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

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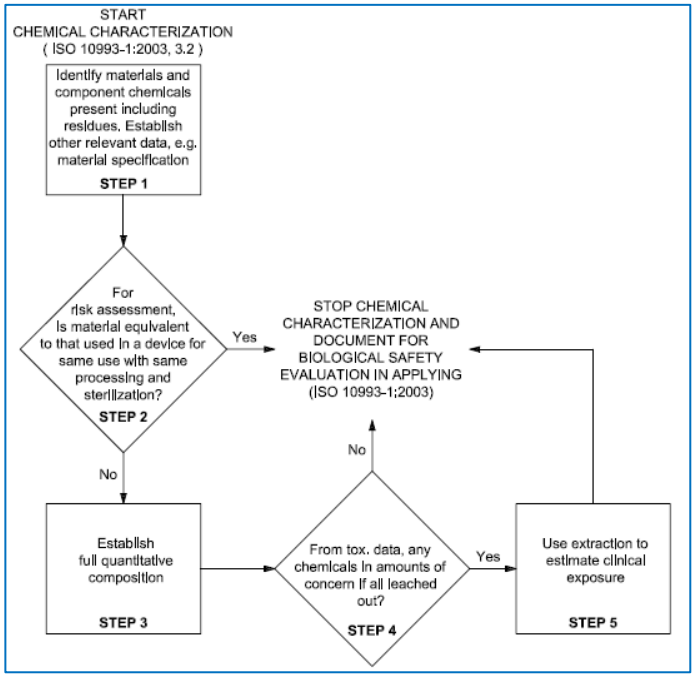
Background of ISO 10993-18



- 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 …

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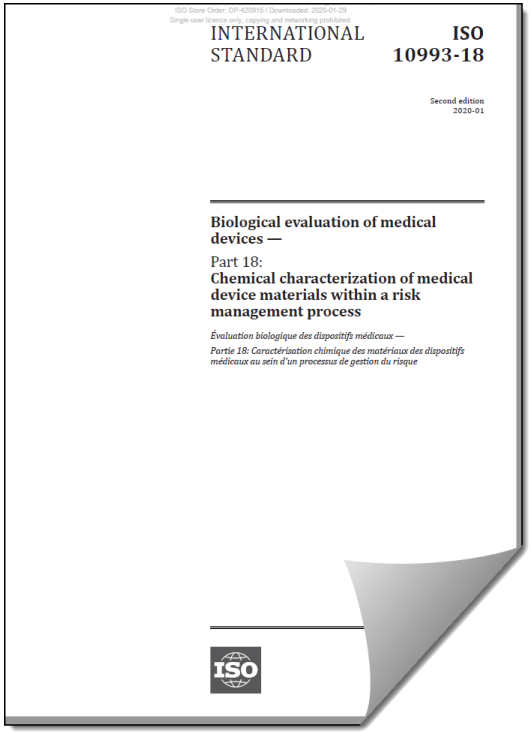
ISO 10993-18:2020
and toxicological risk assessment



- 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

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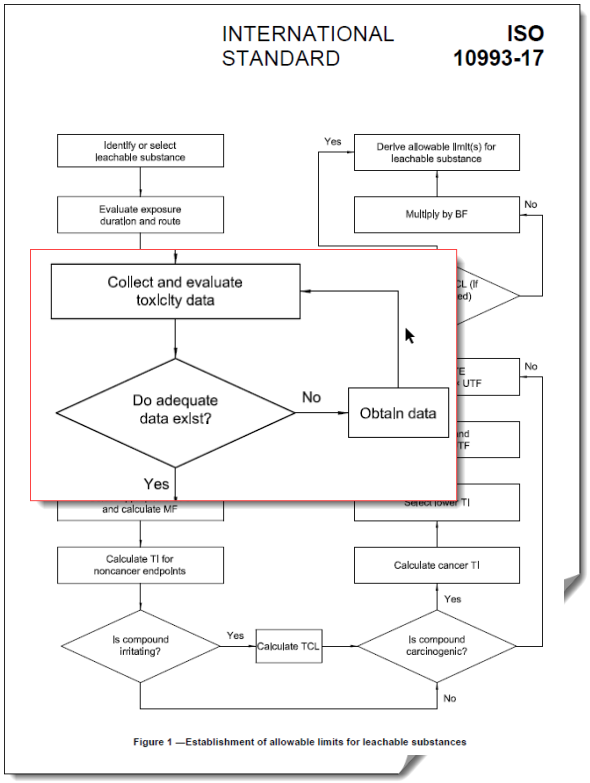
ISO 10993-17:2002



- 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 toxicitydata 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

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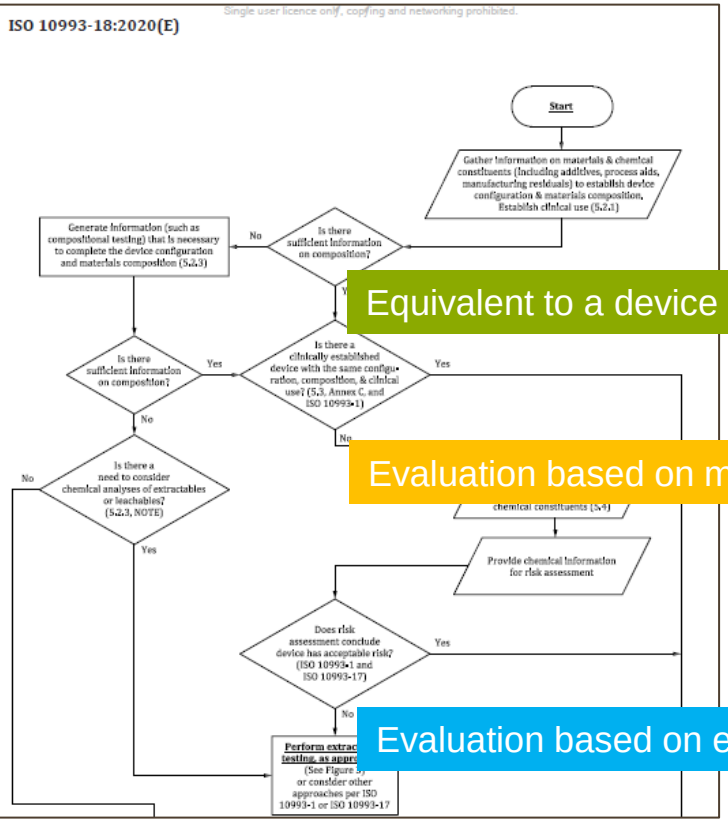
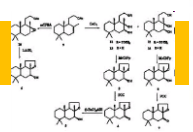
Expectations to Toxicological Risk Assessment

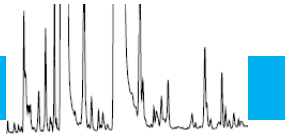


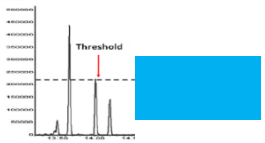
Equivalent to a device on the market

Evaluation based on material composition



Evaluation based on extractables or leachables





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ISO 10993-18:2020 Annex C
Chemical Equivalence

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**.

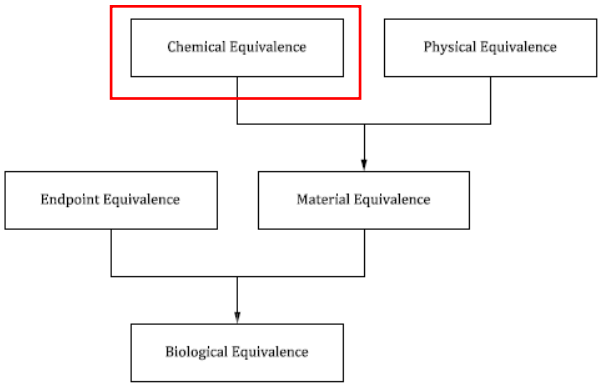

Figure C.1 — Biological equivalence relationship map

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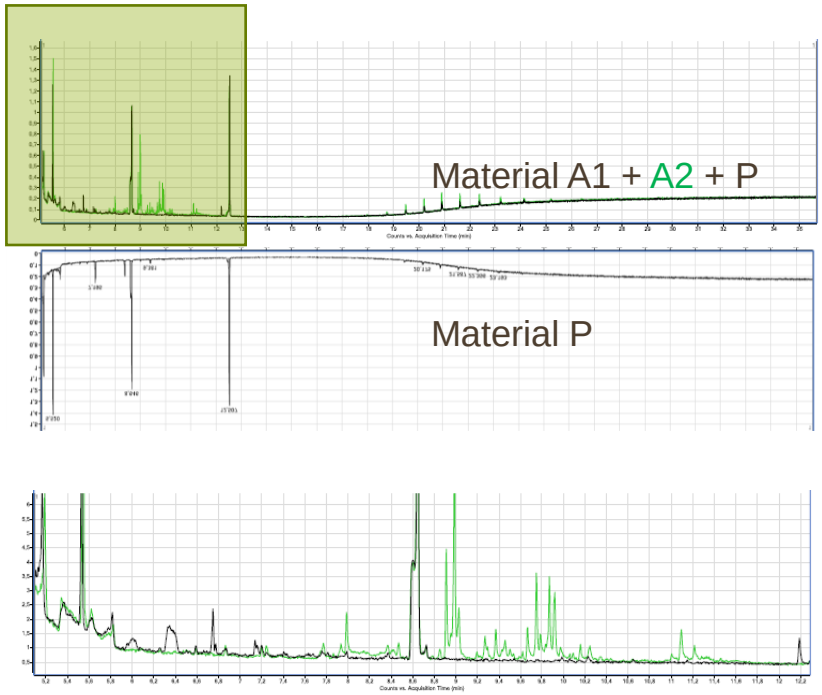
Case study: Material changes



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

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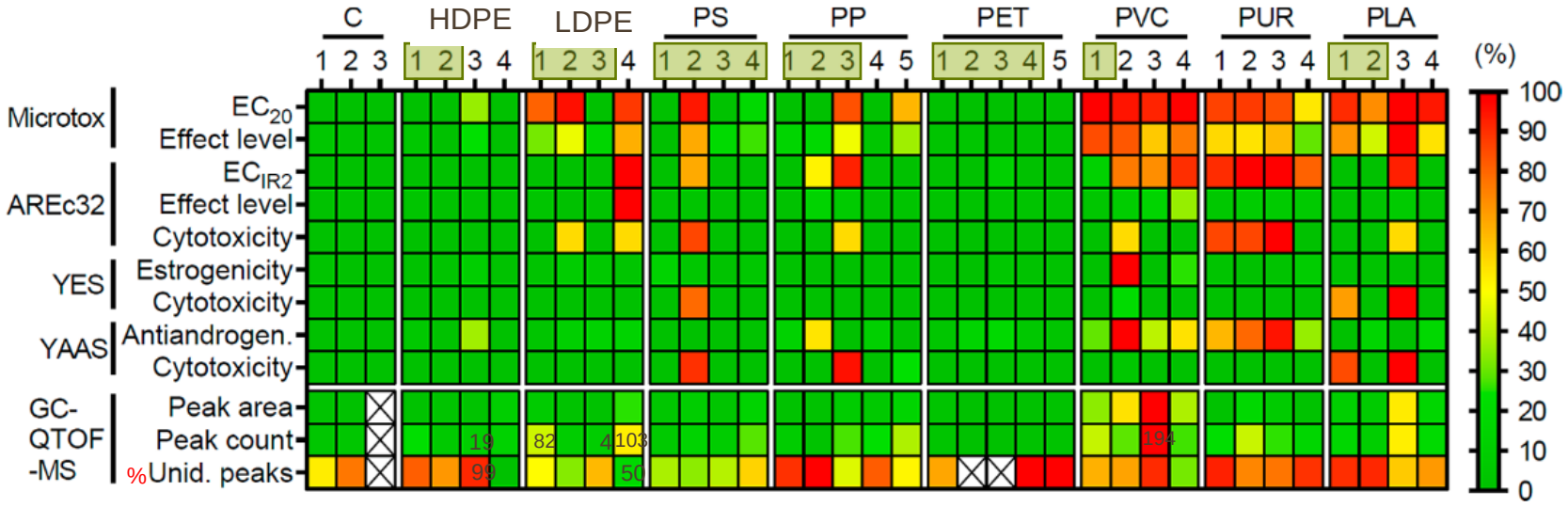
Why material composition



Reference: Environ. Sci. Technol. 2019, (53), p 11467−11477

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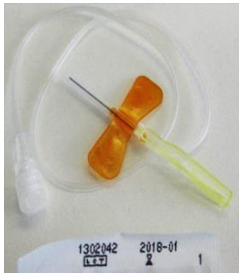
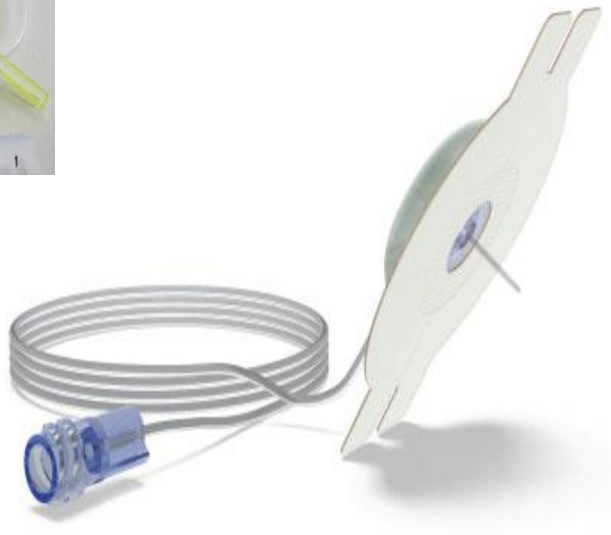
Case study: 2-hexanol (Cas no. 626-93-7)





- Solvent based adhesives and elastomers
  are widely used for delivery systems
- Worst case scenary based on total amount in device
- Max parenteral dose level
  12.6 µg/50 kg b.w./day

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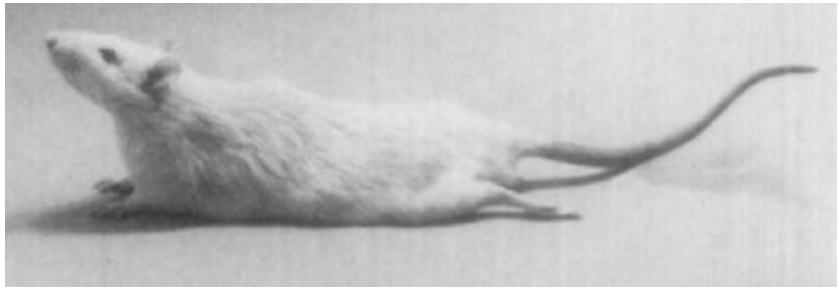
Case study: 2-hexanol (Cas no. 626-93-7)

- 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



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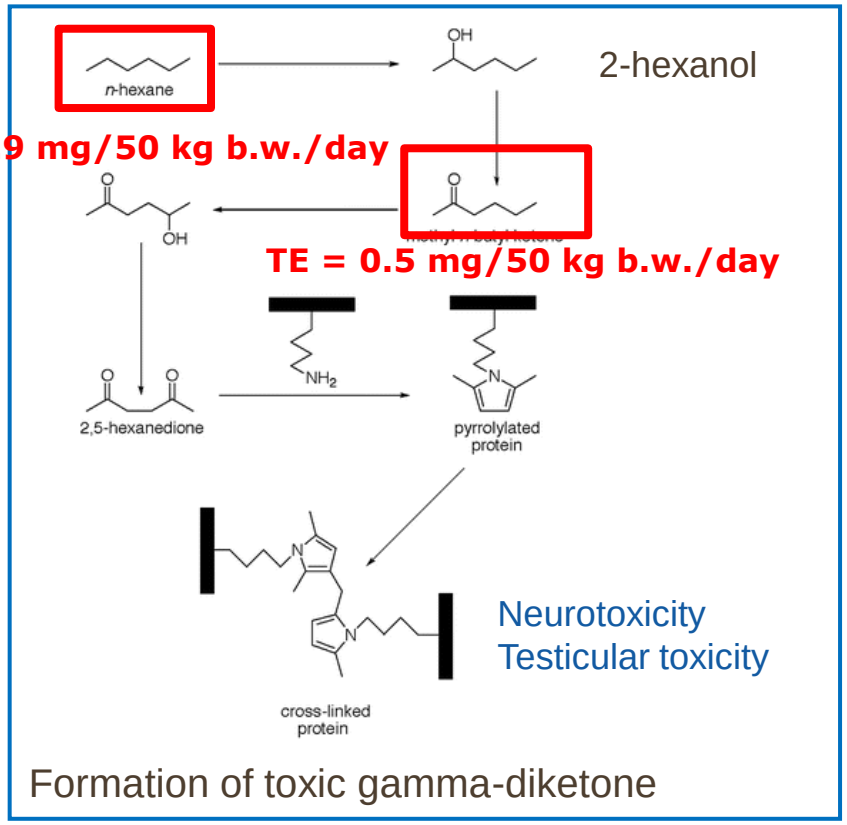
Case study: 2-hexanol (Cas no. 626-93-7)



Formation of toxic gamma-diketone

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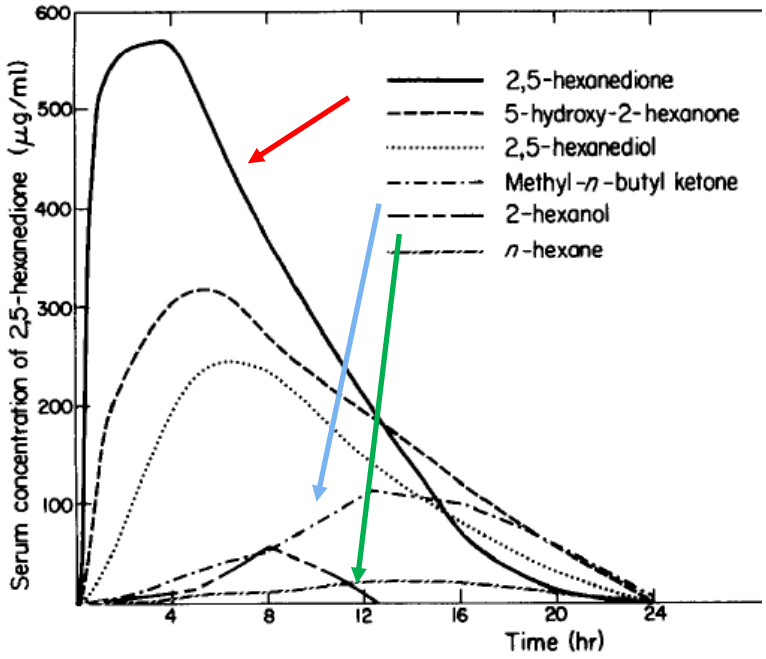
Case study: 2-hexanol (Cas no. 626-93-7) Toxicological Risk Assessment



- 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

Reference: Toxicol Appl Pharmacol, 1980, 52 (3), p 433-441

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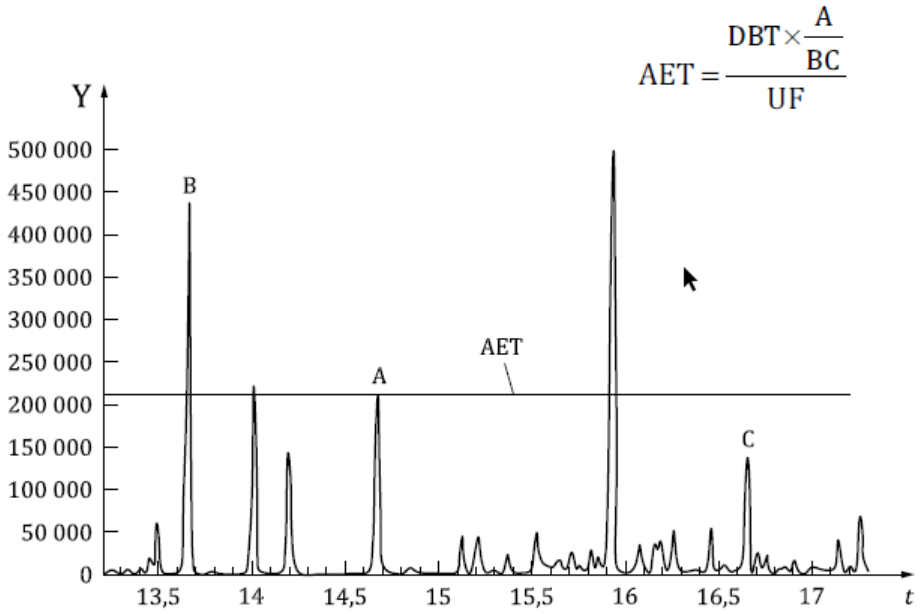
Evaluation of extractables and leachables



- 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

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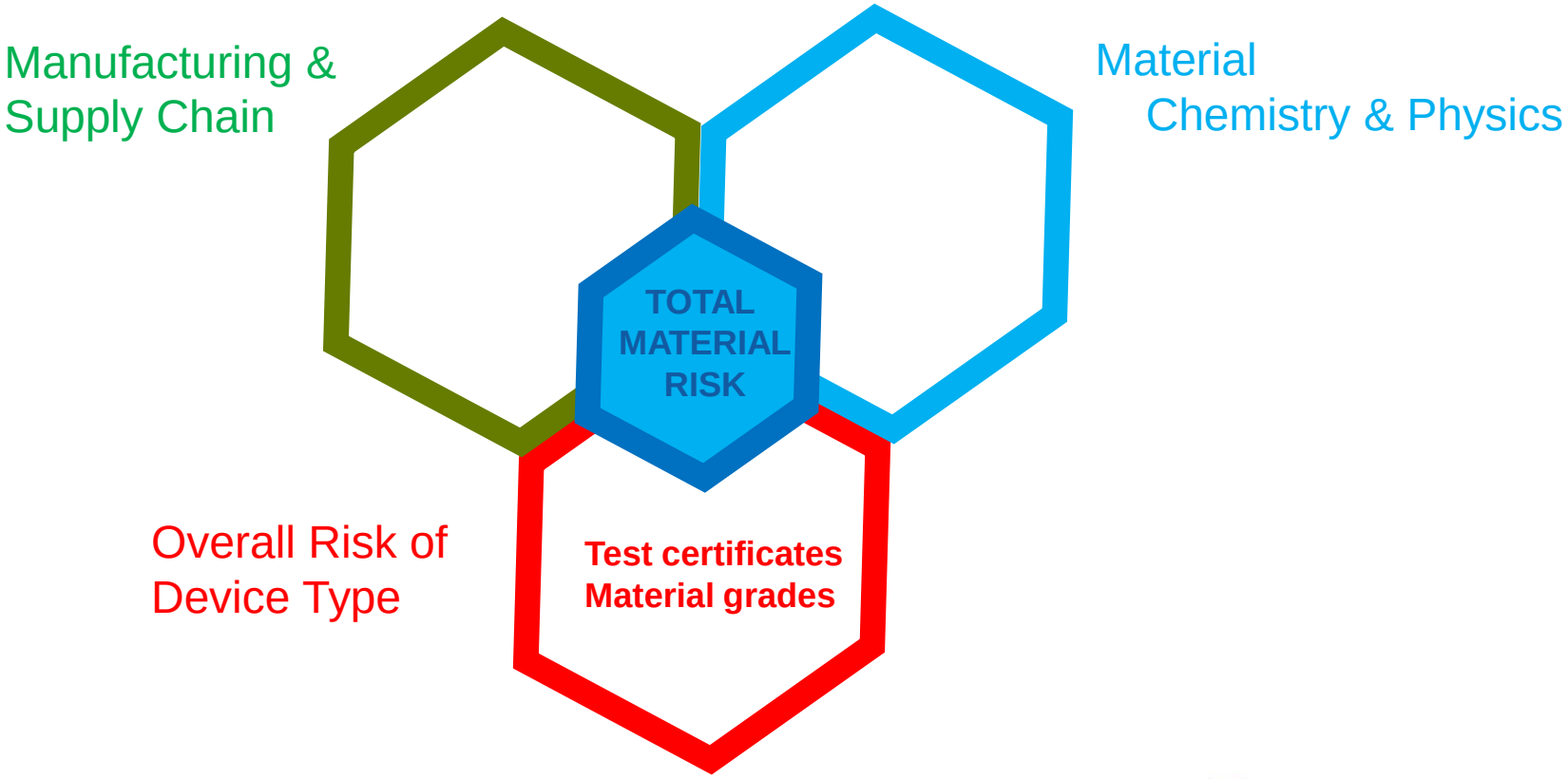
Why material information is important



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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

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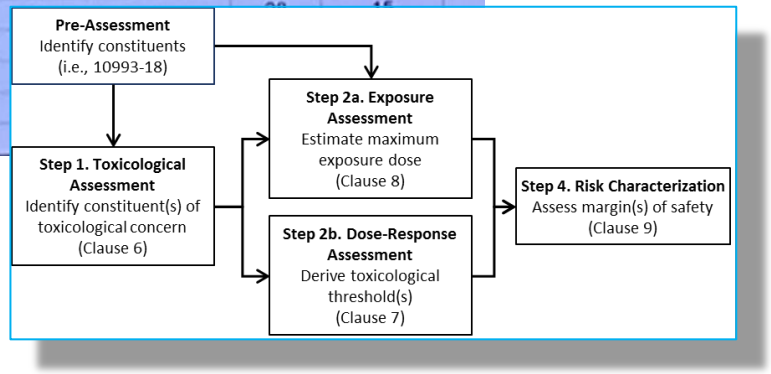
ISO/CD 10997-17:2020 - is in press

ISO/AWI 10993-17 Project Summary

ISO WD 10993-17 Comments

Clause	Total	Technical
Non-Specific	15	0
Table of Contents	1	0
Introduction	21	2
1 Scope	18	5
2 Normative references	4	0
3 Terms and definitions	53	30
4 Overview of toxicological risk assessment principles	28	8
5 Scoping and planning	13	9
6 Hazard identification	70	37
7 Dose-response assessment	61	37
8 Exposure assessment		
9 Risk characterization		
10 Applicability to mixtures		
11 Risk control		



- 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 vers WHO/IPCS 2004
  - The role of hazard identification
  - Relationship between dose and response and how to conclude on the risk based on this

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