Toxicological risk assessment
The Role and challenges to support 10993-18:2020

Nelson Labs Open House 2020 – March 3-4, Leuven, Belgium – Dr. Carsten B Senholt
Background of ISO 10993-18

- ISO 10993-1:2003 clause 3.2 … selection of materials … fitness for purpose with regards to characteristics and properties of the material, which include chemical, toxicological … properties
- ISO 10993-18:2005 was written to address this but did not give much information about requirements or guidance to how chemical data should be used
- ISO 10993-1:2009 and 10993:2018 clause 6.1 Material (information)… is a crucial first step …
ISO 10993-18:2020
and toxicological risk assessment

• Much more detailed process on how to gather and generate sufficient chemical information
  - 2 pages to 12 pages including flowcharts and tables

• **55 references to “toxicological risk assessment”**

• Clause 3.40 (Terms and definitions)
  - Act of determining the potential of a chemical to elicit an adverse effect based on a specified level of exposure

• No standard in the ISO 10993-series describe this process
ISO 10993-17:2002

- Method by which tolerable intake (TI) can (consistently) be calculated from available data on health risks to exposure to a specific chemical
  - mg/kg bw/day

- Defines how to translate TI to a tolerable exposure (TE) based on concomitant and proportional exposure factors
  - mg/day

- Introduces the allowable limit (AL) concept where a benefit factor can be taken into consideration

- Does not give any requirements/guidance on how to gather and evaluate toxicity data in order to achieve a relevant Point-Of-Departure (POD)

- Did not allow use of emerging gap filling processes such as (Q)SAR and read-across
Evaluation based on material composition

Evaluation based on extractables or leachables

Expectations to Toxicological Risk Assessment

Equivalent to a device on the market

ISO 10993-17

SAXOCON
Toxicology Partner
Chemical characteristics of two materials or medical devices are sufficiently similar, such that the composition and processing do not result in additional or different toxicological concerns.
Case study: Material changes

- Comparison of chromatograms
- Works generally well from a risk based approach
Why material composition

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<th>LDPE</th>
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Case study: 2-hexanol (Cas no. 626-93-7)

- Solvent based adhesives and elastomers are widely used for delivery systems
- Worst case scenario based on total amount in device
- Max parenteral dose level 12.6 µg/50 kg b.w./day
Case study: 2-hexanol (Cas no. 626-93-7)

• 90-days repeated oral administration of 675 mg/kg/day in rats causes severe hind limb weakness/paralysis (giant axon degeneration) and atrophy of testicular germinal epithelium

• Consistent with several observation in humans and animals after systemic exposure to other hexacarbons such as n-hexane, 2-hexanone and 2,5-hexanedione
Case study: 2-hexanol (Cas no. 626-93-7)

Formation of toxic gamma-diketone

Testicular toxicity

TE = 2.9 mg/50 kg b.w./day

TE = 0.5 mg/50 kg b.w./day
Case study: 2-hexanol (Cas no. 626-93-7)  
Toxicological Risk Assessment

• 12 fold less exposure to 2,5-hexadione compared to 2-hexanone
• TE for 2-hexanone (0.5 mg/day) is therefore considered protective for exposure to 2-hexanol
• Margin of Safety:

\[
\frac{0.5}{0.0126} \text{ mg/50 kg b.w./day} = 40
\]

• Considered sufficient to cover oral to parenteral extrapolation

Evaluation of extractables and leachables

- Works well for systemic exposure to single-use devices
- Durable devices can be challenging
- External communicating devices will need to be calculated based on dose volume
- Does not work for concentration related toxicological effects
- Selection of analytical methods and UF cause scientific challenges
- Non-Intensionally Added Substances
Why material information is important

- Manufacturing & Supply Chain
- Material Chemistry & Physics
- Overall Risk of Device Type
- Test certificates
- Material grades

TOTAL MATERIAL RISK
Challenges

• Complete and reliable material composition can be hard to obtain
  • Proprietary information
  • Long supply chain
  • Non intentionally added substances

• Raw materials are not the final finished device
  • Sterilisation and other manufacturing processes

• Design of extraction studies can vary considerably (Annex D)
  • Extraction conditions
  • Analytical methods used

• Extractable/Leachable studies without any pre-knowledge of the material
ISO/CD 10997-17:2020 - is in press

- Intent to cover the broad process from obtaining data and how to conclude (characterize) the risk based on these
- Substantial amount of technical comments to
  - ISO Guide 73 risk terminology versus WHO/IPCS 2004
  - The role of hazard identification
  - Relationship between dose and response and how to conclude on the risk based on this