Introduction to Chemical Characterization (E&L)

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Phase 2: Testing and Risk Assessments

Written Assessments: Addressing Risk Associated with Chemistry Data

- Interprets chemistry data to make conclusions about specific biological risks considering the following:
  - The nature and duration of patient contact
  - The quality of chemical data available
  - The toxicological information available on the compounds observed (or not observed)

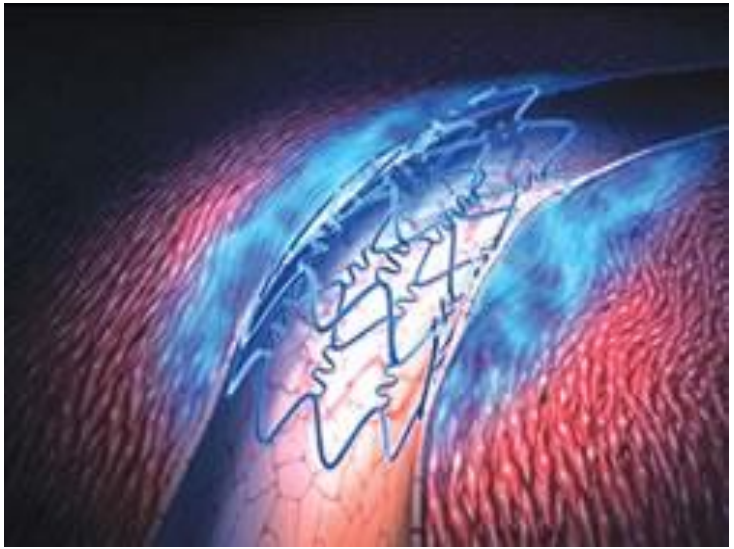
E&L Results: Interpretation of the Toxicological Risk

Recognize the **requirements** of a toxicologist to conduct a suitable **Toxicology Risk Assessment**

Apply appropriate **Thresholds of Toxicolgical Concern (TTC)** to E&L data

Understand the risks to the patient

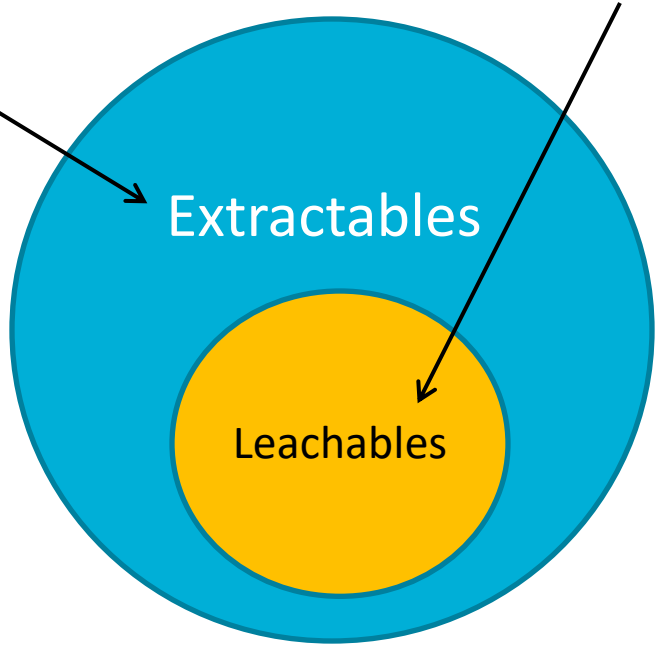
Perform Tolerable Intake (TI), Tolerable Exposure (TE), and Margin of Safety calculations



E&L Defined

Exaggerated extraction relevance to simulated clinical use of the device

Extractables:
What **CAN** come off the device



Leachables:
What is **EXPECTED** to come off the device

Why Consider E&L

FDA

Regulatory bodies have been requesting E&L more frequently

Standards for Material Characterization

- Provides guidance for the biological evaluation of medical devices within a risk management process

ISO 10993-1

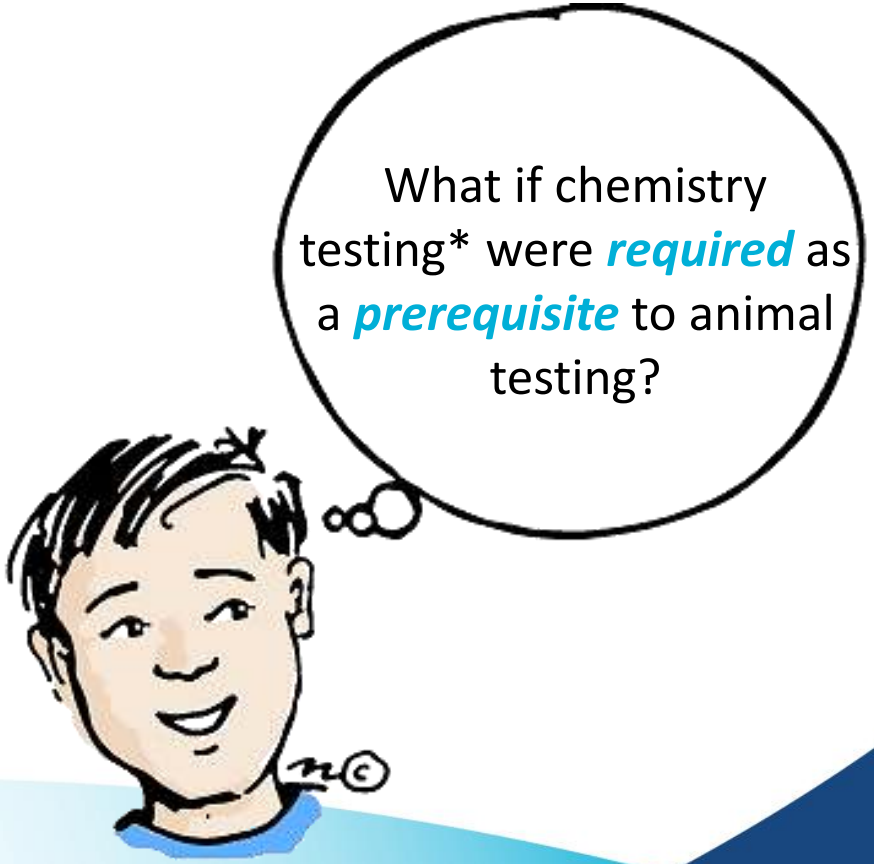
- Provides guidance for establishing limits for compounds related to materials

ISO 10993-17

- Outlines the test options for device materials

ISO 10993-18

Chemistry is the **FUTURE, and the FUTURE IS NOW**



*Good information on materials and processing may be substituted for testing

Meet the New Standard: Table A.1 from ISO 10993-1

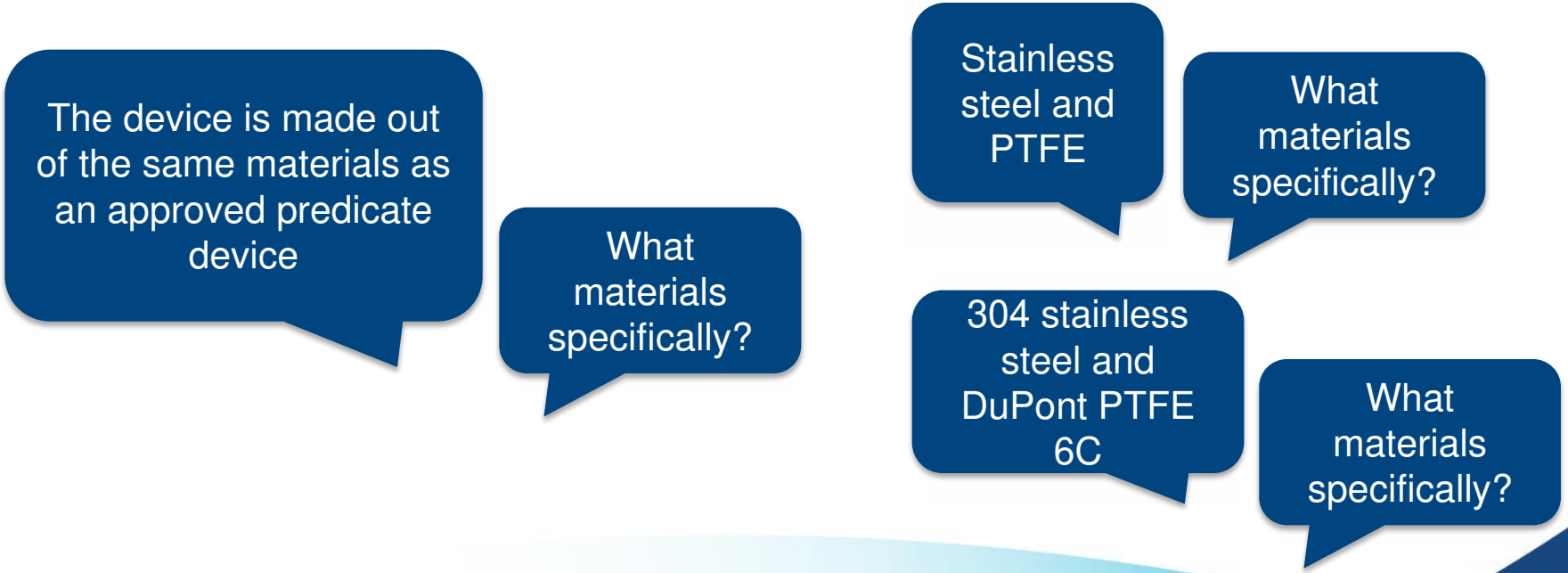
Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity		Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/ developmental toxicity[d,e]	Degradation[f]
Surface medical device	Intact skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/ bone/ dentin[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E[j]			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

- **Issued August 2018**
- **Replaced 2009 version**

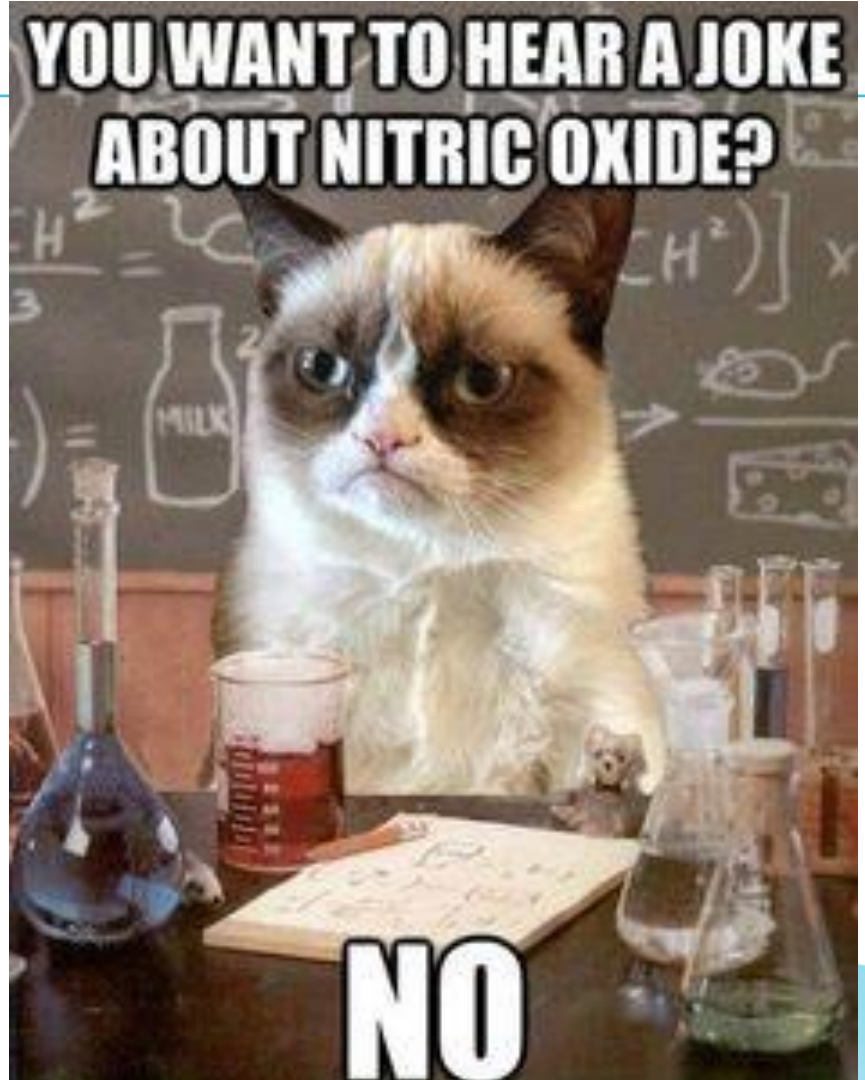
What is good material information?

- When talking about materials with the goal of avoiding chemistry testing, one must be totally unambiguous.



What is good material information?

- Not all materials with the same name are the same
- **Per the recent FDA guidance document**: The best way to specify a material is with as much of the following as possible:
  - The name and CAS number
  - The chemical supplier with structural information and details of manufacturing process
  - The specific amounts of each chemical in a material formulation
  - Processes that the material is exposed to



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The Goals of E&L

- No problem?
- Discolored hair?
- Terrible rash?
- Chronic skin problems?

How could we know (without testing on me)?

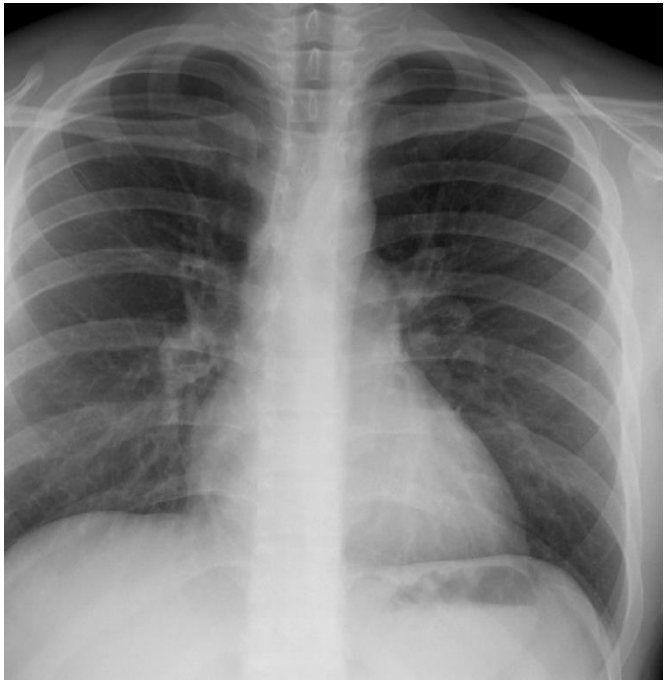
The Goals of E&L

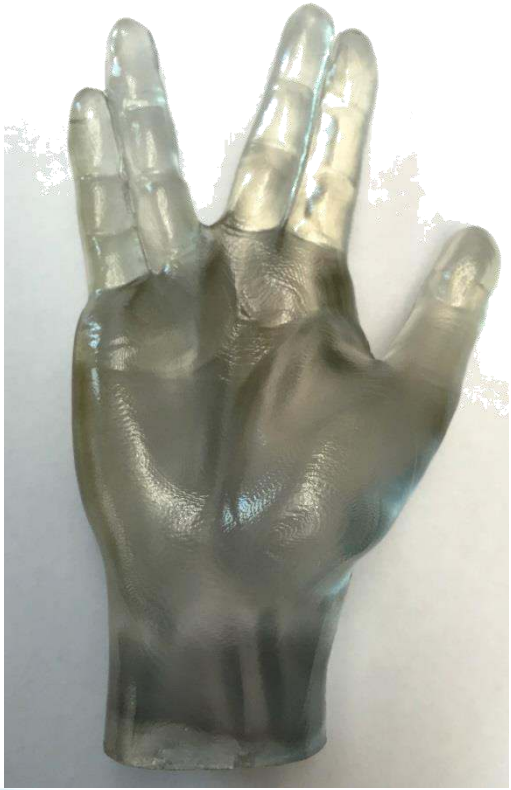
1. Predict relevant biological endpoints through analytical chemistry tests and deduction (sparing cost, time, and animal life)
2. Gain understanding of device materials and processing towards prevention and correction of problems

How Does E&L Work?

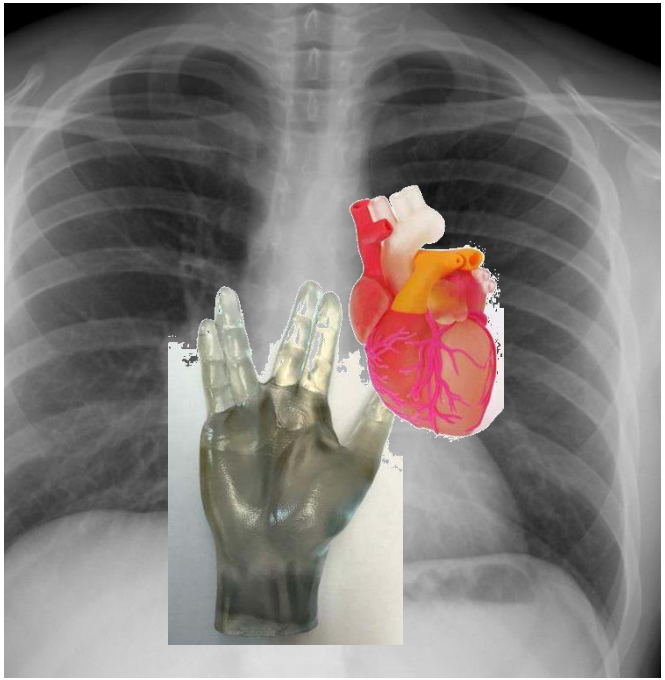
- The device is ***extracted*** per ISO 10993 standards
- The extraction liquid is ***analyzed*** using a variety of analytical chemistry techniques

How Does E&L Work: What are we looking for?





How Does E&L Work: What are we looking for?



- **ANY** substance that could leave the device during use and enter the body
  - Metals
  - Production oils and other residuals
  - Plastic additives
  - Byproducts

Who are we Looking for?

Who are we Looking for?

- Do we look for molecules with glasses?

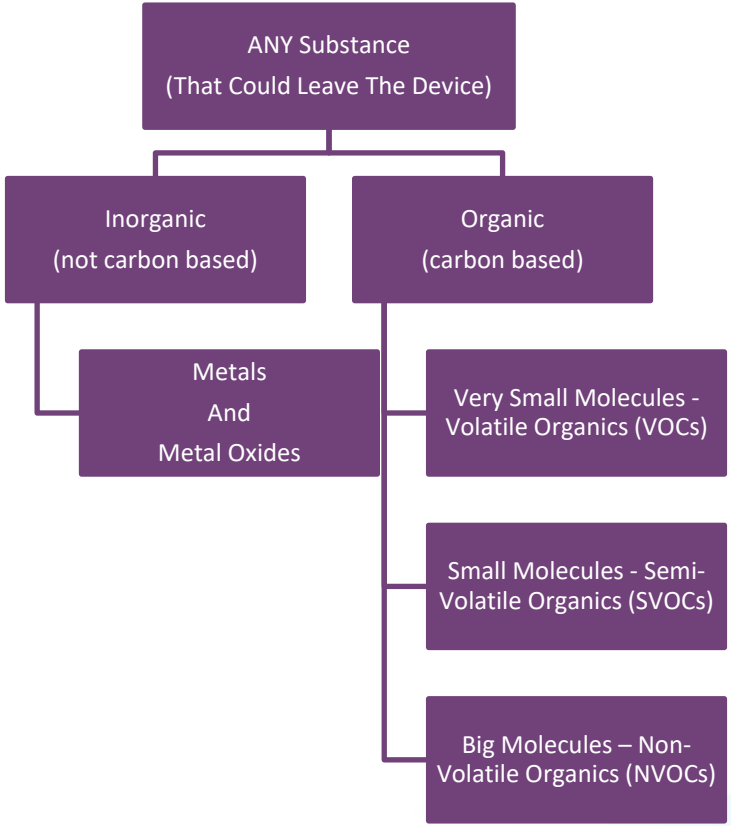
Who are we Looking for?

- Do we look for molecules with glasses?
- …and molecules that are boys?

Who are we Looking for?

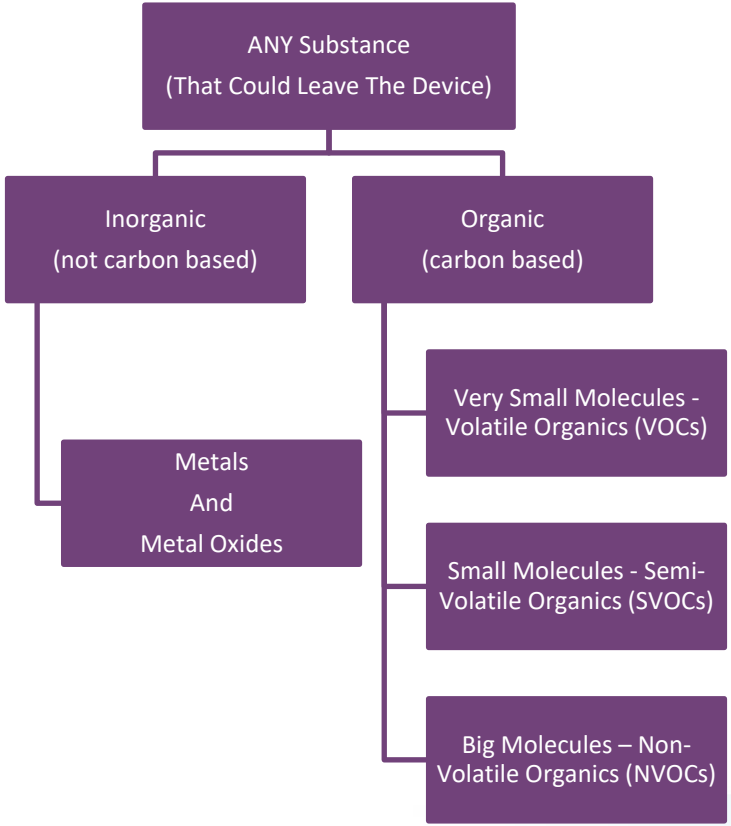
- Do we look for molecules with glasses?
- …and molecules that are boys?
- …and those at least as tough as Dr Dew?

How Does E&L Work: What are we looking for?



We cast a **wide net**, looking for essentially everything

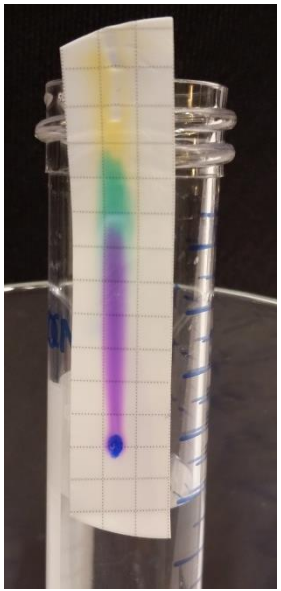
How Does E&L Work: Chromatography



- Before substances can be identified and measured, **they have to be separated** from each other.
- Organic compounds can be separated using **chromatography**.

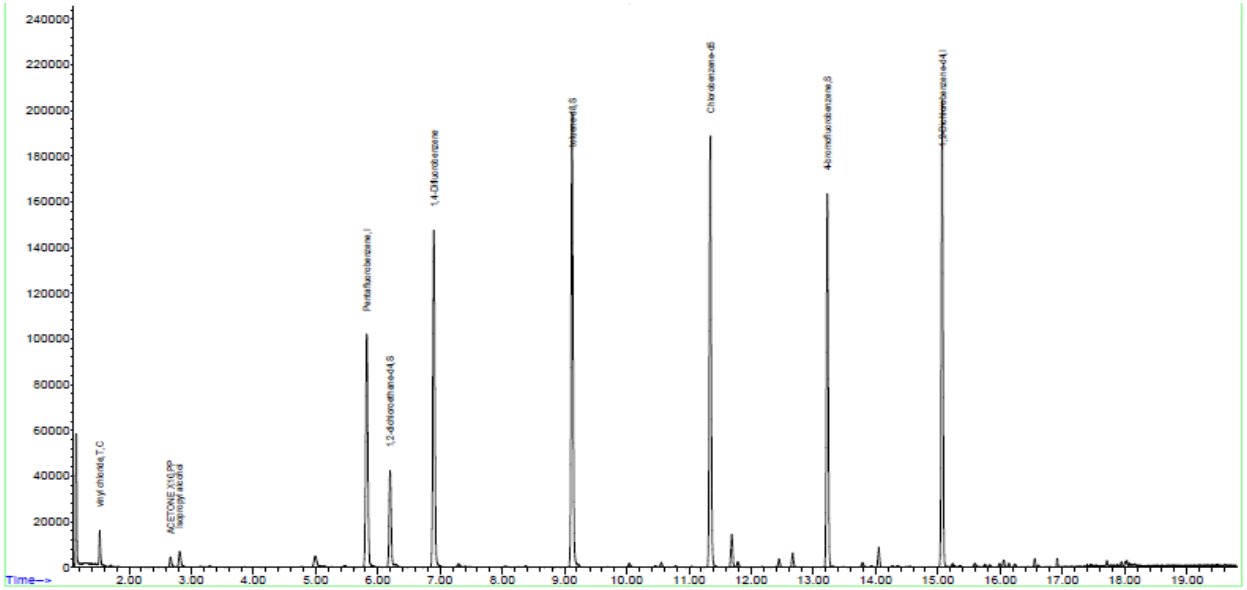
Chromatography Activity

- Chromatography literally means **“color writing”**
- Originally used to separate plant pigments

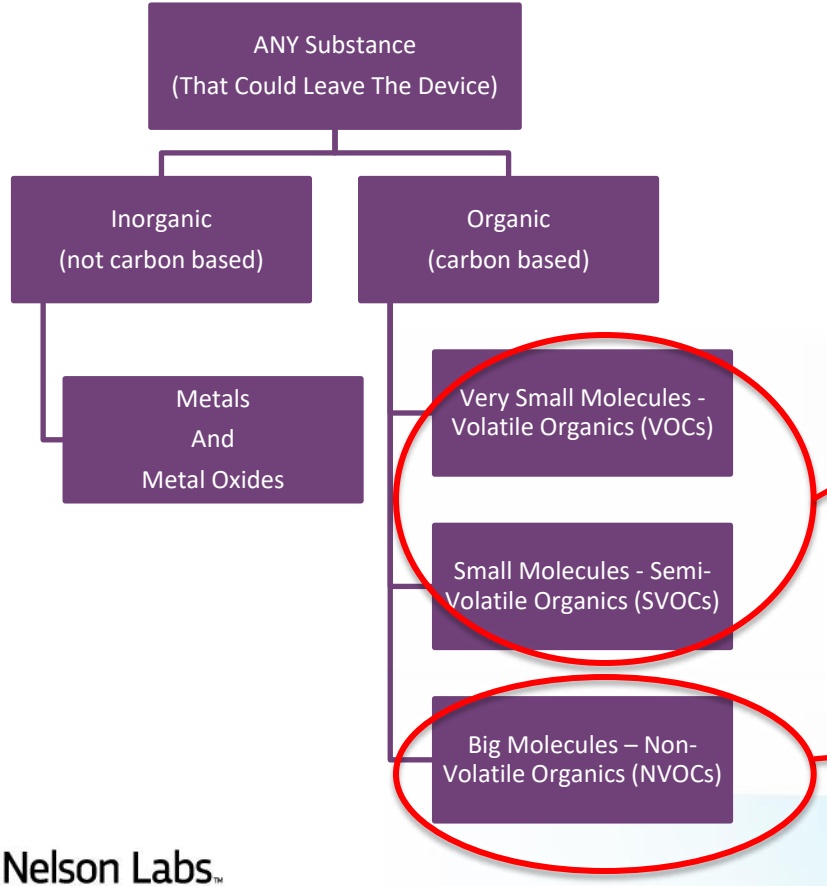


How Does E&L Work: Chromatography

- *MUCH* better than paper: gas chromatography (GC) and liquid chromatography (LC)



How Does E&L Work: Chromatography



Small molecules evaporate easily, great for gas chromatography (**GC**)

Big molecules do not evaporate easily, great for liquid chromatography (**LC**)

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How Does E&L Work: Identification and Quantification

- After separation by GC or LC, compounds must be detected and identified.
- Mass spectrometry can detect and identify molecules based on how much they weigh and how they break apart.

How Does E&L Work: Identification and Quantification

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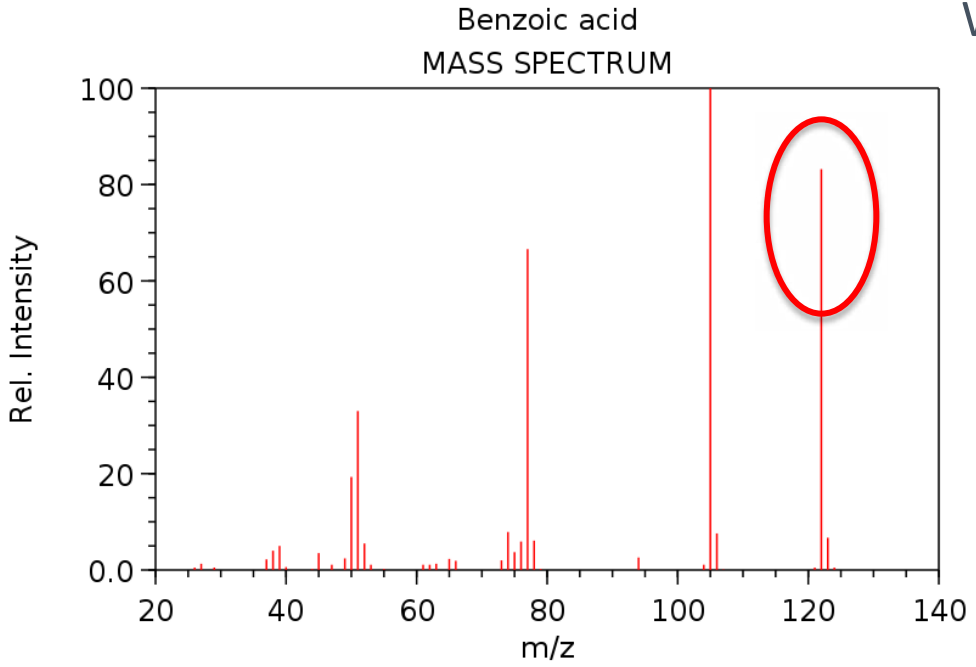
How Does E&L Work: Identification and Quantification

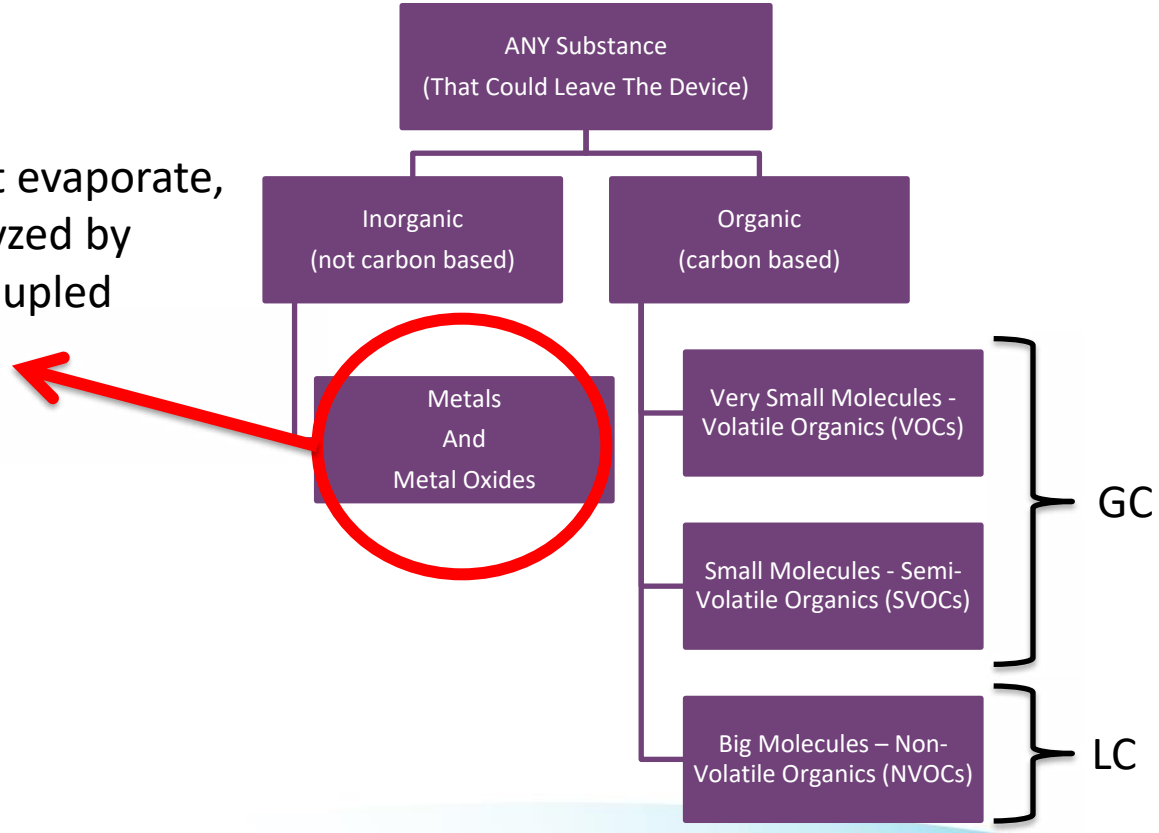
Heaviest Piece = Whole Molecule (or Car)



NIST Chemistry WebBook (http://webbook.nist.gov/chemistry)

How Does E&L Work: Metals – ICP/MS

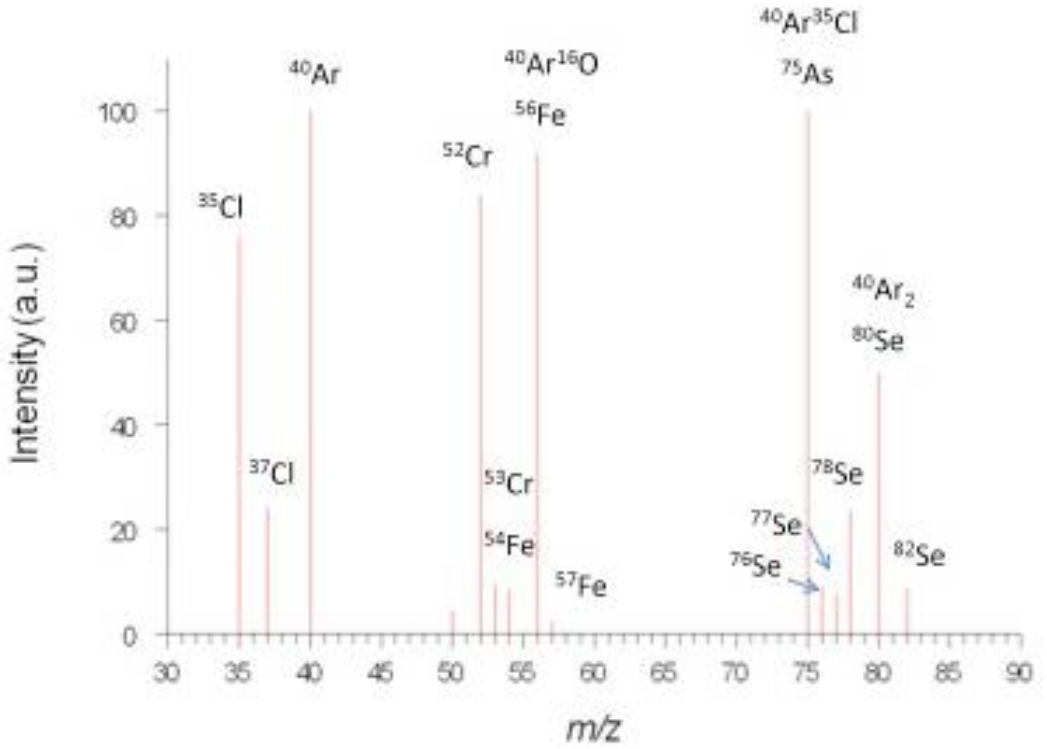
Metals do not evaporate, must be analyzed by inductively coupled plasma **(ICP)**



How Does E&L Work: Metals – ICP/MS

Liquid sample is aerosolized and introduced to argon plasma

The plasma will dry the aerosolized liquid, rip the molecules apart, and remove an electron



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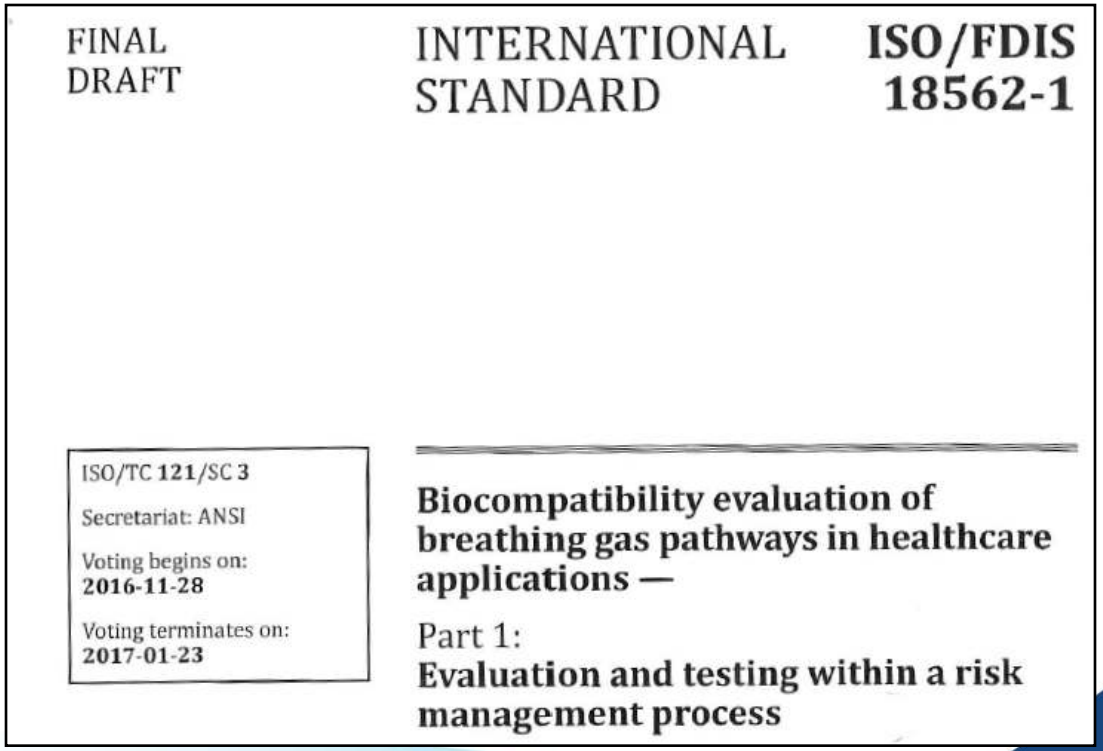
Gas Path Devices: ISO 18562 (2017)

- Takes a risk-based approach
- Narrows approach down to 3 categories:
  - VOCs
  - Particulates
  - Extractables in Condensate



FINAL DRAFT

INTERNATIONAL STANDARD

ISO/FDIS 18562-1

ISO/TC 121/SC 3

Secretariat: ANSI

Voting begins on:
2016-11-28

Voting terminates on:
2017-01-23

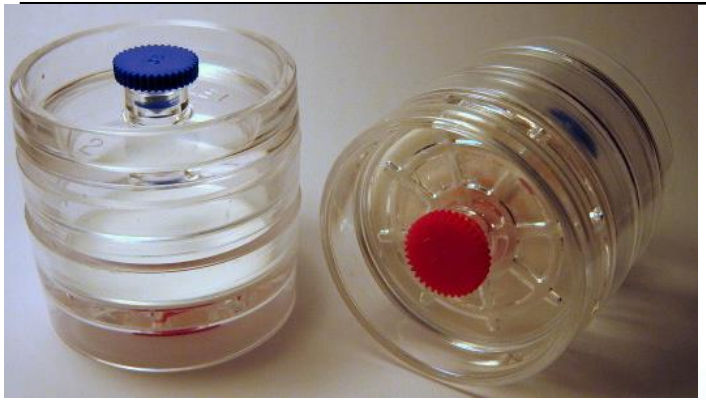
Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 1:
Evaluation and testing within a risk management process

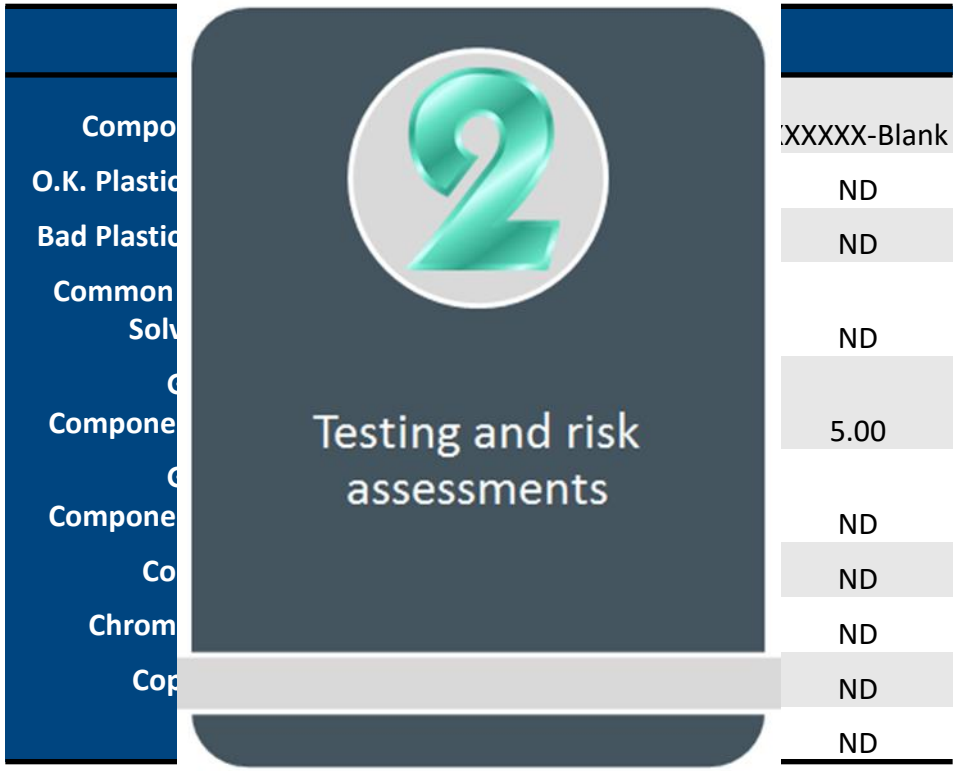
Gas Path Devices: ISO 18562 (2017)

Test Matrix: ISO 18562

Standard	Test	Analytical Approach
ISO 18562-2:2017	Volatile Organic Compounds	EPA TO-15 Method: Volatiles in Air via Canister Sampling. Samples will be taken at three time points within a 24-hour period
ISO 18562-3:2017	2.5 µm & 10 µm Particulates	NMAM 0.500 Method (Gravimetric Analysis) or Light Scatter Analysis
ISO 18562-4:2017 ISO 10993-18:2009	Extraction of Device for Leachables	Volatile Organic Compounds via headspace GC/MS
		Semi-Volatile Organic Residue GC/MS
		Non-Volatile Organic Residues LC/MS/MS and/or LC/QToF/MS
		Metals ICP/MS, ICP/OES, and CVAAS



The Results of E&L: Following-Up



Compo	XXXXX-Blank
O.K. Plastic	ND
Bad Plastic	ND
Common Solv	ND
Compone	5.00
Compone	ND
Co	ND
Chrom	ND
Cop	ND
	ND

The Results of E&L: Following-Up

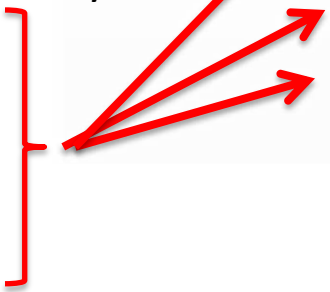
Results, µg/device				
Compound	Reporting Limit	XXXXXX-P1	XXXXXX-P2	XXXXXX-Blank
O.K. Plasticizer	1.00	1.50	2.00	ND
Bad Plasticizer	10.00	10.05	11.00	ND
Common Lab Solvent	10.00	12.34	14.32	ND
Glue Component 1	5.00	5.00	5.10	5.00
Glue Component 2	50.00	50.50	60.50	ND
Cobalt	0.10	0.27	0.27	ND
Chromium	0.10	0.32	0.32	ND
Copper	0.10	0.20	0.20	ND
...	1.00	ND	ND	ND

Step 2: Look at Options for Evaluations

Device with Permanent Contact
Tissue/bone

Required Endpoint for Evaluation:

- Cytotoxicity
- Sensitization
- Irritation
- Material Mediated Pyrogenicity
- Acute Systemic Tox
- Subacute/Subchronic Tox
- Chronic Tox
- Genotox
- Carcinogenicity
- Implantation



General Options to Address Risks:

- Written evaluation addressing risk without testing
- Traditional biological tests
- Chemistry testing followed by written evaluation

Two guys walk into a bar.

The first guy orders an H_2O.

The second guy says “I’ll have an H_2O, too.”

… The second man dies.

Real Example: Feeding Tubes

- Sponsor was submitting a 510(k) for a feeding tube and syringe set based on predicate devices from the same manufacturer
- FDA responded that predicates were not sufficient and E&L was needed

Real Example: Feeding Tubes

- **3 Material Options** for the tube itself
- **1 Syringe Set** which can connect to any tube

  - Extract and **Test as 4 Devices** for the tube itself
  - Give special attention to **intended population**

Real Example: Feeding Tubes

- **Extraction:** In water and IPA for 72 hours at 37 C
- **Extracts (and blanks)** were analyzed for VOCs, SVOCs, NVOCs, and metals by **GC/MS, LC/MS, and ICP/MS**

- **Initial Results:**
  - 27 compounds and metals were found total (some in multiple devices and solvents)
  - In 22 cases, the levels were below the TTC
  - 5 compounds/metals were assessed

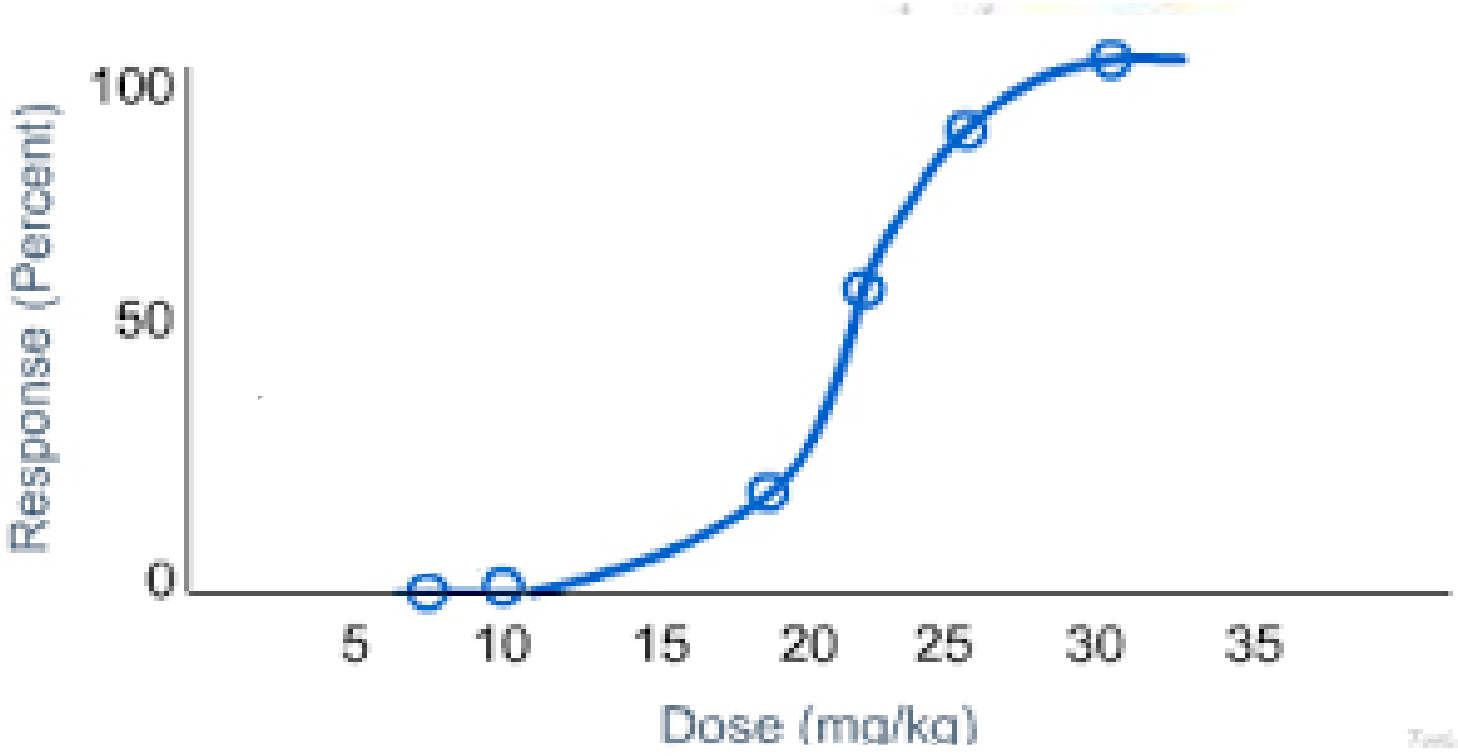
Toxicological Risk Assessments

Toxicological Risk Assessments

Applying chemistry to the biocompatibility or biological safety of your device

Great - you have your chemistry data. Now what?

Toxicological Risk Assessments



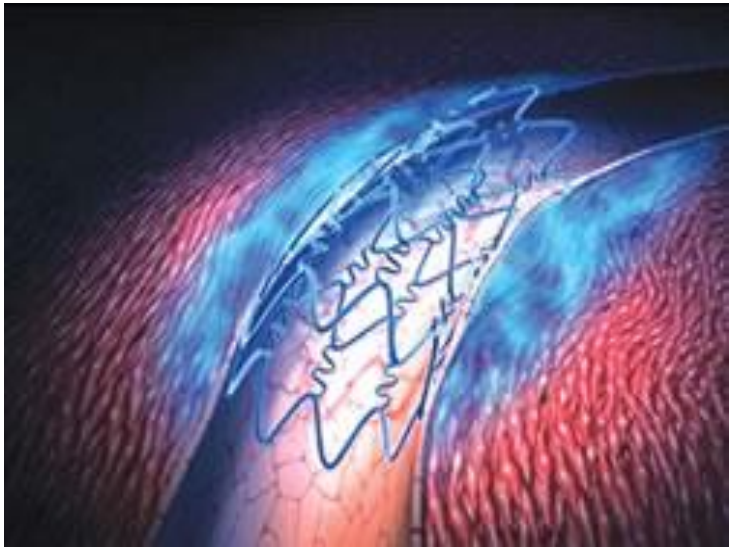
E&L Results: Interpretation of the Toxicological Risk

Recognize the **requirements** of a toxicologist to conduct a suitable **Toxicology Risk Assessment**

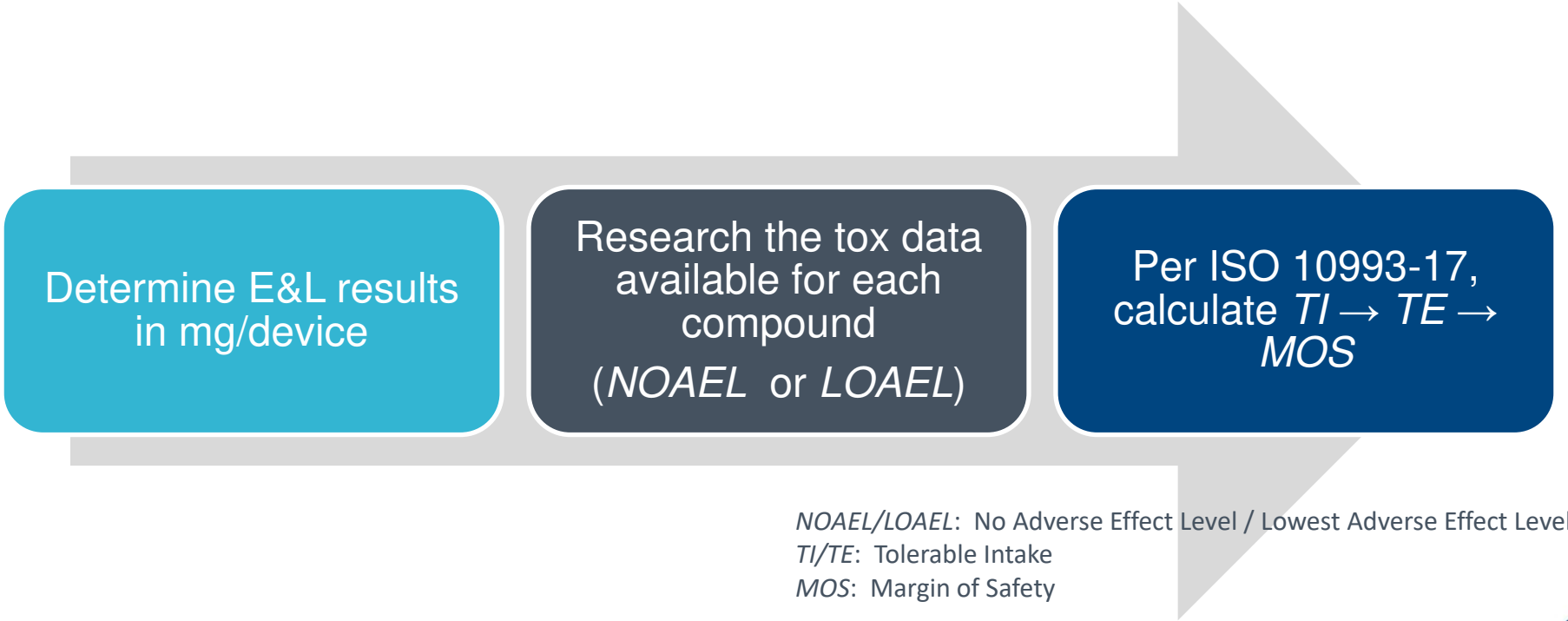
Apply appropriate **Thresholds of Toxicolgical Concern (TTC)** to E&L data

Understand the risks to the patient

Perform Tolerable Intake (TI), Tolerable Exposure (TE), and Margin of Safety calculations



Toxicological Risk Assessment

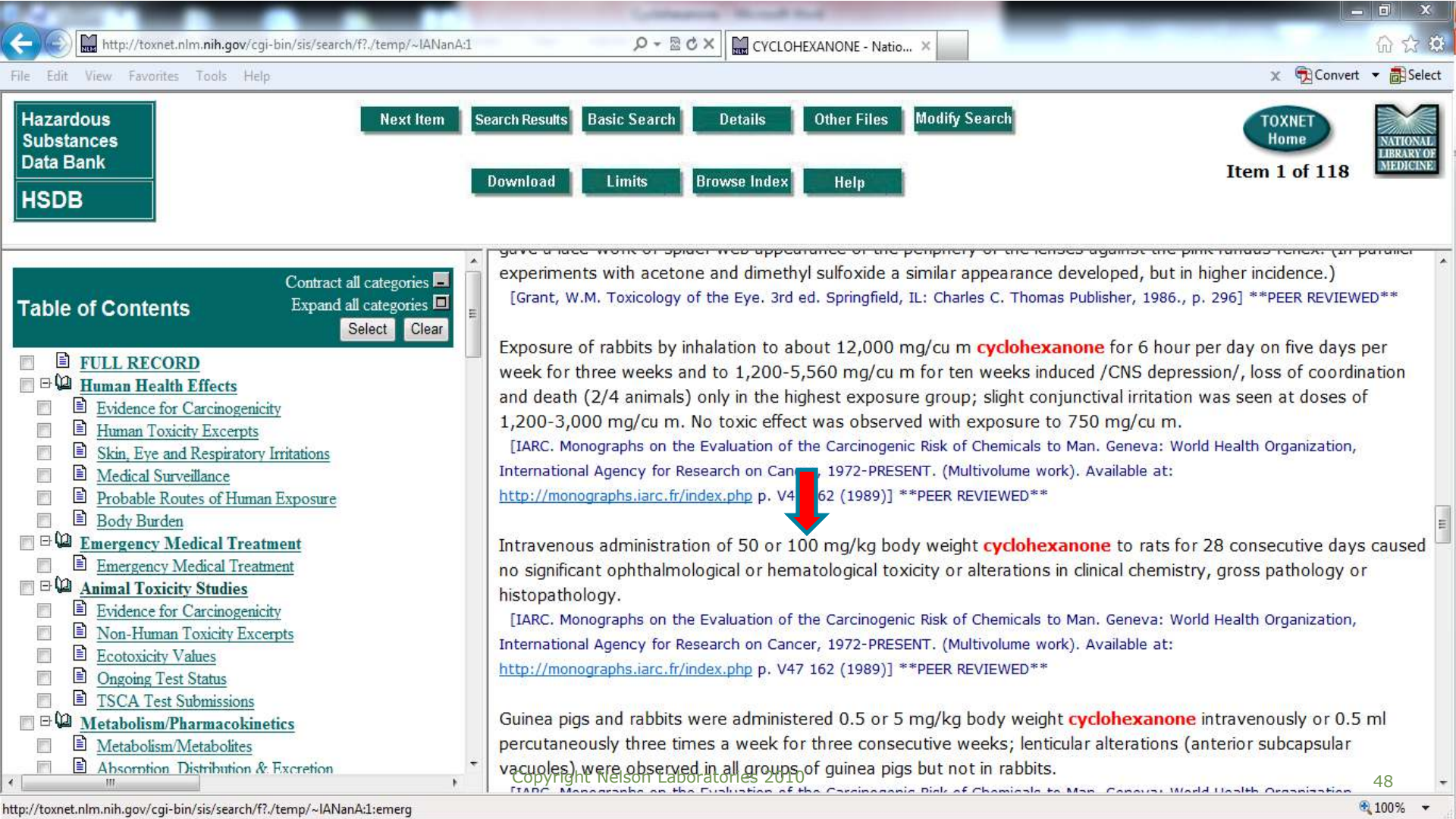


NOAEL/LOAEL: No Adverse Effect Level / Lowest Adverse Effect Level
TI/TE: Tolerable Intake
MOS: Margin of Safety

E&L Results and Example Calculations

Result: Cyclohexanone detected at 3.2 mg/device

Determine an appropriate NOAEL



Example Calculations

$$TI = \frac{NOAEL \text{ or } LOAEL}{(UF1 \times UF2 \times UF3)}$$

UF1: Inter-individual variation among humans (default 10)
UF2: Extrapolation of effects between animals and humans (default 10)
UF3: Quality and relevance of experimental data

Calculate the TI

$$TI = \frac{\frac{100\ \text{mg}}{\text{kg} \cdot \text{day}}}{(10 \times 10 \times 1)} = \underline{1\ \text{mg/kg} \cdot \text{day}}$$

UF1: Inter-individual variation among humans (default 10)
UF2: Extrapolation of effects between animals and humans (default 10)
UF3: Quality and relevance of experimental data

Example Calculations

$$TE = TI \times mB \times UTF$$

$$(UTF = CEF \times PEF)$$

m_B: Body weight (default adult male 70 kg; adult female 58 kg)
UTF: Utilization Factor
CEF: Concomitant Exposure Factor (default 0.2)
PEF: Proportional Exposure Factor (default 1)

Calculate the TE

$$TE = \frac{1\ \text{mg}}{\text{kg}\cdot\text{day}} \times 70\ \text{kg} \times 0.2 = \underline{14\ \text{mg/day}}$$

m_B: Body weight (default adult male 70 kg; adult female 58 kg)
UTF: Utilization Factor
CEF: Concomitant Exposure Factor (default 0.2)
PEF: Proportional Exposure Factor (default 1)

Example Calculations

$$\mathrm{MOS} = \frac{\mathrm{TE}}{\mathrm{E\&L\ Device\ Result}}$$

Calculate the MOS

$$\mathrm{MOS} = \frac{14\ \mathrm{mg/day}}{3.2\ \mathrm{mg/device}} = \underline{4.3}$$

A MOS greater than a value of 1 is indicative of low toxicological hazard for the evaluated substance

Is Octoberfest Lethal?

- Oktoberfest 2017 7.5 million liters of beer was consumed by 6.2 million visitors so that's 1.2 liters per person.
- 5.5% alcohol per beer so that's 66 ml or 51816.6 mg per day
- NOAEL for repeat dose toxicity =1730mg/kg* (male rats).

- *ECHA Dossier Ethanol EC number: 200-578-6 | CAS number: 64-17-5

Example Calculations

$$TI = \frac{NOAEL \text{ or } LOAEL}{(UF1 \times UF2 \times UF3)}$$

UF1: Inter-individual variation among humans (default 10)
UF2: Extrapolation of effects between animals and humans (default 10)
UF3: Quality and relevance of experimental data

Example Calculations

$$TI = (1730mg/kg)/10X10X1$$
$$= 17.3mg/kg/day$$

UF1: Inter-individual variation among humans (default 10)
UF2: Extrapolation of effects between animals and humans (default 10)
UF3: Quality and relevance of experimental data

Example Calculations

$$TE = TI \times mB \times UTF$$

$$(UTF = CEF \times PEF)$$

m_B: Body weight (default adult male 70 kg; adult female 58 kg)
UTF: Utilization Factor
CEF: Concomitant Exposure Factor (default 0.2)
PEF: Proportional Exposure Factor (default 1)

Example Calculations

TE= 17.3mg/kg/day X 70 kg X 0.2 =

242.2 mg/day

m_B: Body weight (default adult male 70 kg; adult female 58 kg)
UTF: Utilization Factor
CEF: Concomitant Exposure Factor (default 0.2)
PEF: Proportional Exposure Factor (default 1)

Example Calculations

$$\mathrm{MOS} = \frac{\mathrm{TE}}{\mathrm{E\&L\ Device\ Result}}$$

Example Calculations

$$MOS=(242.2\ mg/day)/(51816.6\ mg/day)\ =0.005$$

A MOS greater than a value of 1 is indicative of low toxicological hazard for the evaluated substance

Side Note

- From witnesses at Oktoberfest “A typical German at Oktoberfest will easily have 3 steins per session each at a liter- that makes 130.2 grams per day. Maybe the average of 1.2 L takes into account the light-weight Americans that go there.

Conclusion

This risk assessment was supported by information gathered from **extractable and leachable** chemical characterization testing data on the system, **published literature**, and the **derived margins of safety** of the compounds extracted from the system.

This risk assessment indicates that the likelihood of adverse effects from the device is considered low for all compounds.

Conclusion on Toxicological Assessments

- Biocompatibility evaluations must be strategic & science based
- ***Material Characterization***: Thorough understanding of the device materials and processing can help to minimize biocompatibility testing
- ***Chemical Characterization (E&L)***: Provides the key information needed to conduct a proper risk toxicological assessment
- Goals: Save animal life, save time, save money, and **IMPROVE PATIENT CARE**!

QUESTIONS?