



Toxicology

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Oktoberfest!!

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

Toxicological Risk Assessments



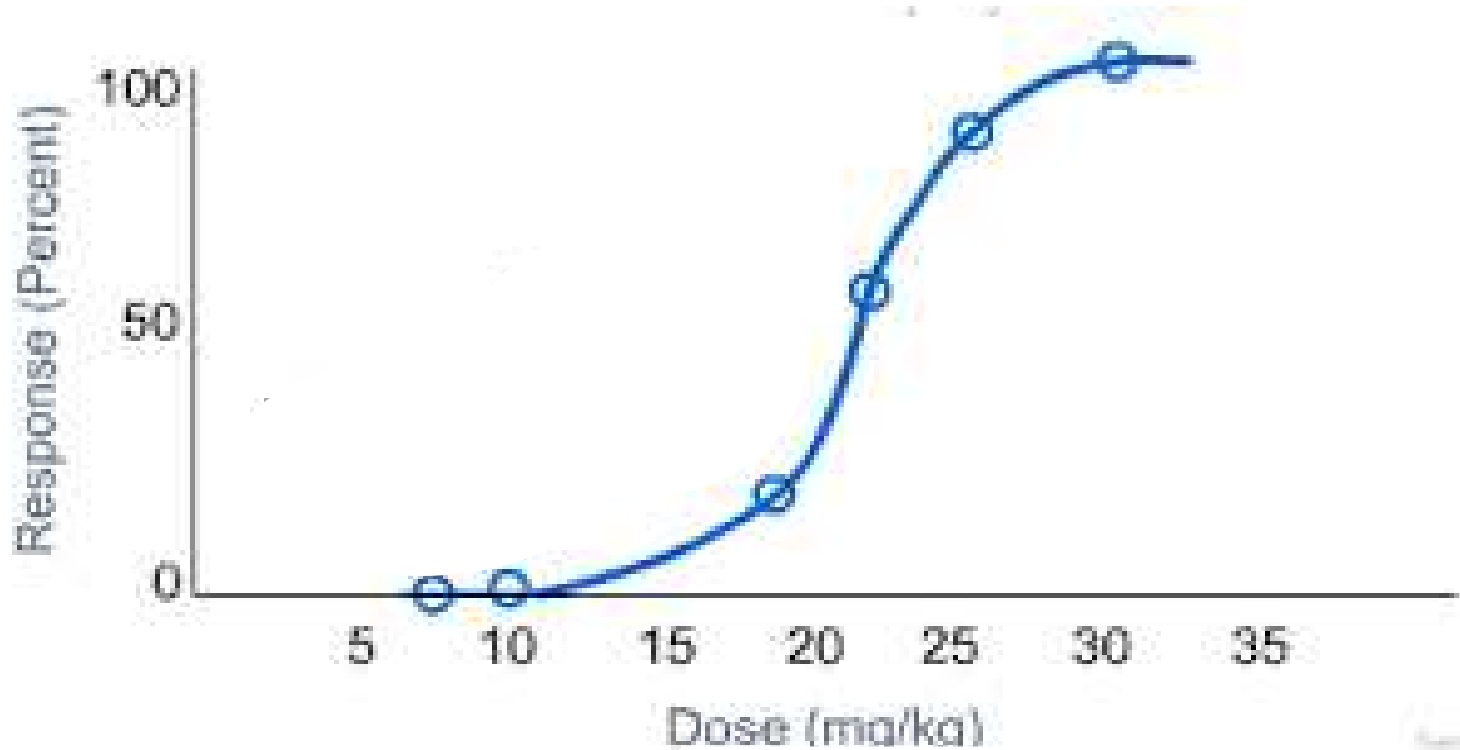
Toxicological Risk Assessments



Applying chemistry to the biocompatibility or biological safety of your device

Great - you have your chemistry data. Now what?

Toxicological Risk Assessments



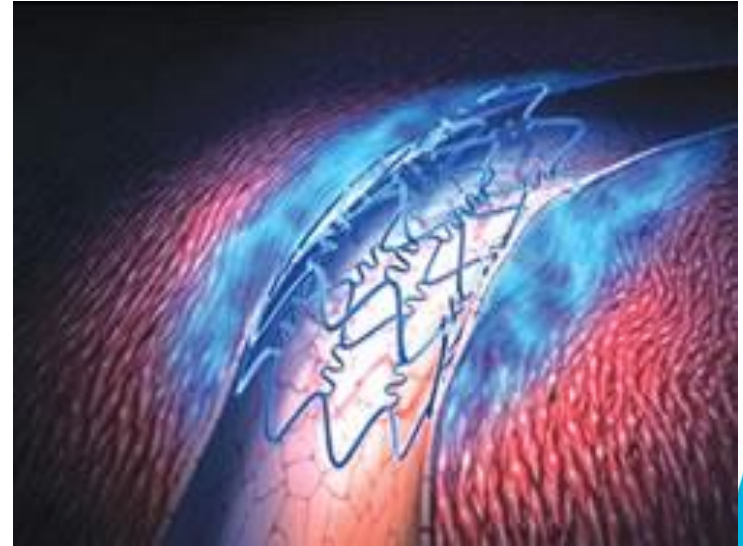
E&L Results: Interpretation of the Toxicological Risk

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

Apply appropriate **Thresholds of Toxicological 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

Determine E&L results
in mg/device

Research the tox data
available for each
compound
(*NOAEL* or *LOAEL*)

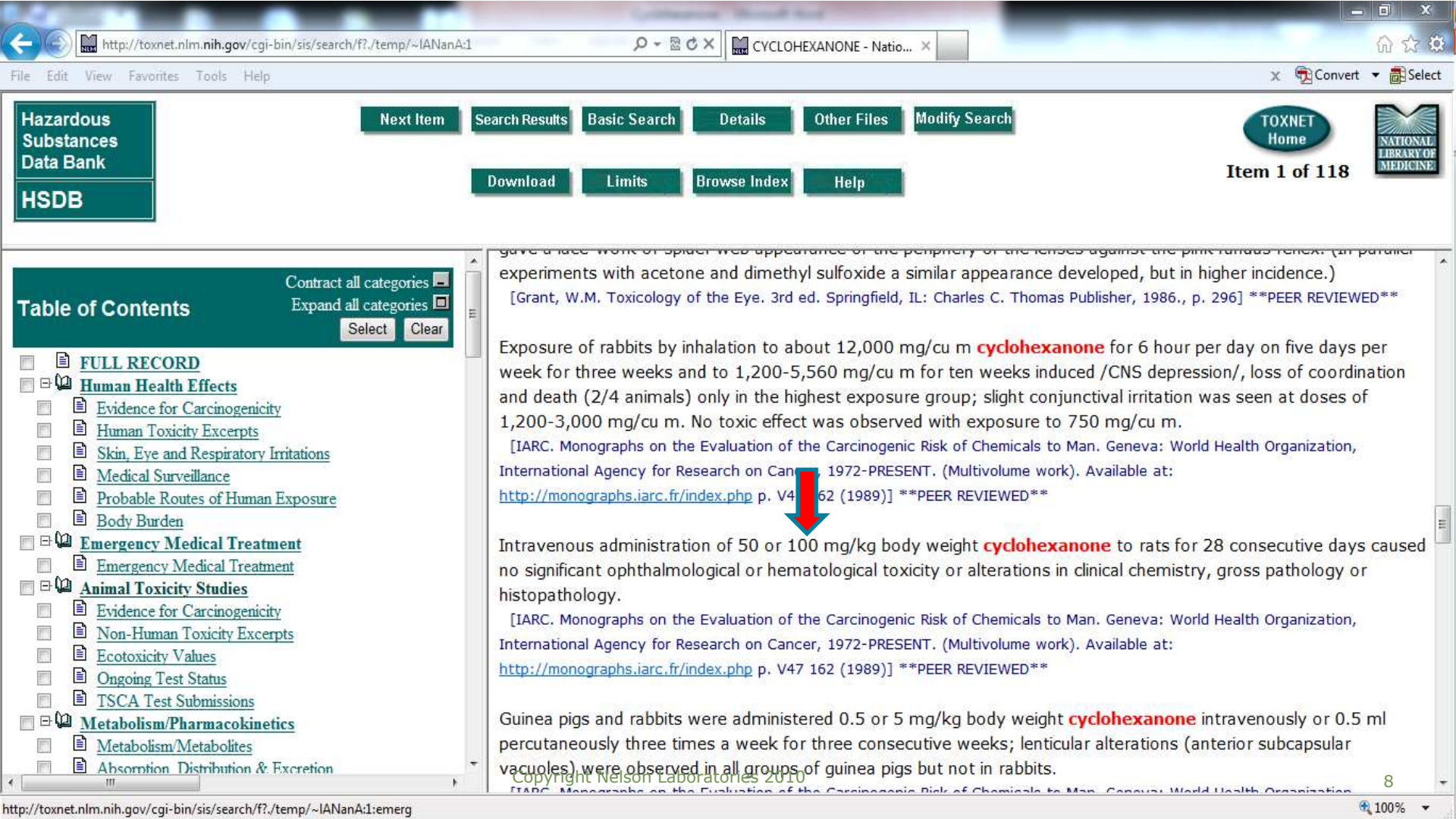
Per ISO 10993-17,
calculate $TI \rightarrow TE \rightarrow$
MOS

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



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HSDB

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gave a lace work or spider web appearance of the periphery of the lenses against the pink fundus reflex. (In parallel experiments with acetone and dimethyl sulfoxide a similar appearance developed, but in higher incidence.)
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 296] **PEER REVIEWED**

Exposure of rabbits by inhalation to about 12,000 mg/cu m **cyclohexanone** for 6 hour per day on five days per week for three weeks and to 1,200-5,560 mg/cu m for ten weeks induced /CNS depression/, loss of coordination and death (2/4 animals) only in the highest exposure group; slight conjunctival irritation was seen at doses of 1,200-3,000 mg/cu m. No toxic effect was observed with exposure to 750 mg/cu m.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: <http://monographs.iarc.fr/index.php> p. V4 162 (1989)] **PEER REVIEWED**



Intravenous administration of 50 or 100 mg/kg body weight **cyclohexanone** to rats for 28 consecutive days caused no significant ophthalmological or hematological toxicity or alterations in clinical chemistry, gross pathology or histopathology.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: <http://monographs.iarc.fr/index.php> p. V47 162 (1989)] **PEER REVIEWED**

Guinea pigs and rabbits were administered 0.5 or 5 mg/kg body weight **cyclohexanone** intravenously or 0.5 ml percutaneously three times a week for three consecutive weeks; lenticular alterations (anterior subcapsular vacuoles) were observed in all groups of guinea pigs but not in rabbits.

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

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)

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)

Example Calculations

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

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

Is Oktoberfest 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

$$\begin{aligned} TI &= (1730mg/kg)/10 \times 10 \times 1 \\ &= 17.3mg/kg/day \end{aligned}$$

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

$$\text{TE} = 17.3 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2 = 242.2 \text{ mg/day}$$

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

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

Example Calculations

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

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?

