Toxicology

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Octoberfest!!

- Oktoberfest 2017 7.5 million liters of beer was consumed by 6.2 million visitors so that's 1.2 liters per person.

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Toxicological Risk Assessments

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Toxicological Risk Assessments

Applying chemistry to the biocompatibility or biological safety of your device

Great - you have your chemistry data. Now what?

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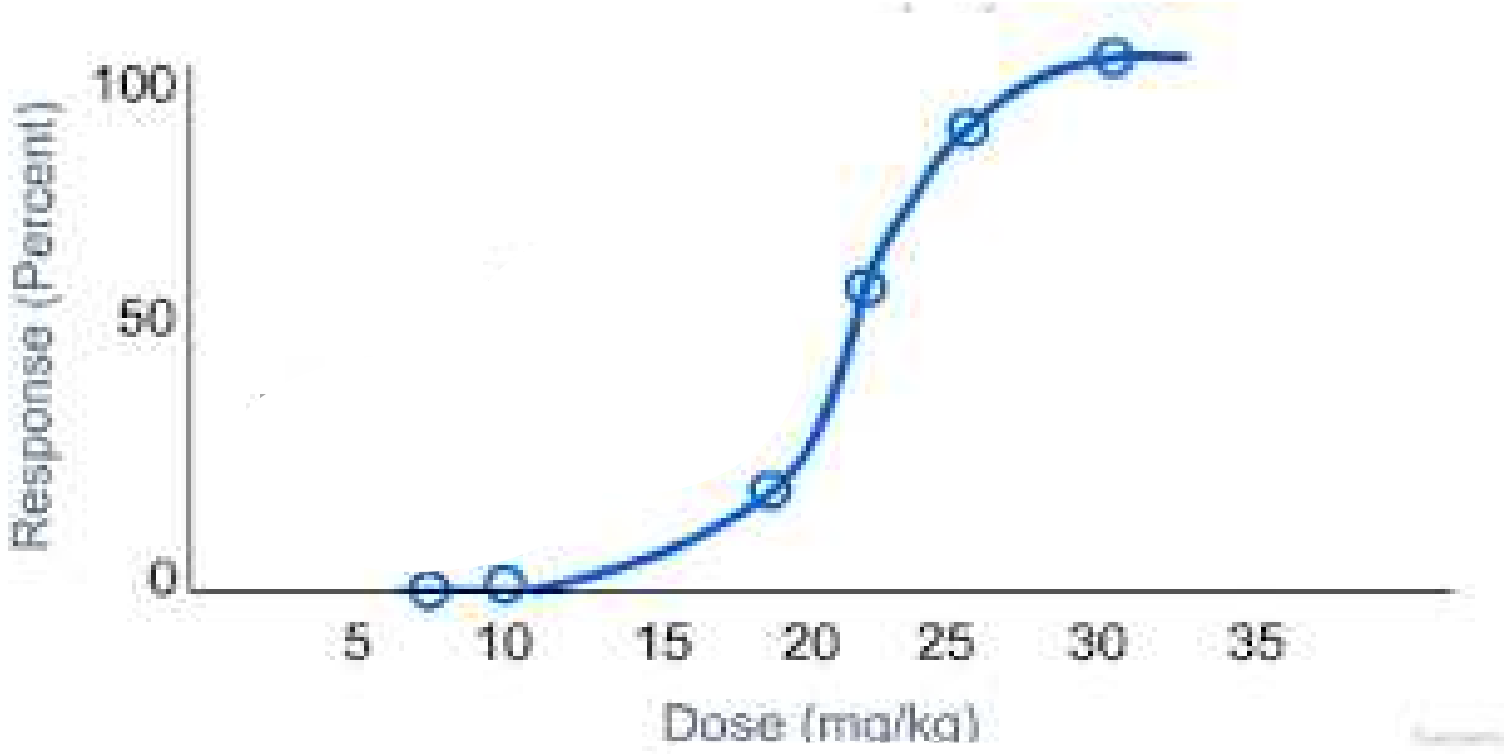
Toxicological Risk Assessments



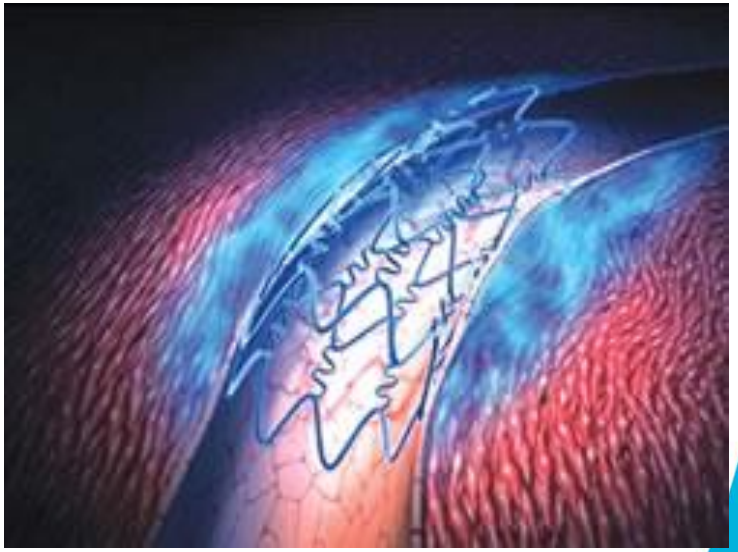
E&L Results: Interpretation of the Toxicological Risk

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



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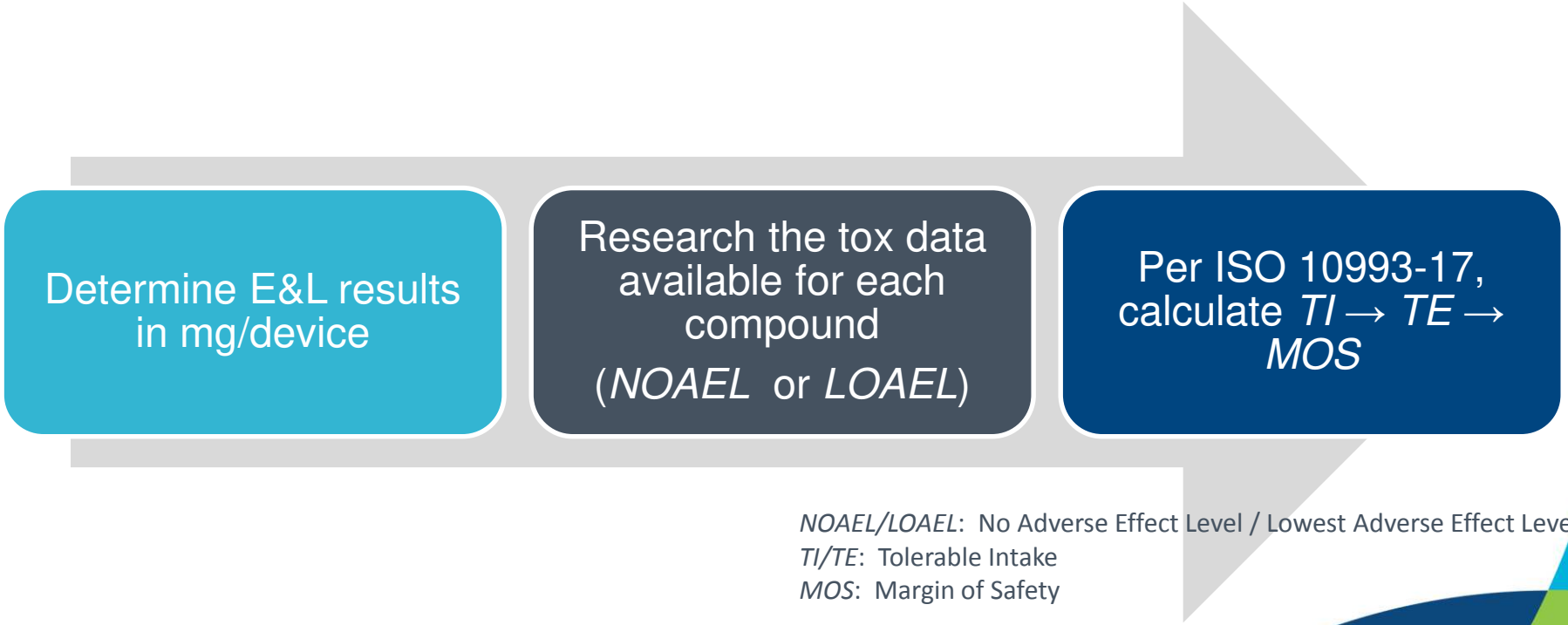
Toxicological Risk Assessment



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

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E&L Results and Example Calculations

Result: Cyclohexanone detected at 3.2 mg/device

Determine an appropriate NOAEL

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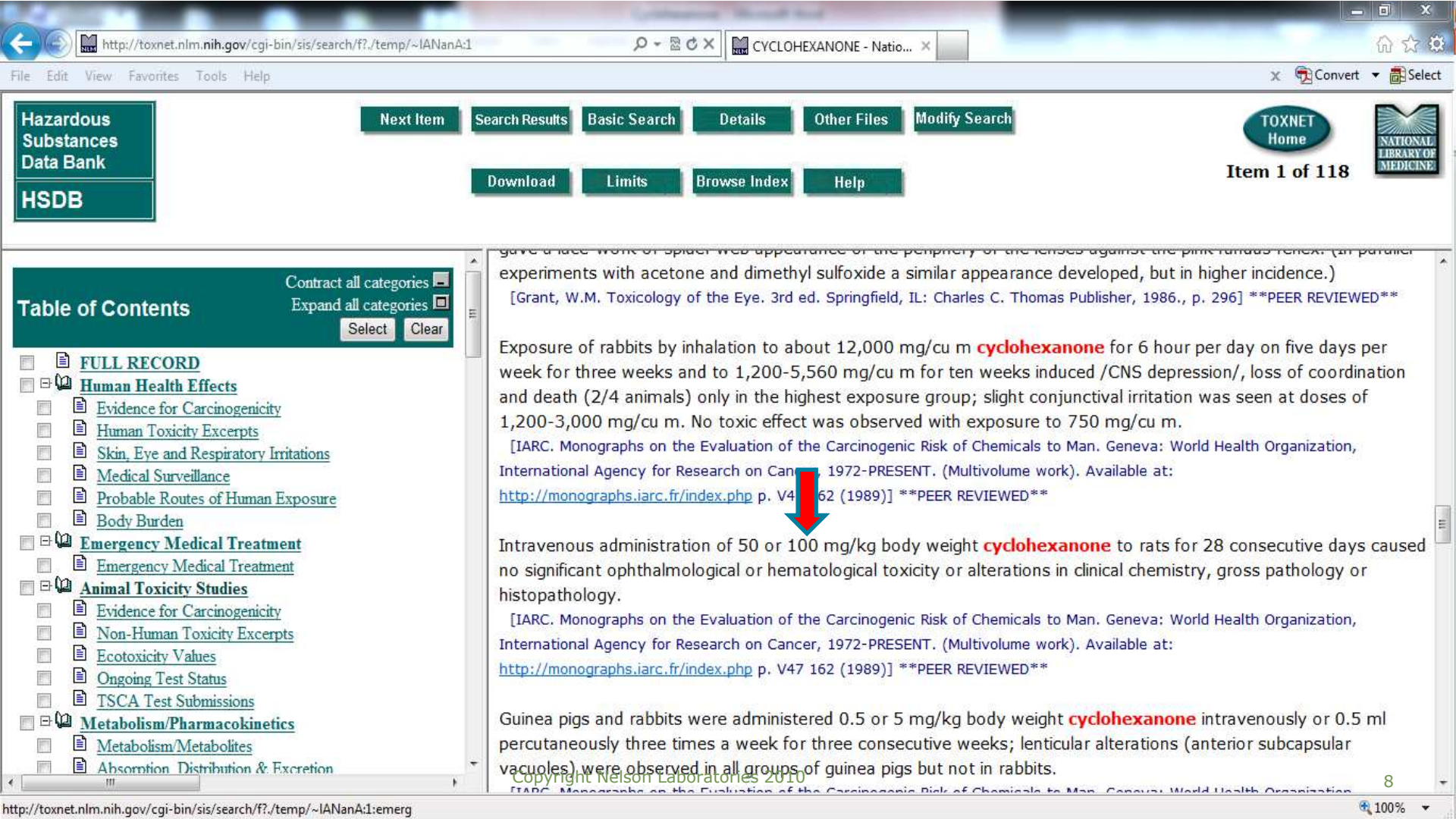

Example Calculations

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

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

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Example Calculations

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

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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)

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Example Calculations

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)

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Example Calculations

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

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Example Calculations

Calculate the MOS

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

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

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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

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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

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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

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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)

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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)

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Example Calculations

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

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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

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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.

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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.

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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**!

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QUESTIONS?

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