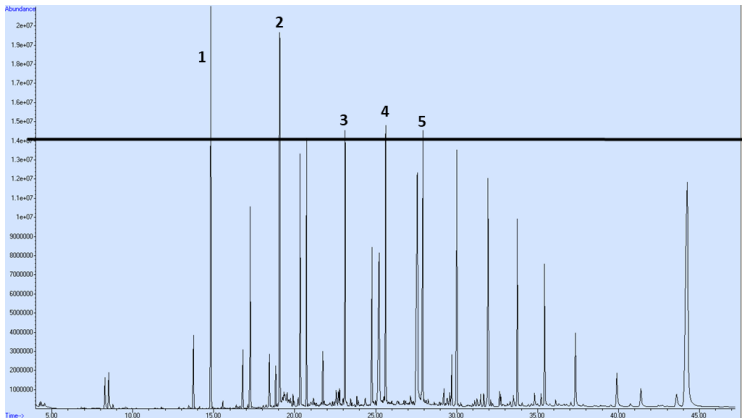
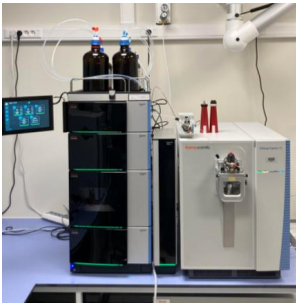




# Analysis



1. Techniques
2. Evaluation threshold



# 1. Analytical techniques



Volatile Organic Compounds  
(VOCs)



Semi-Volatile Organic Compounds  
(SVOCs)



Non-Volatile Organic Compounds  
(NVOCs)



Elements

# 1. Analytical techniques



HS-GC/MS  
**Screening**



GC/MS  
**Screening**



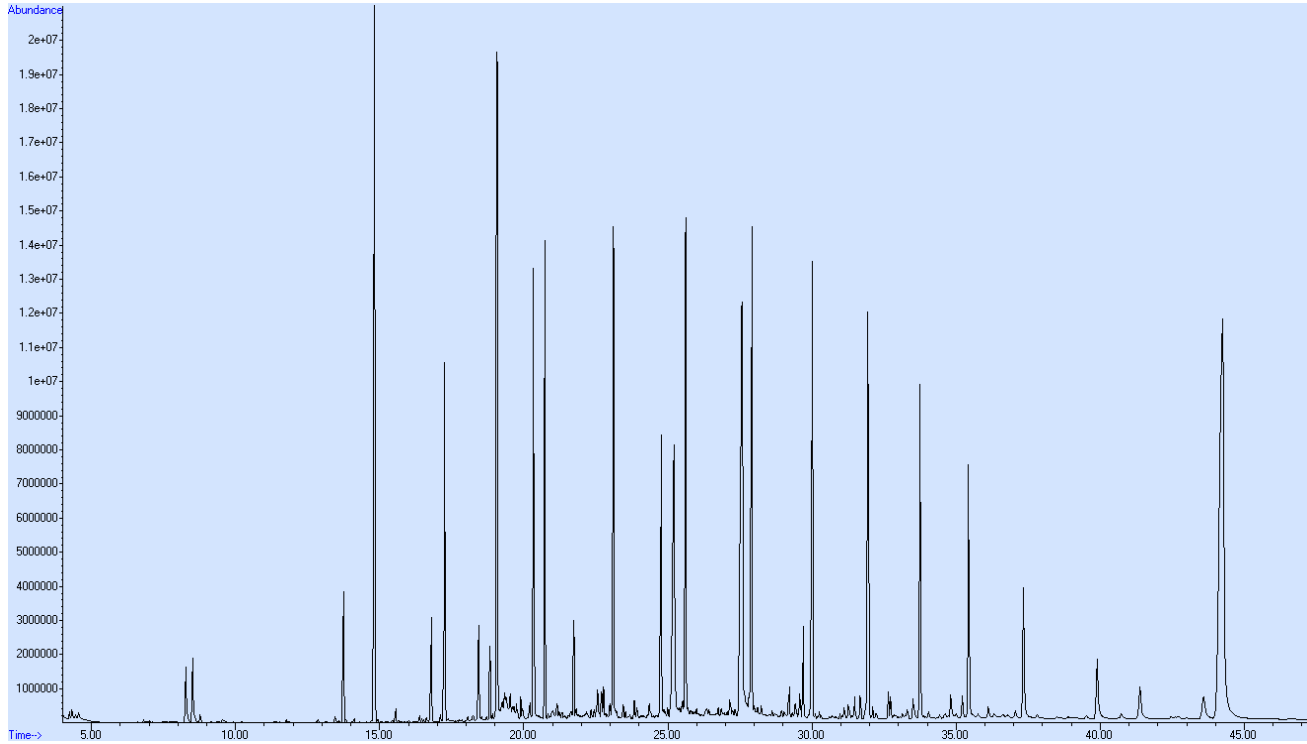
LC/MS  
**Screening**



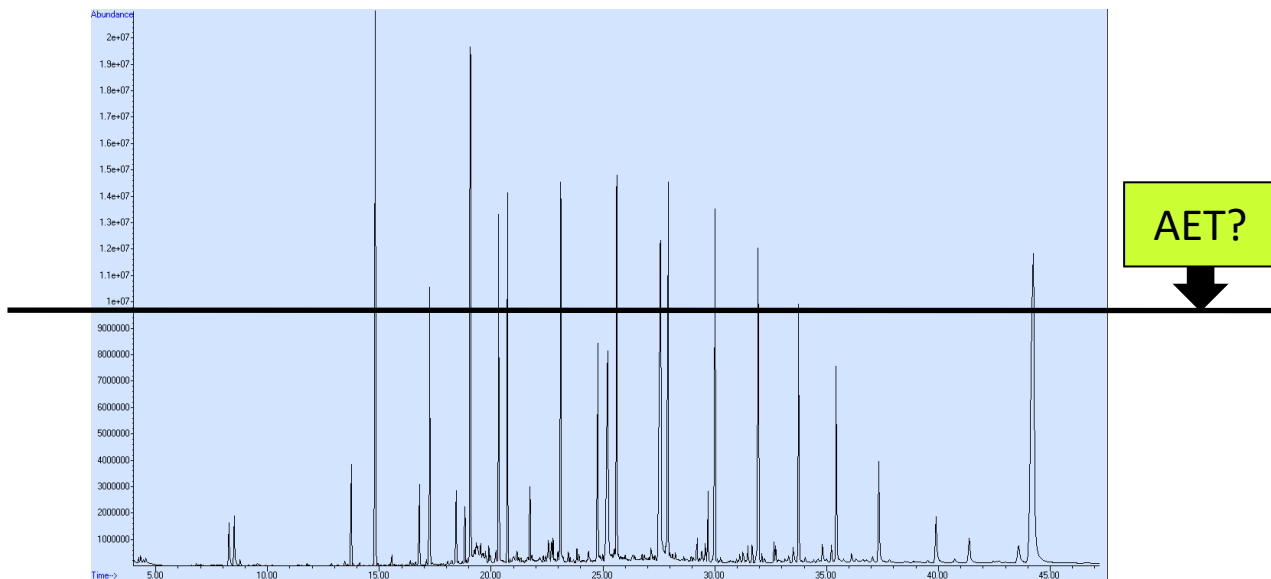
ICP/OES  
ICP/MS  
**Target**



# 1. Analytical techniques



## 2. Analytical Evaluation Threshold (AET)



*“Threshold below which the analyst need not identify or quantify leachables or extractables or report them for potential toxicological assessment”*



## 2. Analytical Evaluation Threshold (AET)

$$\text{AET} = \frac{\text{DBT} \times \frac{\text{A}}{\text{BC}}}{\text{UF}}$$

Source: ISO 10993-18 (2020)

## 2. Analytical Evaluation Threshold (AET)

$$AET = \frac{DBT \times \frac{A}{BC}}{UF}$$

Source: ISO 10993-18 (2020)

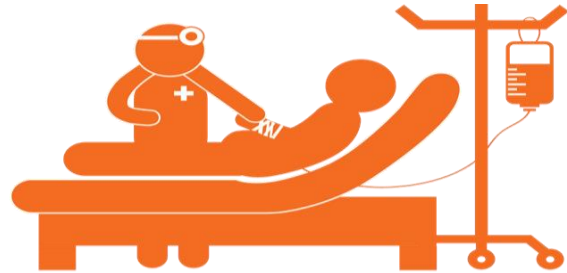
Dose Based Threshold

Threshold of Toxicological Concern ( $\mu\text{g}/\text{day}$ )

< DBT



> DBT



## 2. Analytical Evaluation Threshold (AET)

$$AET = \frac{DBT \times \frac{A}{BC}}{UF}$$

Source: ISO 10993-18 (2020)

Dose Based Threshold

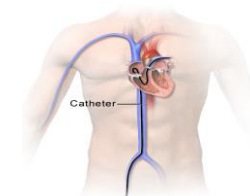
Threshold of Toxicological Concern (µg/day)

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

Medical device contact category	Limited (<24 h)	Prolonged (24 h to 30 d)	Long-term <sup>a</sup> (>30 d)		
			> 1 month to 12 months	> 1 year to 10 years	> 10 years to lifetime
Duration of body contact	≤ 1 month		> 1 month to 12 months	> 1 year to 10 years	> 10 years to lifetime
Daily intake (µg/d) of any one constituent	120		20	10	1,5 <sup>b</sup>

<sup>a</sup> Long-term includes devices commonly described as permanent contacting (see ISO 10993-1).

<sup>b</sup> The 1,5 µg/d value is based on 10<sup>-5</sup> cancer risk and 60 kg (adult) body weight[6][17].



## 2. Analytical Evaluation Threshold (AET)

$$\text{AET} = \frac{\text{DBT} \times \frac{\text{A}}{\text{BC}}}{\text{UF}}$$

Source: ISO 10993-18 (2020)

### Uncertainty Factor

to account for the analytical uncertainty of the screening methods used to estimate extractables' concentrations in an extract

## 2. Analytical Evaluation Threshold (AET)

$$\text{AET} = \frac{\text{DBT} \times \frac{A}{BC}}{\text{UF}}$$

Source: ISO 10993-18 (2020)

### Uncertainty Factor

to account for the analytical uncertainty of the screening methods used to estimate extractables' concentrations in an extract

$$\text{UF} = \frac{1}{(1 - \text{RSD})}$$

Table 1: Overview of the statistical evaluation of the RRF values for GC/MS and LC/MS (APCI and ESI)

Technique/ Method	Nelson Labs SOP	N° of RRF Entries	Average RRF	Standard Deviation	RSD	Uncertainty Factor (UF)
GC/MS	SOP0487 SOP0245	2194	0.61	0.30	0.49	2
LC/MS (APCI)	SOP0264	652	0.84	0.67	0.80	5
LC/MS (ESI)	SOP0268	201	1.04	0.79	0.76	(4) =>5

## 2. Analytical Evaluation Threshold (AET)

$$AET = \frac{DBT \times \frac{A}{BC}}{UF}$$

Source: ISO 10993-18 (2020)

A: # devices used to generate the extract

B: Volume of the extract (mL)

C: Clinical exposure (# devices/day)



## 2. Analytical Evaluation Threshold (AET)

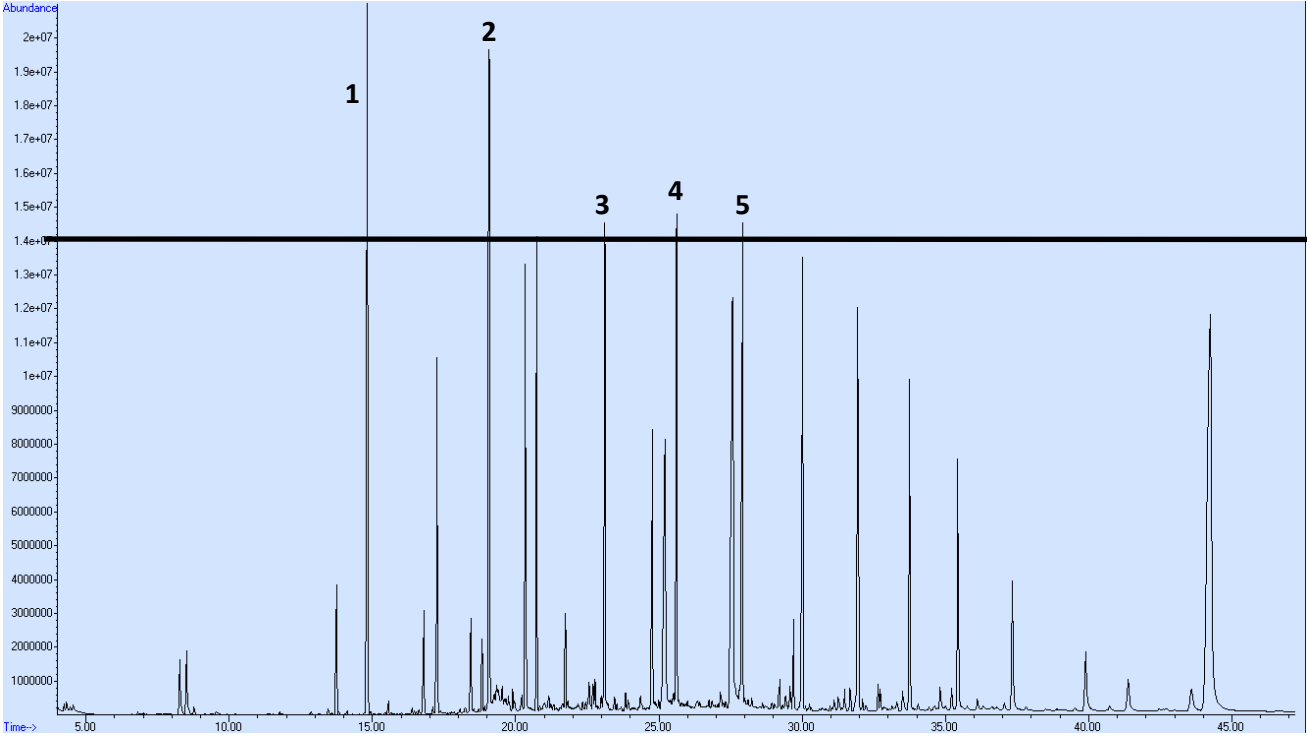
$$AET = \frac{DBT \times \frac{A}{BC}}{UF}$$

Source: ISO 10993-18 (2020)

- Long-term contacting device (> 10 years)
- 1 device (A) extracted in 50 mL (B)
- Clinical exposure (C) = 2 devices / day
- UF = 2

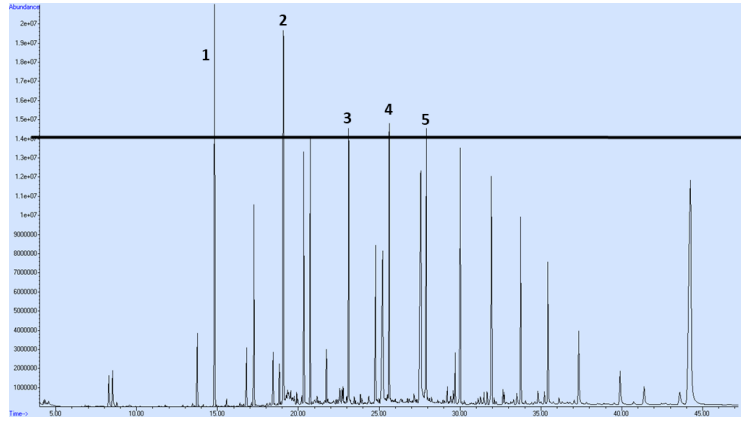
$$AET \left( \frac{\mu\text{g}}{\text{mL}} \right) = \frac{1.5 \frac{\mu\text{g}}{\text{day}} \times \frac{1 \text{ device}}{50 \text{ mL} \times 2 \text{ devices/day}}}{2} = 0.0075$$

# 2. Analytical Evaluation Threshold (AET)



AET!



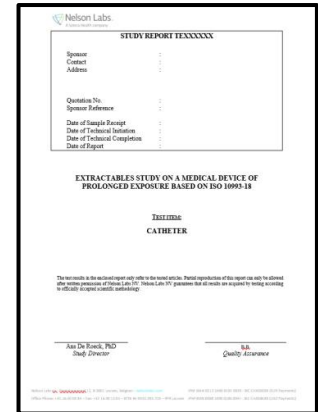


AET!

Identification



Quantification



# Sample Preparation



# Analysis

- Crucial first step!
- Think before you start!
  - Are you testing what you need to test?
  - Are the chosen extraction conditions justifiable?

- Screen broad at the right limit!





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