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ICH M7 and implications for risk assessment for medical devices

01 March 2021, Susanne Dorn

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- Biological evaluation of medical devices
  - → A short overview
- Toxicological assessment of extractable and leachable substances
  - → How are *in silico* methods integrated in the process

Biological evaluation of medical devices- current approach (ISO 10993-1:2018/18562-1:2017)

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Categorization

- Categorization of medical device
- Identification of relevant endpoints

Material characterization

- Reference device available?
- Characterization of material used (qualitative and quantitative composition)
- Chemical/toxicological characterization of released chemicals (extractables and leachables)

In vitro testing

- If data gaps or toxicological concern identified
- So far *in vitro* tests of cytotoxicity, genotoxicity and irritation for medical devices validated

In vivo testing

- Only with scientific justification
- In possible waiving clinical data

Toxicological assessment of released chemicals

Toxicological characterization according to ISO 10993-17

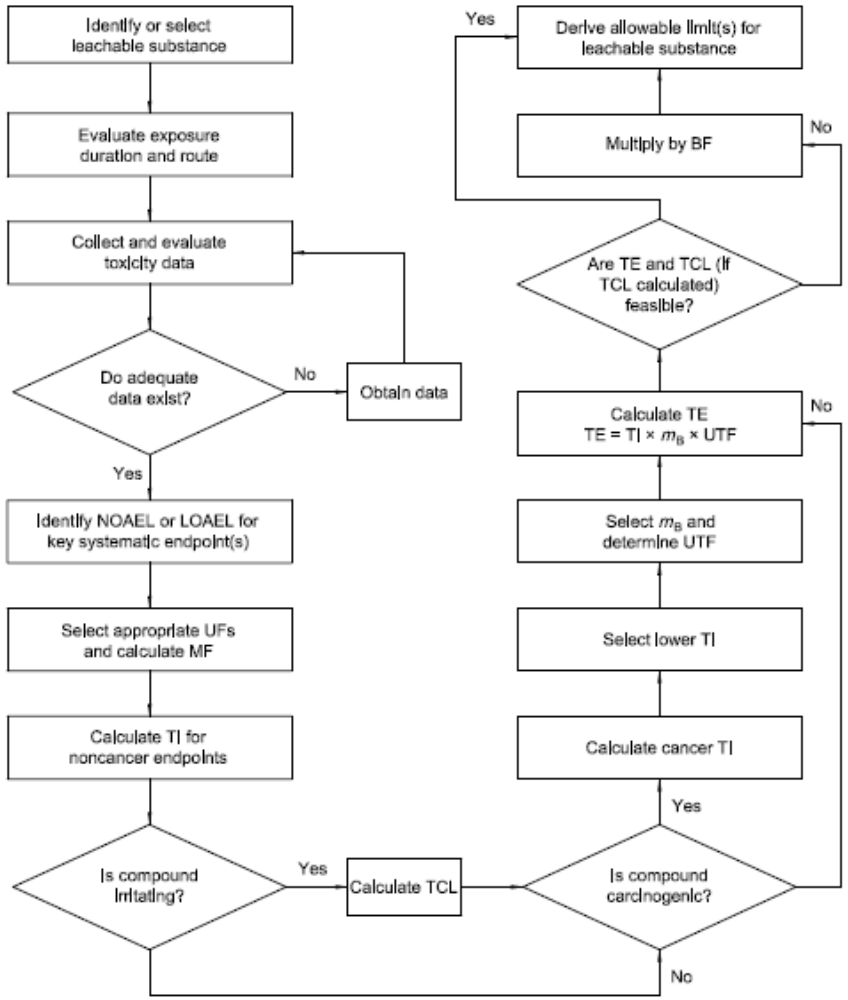

Figure 1 —Establishment of allowable limits for leachable substances

- **Use analytical data from chemical characterization**
  - Identification of extractables & leachables
  - Quantitation
- **Consider intended use**
  - Type (route) and duration of contact
  - Contact surface
  - Patient population
- **Calculation of margin of safety**

For data-poor substances**:**
- Read-across
- (Q)SAR
- **Threshold of toxicological concern (TTC)** approach

Threshold of toxicological concern (TTC)

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ISO TS 21726:2019 (based on ICH M7 recommendation)

- Less-Than-Lifetime (LTL) Exposure -

Medical device contact category	Limited (<24 h)	Prolonged (24 h to 30 d)	Long-term[a] (>30 d)		
Duration of body contact	≤ 1 month		> 1 month to 12 months	> 1 year to 10 years	> 10 years to lifetime
Daily intake (µg/d) of any one constituent	120		20	10	1,5[b]

[a] Long-term includes devices commonly described as permanent contacting (see ISO 10993-1).

[b] The 1,5 µg/d value is based on 10^{-5} cancer risk and 60 kg (adult) body weight[6][17].

"...protective for [genotoxic or non-genotoxic] carcinogens, systemic toxicants, and reproductive toxicants ... for oral or parenteral routes, ...adults, paediatrics and pregnant women...generally applicable for medical device use(s)"

Threshold of toxicological concern (TTC)

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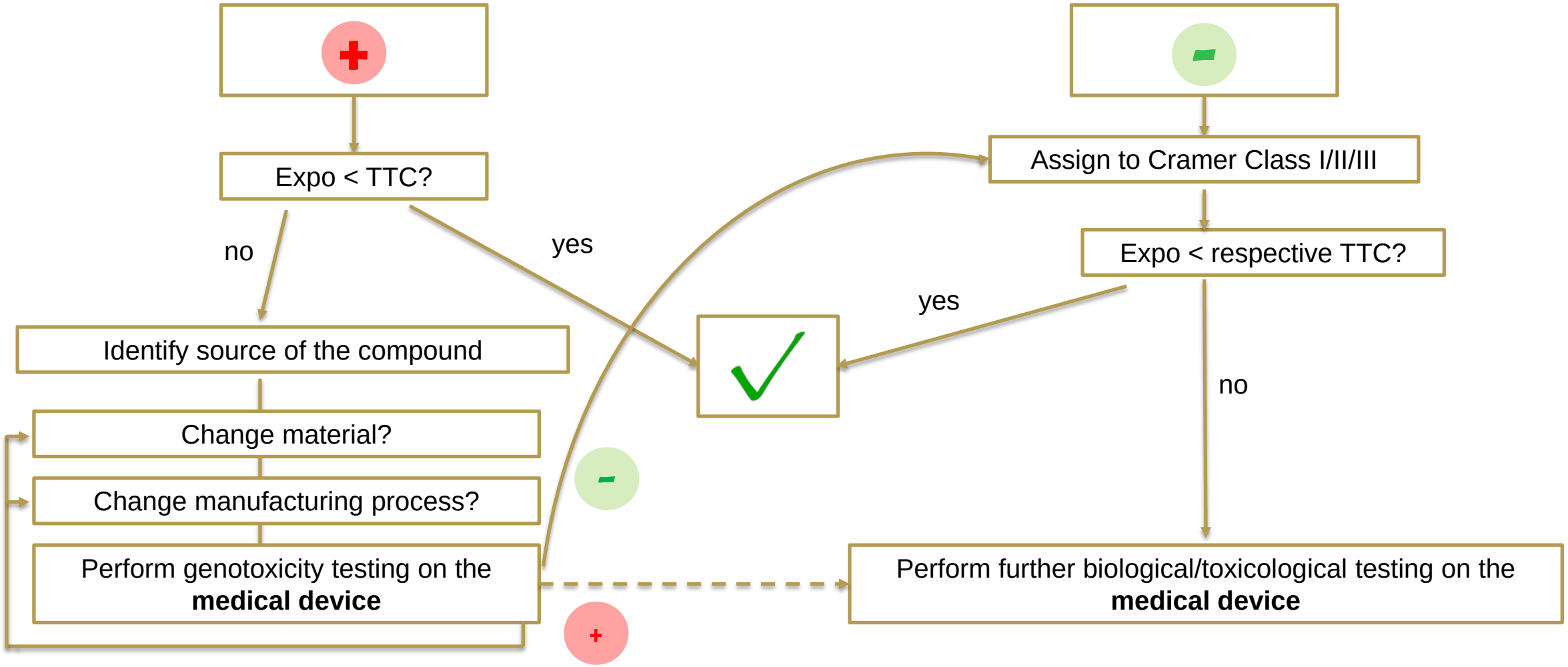
ISO TS 21726:2019

"When experimental data or model-derived predictions suggest that an identified constituent is not likely to have carcinogenic effects (e.g. **negative mutagenicity data** or negative results in **at least two computational models** that operate using different approaches; system-based and statistically based), then categorizing the constituent into its appropriate Cramer Class and use of the corresponding TTC value is recommended"

Classification		TTC (µg/day)			
Mutagenic		≤ 1 month	> 1 m – 12 m	> 12 m – 10 yrs	> 10 yrs
		120	20	10	1.5
Non-mutagenic	Cramer Class III	90			
	Cramer Class II	540			
	Cramer Class I	1800			

Conclusions for risk assessment

When the *in silico* screening outcome is...



Dermal Sensitisation Threshold (DST)

Dermal Sensitisation Threshold (DST)

– An analogous approach for quantitative risk assessment for skin sensitisation -

Classification	DST (µg/cm²)
Non-reactive	900
Protein reactive	64
High Potency Category (HPC)	1.5

DST values are established for skin sensitisation
→ Applicability for parenteral exposure?

Safford, R.J., 2008, Regul. Toxicol. Pharmacol. 51 (2), 195–200.
Safford, R.J. et al., 2015, Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Nishijo, T. et al., 2020, Regul. Toxicol. Pharmacol. 117, 104732.

How to deal with unidentified substances?

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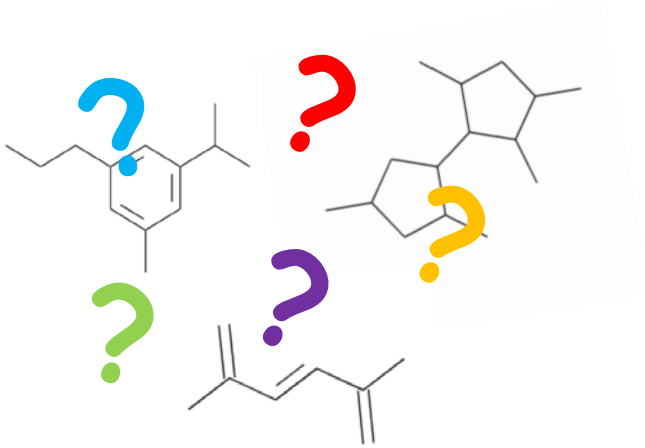
Unknown substances in analytical studies

- TTC principle used to derive an analytical evaluation threshold (AET)
  - Threshold below which there is insufficient quantity present to elicit toxicity, **irrespective of the substance's identity**
  - Dose (µg/d) converted to concentration (µg/mL)
    - → Extractables at concentrations < AET do not need to be identified or quantified for toxicological risk assessment
- Use default TTC values for evaluation (CAVE: cohort of concern)
- Approaches for "partially identified" extractables
  - → Apply (Q)SAR analysis "to facilitate some level of safety assessment"*, e.g. regarding mutagenicity
  - → Grouping / read-across approach



*Christiaens, P. et al., 2020, PDA J Pharm Sci Technol. 74(1):108-133.

Summary

- *In silico* methods gain relevance in biological evaluation of medical devices, since the assessment of extractables & leachables plays more and more a key role

  → Grouping/read-across approaches

  → Refinement of worst-case assessments using TTC or similar values

- The limited analytical identification of extractables & leachables is a challenge

  → There are approaches to use (Q)SAR, grouping / read-across for partially identified substances

  → Regulatory acceptance might be dependent on the overall extraction profile and quality of partial identification

Thank you!

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I declare that I have no conflict of interest.