

Toxicological Risk Assessment Challenges and Future Directions

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Toxicological Risk Assessment

INTERNATIONAL STANDARD

ISO 10993-17

Second edition
2023-09

Biological evaluation of medical devices —

Part 17:
Toxicological risk assessment of medical device constituents

ISO 10993-17:2023

Biological evaluation of medical devices — Part 17: Toxicological risk assessment of medical device constituents

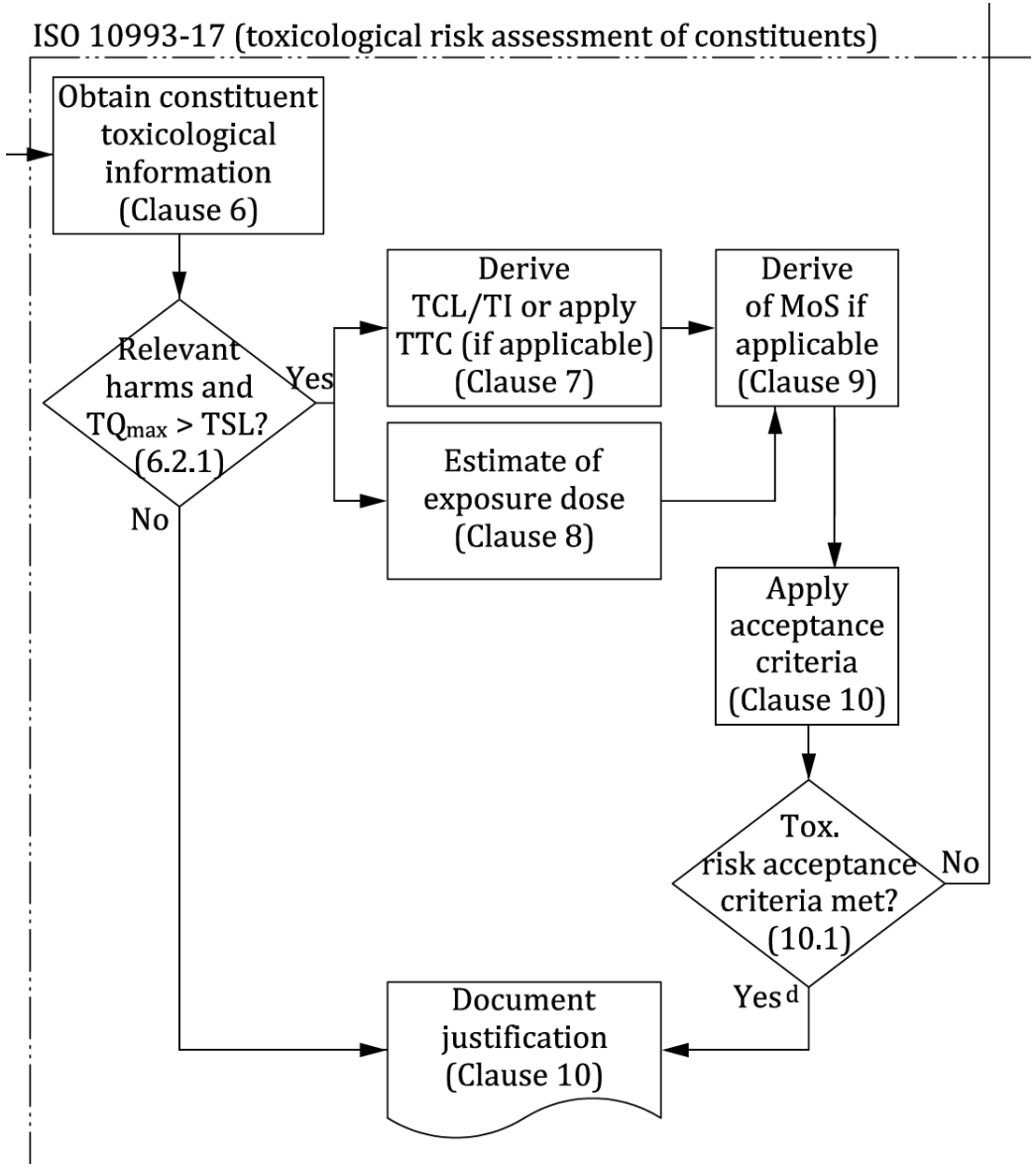


FDA will accept declarations of conformity to the 2002 version until the end of 2026

Extent of recognition??

- Full Standard with Following Exceptions:
  - **Errors** (one with units and another with a calculation)
  - **Table E.2** (example of calculation of actual release kinetics (because it doesn't mention justification for late bolus release)
  - Issues with **scaling factor** phrase (largest surface area vs largest device)

Overall TRA Process



Toxicological Screening Limit

- TSL, to be compared to TQmax, when cumulative exposure dose is < than TSL, it represents a negligible tox risk and no additional risk estimation is recommended
- TSLs according to this document apply to systemic toxicity (acute, subacute, subchronic and chronic), genotoxicity, carcinogenicity, reproductive or developmental toxicity for oral or parenteral routes, as well as adults, paediatrics (6 months of age or older) and pregnant women
- TSL is based on TTC (ICH M7)
- 120 µg= short-term limit (≤ 30 days); 600 µg= long-term limit(> 30 days)

Does not apply to preterm or very young infants ≤ 6 months

Be Careful Screening out Constituents with TSL!

- Review chemicals carefully for CMR substances (or other “excluded compound classes”)
- Look for substances with TI values likely below 2 µg/kg/day
  - PFAS, MDA, similar substances that are not officially regulated
- Screen for potent mutagens (though limit is protective for mutagenic substances there may be some with higher potency that should be reviewed in TRA)
- Consider Reasonably foreseeable misuse: could device be used in very young patients (TSL would not apply)

Estimating Bioavailability for Route-to-Route Adjustment

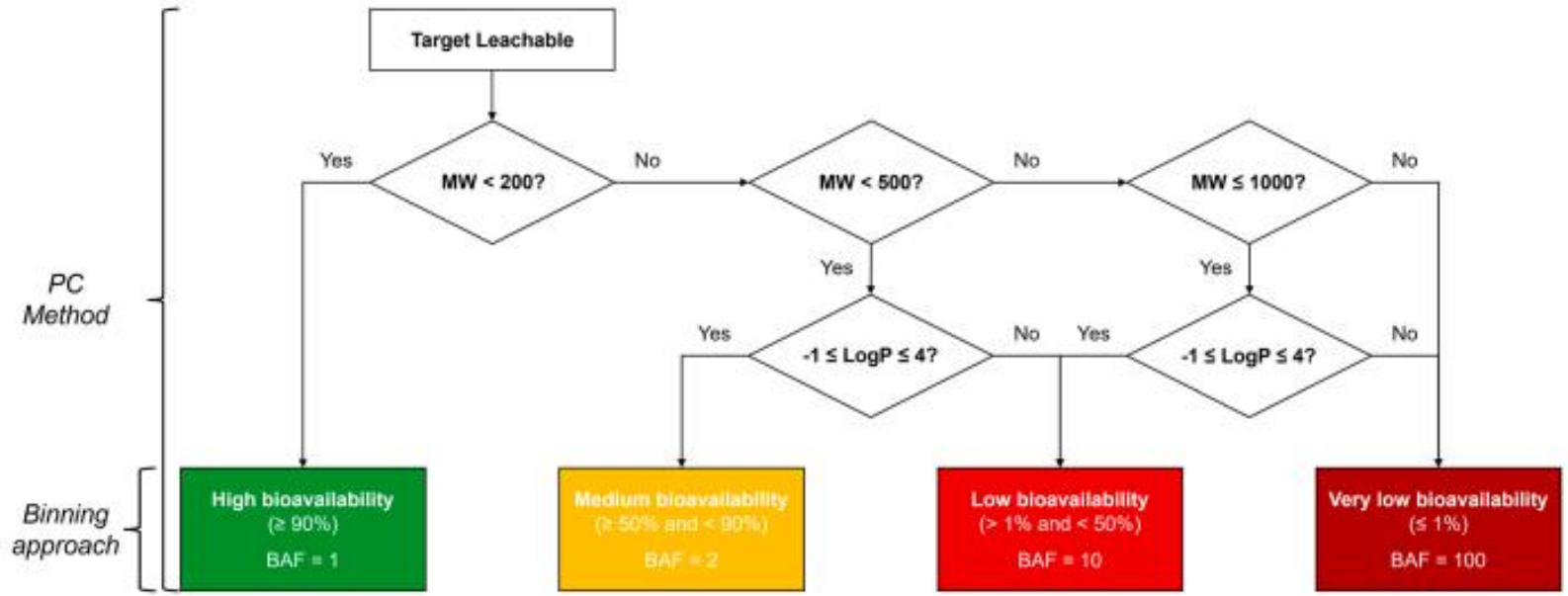


Fig. 1. PC method for estimating bioavailability based on LogP and MW. Factors are assigned from four bins which represent a range of bioavailability values; this step is called the "Binning Approach". BAF: Bioavailability Adjustment Factor.

ISO 10993-17:2023, Areas for Further Development



Application of TTC in Medical Device TRAs (new revision of ISO/TS 21726)-Taylor Builee (Project Leader)



Sources of Hazard Information: ISO/PWI TS 24830 Sources of hazard information for medical device constituents - Dr. Kelly Coleman (Project Leader)



Best Practices for Read-Across; ISO/NP TS 24830 Application of in-silico/read-across approaches for identifying a medical device constituent analogue - Dr. Carsten Senholt (Project Leader)

ISO/TS 21726: 2019

Current: TTCs are based on ICH M7 for all harms

Consistent with ISO/TS 21726:2019, Thresholds of Toxicological Concern (TTC) values should be protective for DART endpoints in the absence of data

ICH M7 TTCs are applicable to all patient populations

Cramer Class TTC values should be protective if considered on a µg/kg/day vs µg/day basis

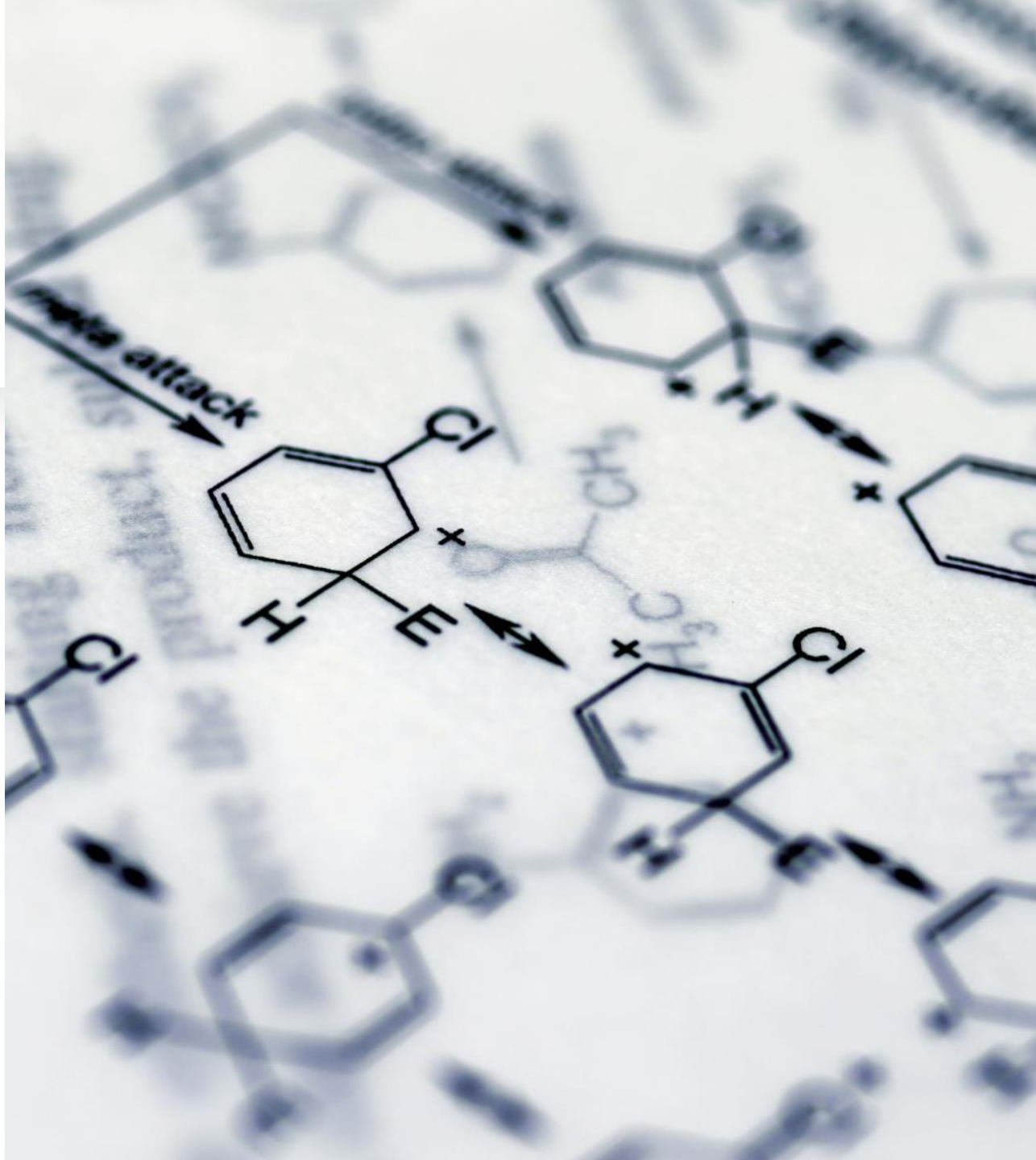
Application of TTC for Chemical Toxicological Risk Assessment

- When worst-case Estimated Exposure Dose (based on TQ_{max}) < TTC, then toxicological risk from exposure to the chemical can be considered negligible because current TTC values are highly conservative and applied to a broad range of chemicals with widely varying toxicity
- Use as de facto TI (in absence of a chemical specific PoD)
- TTC (in µg/kg/day) compared to EED_{max} (in µg/kg/day)
  - Note: EED_{max} is required to be expressed in microgram per kilogram of body mass per day (µg/kg/d) per ISO 10993-17:2023

Note: per ISO/TS 21726, TTCs, including Cramer Class, are applicable to all patient populations when appropriately expressed in µg/kg/day. Use of TTCs in µg or µg/d for chemical toxicological risk assessment is not in accordance with ISO 10993-17:2023. Mutagenic TTCs in µg/d can be used as a dose-based threshold value for chemical screening studies.

Example of Application TTC to Infant Patient Population (< 6 months)

- **Assumptions**: Device = long-term implant (>1 year). TQ_{max} of Chemical A = 110 µg; estimated body weight 3.5 kg, no toxicology data available for Chemical A.
- TSL (i.e., 120 µg and 600 µg) is not applicable because it is not intended for this subpopulation.
- Because 110 µg (TQ_{max}) > 10 µg/d (TTC), then TRA needs to be conducted, documented, and manage the risk (if necessary) for this subpopulation.



Assumed Release Kinetics (EED_{max})

$TQ_{max} \div BW \div$ Releasing Days (R_d)= EED_{max} (µg/kg/day)

Device Category	R_d for each time period of assumed constituent release			
	≤ 1 d	2 d to 30 d	31 d to 365 d	≥ 366 d
Limited	1	Not applicable	Not applicable	Not applicable
Prolonged	1	2	Not applicable	Not applicable
Long-term (31-365 d)	1	2	31	Not applicable
Long-term	1	2	31	366

Releasing Days (R_d)= fewest number of days in each time period

Risk Estimation

$TQ_{max} \div BW \div$ Releasing Days (R_d)= EEDmax (µg/kg/day)

$$MoS = \frac{TI/TTC \text{ or } TCL}{EEDmax}$$

Device Category	EEDmax and TI (TTC) for each time period of assumed constituent release (µg)			
	≤ 1 d	2 d to 30 d	31 d to 365 d	≥ 366 d
Long-term	110	55	3.55	0.3
EEDmax (µg/kg/day)				
	31	16	1	0.09
TI (TTC) (µg/kg/day)				
	2	2	0.33	0.17
MoS				
	0.06	0.13	0.33	**1.9**

MoS <1 values needs further risk analysis or risk evaluation or risk control, see ISO 10993-17:2023, 10.2

Risk Estimation
(Use of TTC not consistent with ISO 10993-17)

Device Category	TQ (µg)			
	≤ 1 d	2 d to 30 d	31 d to 365 d	≥ 366 d
Long-term	110	55	3.55	0.3
TTC (µg/day)				
	120	120	20	10
MoS				
	1.09	2.18	5.6	33

All MoS>1 (i.e., a false negative outcome)

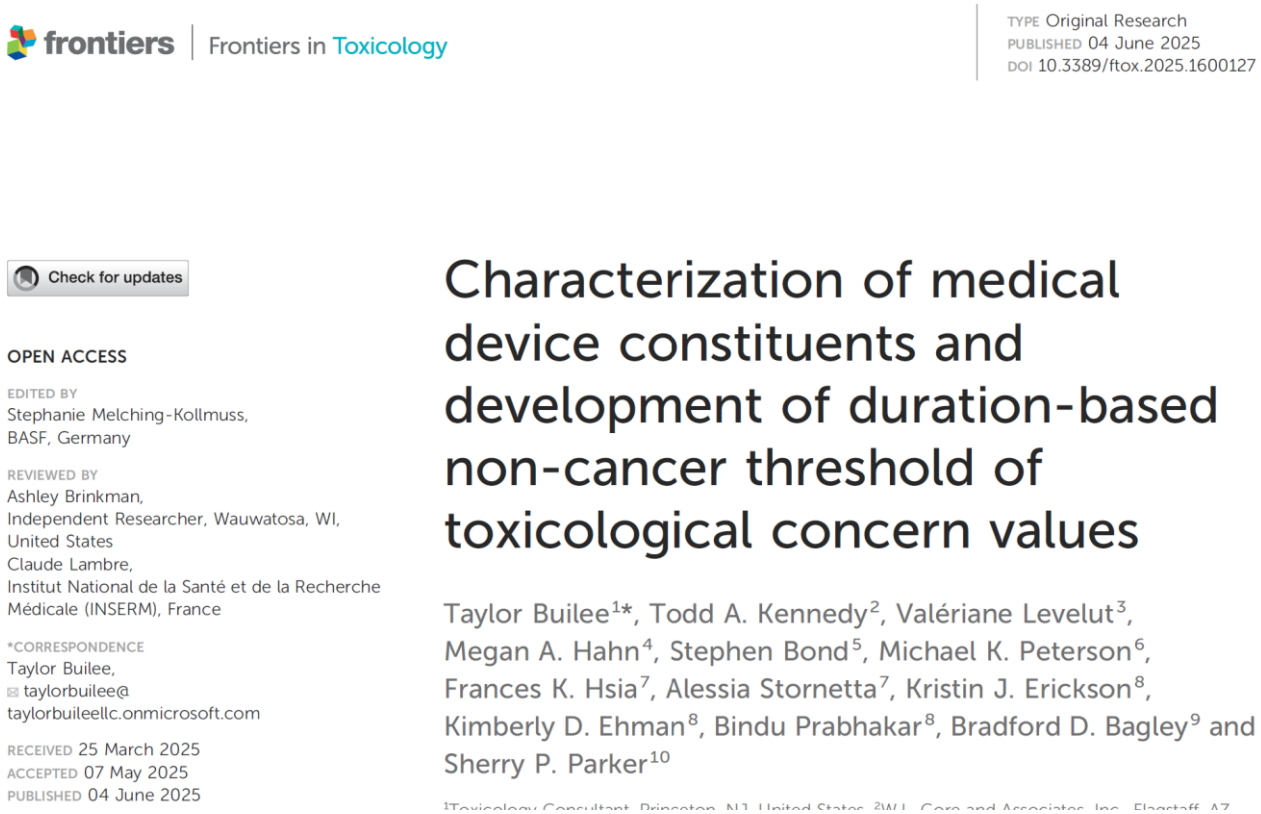
These EED_{max} values are not adequately conservative based on toxicological risk assessment principles, see ISO 10993-17:2023, 10.1.

Use of TTC without BW Adjustment in TRA

TTC in µg/person/day		**Allowable Limits µg/day**					
		Adults (60 kg)		Children (10 kg)		Neonates (3.5 kg)	
Cancer/Non-Cancer (C/NC)	Non-Cancer (NC)	C/NC	NC	C/NC	NC	C/NC	NC
120 µg/day (limited, prolonged)	1800 µg/day (Cramer Class I)	2	30	12	180	34	514
20 µg/day (long-term, 1 month-1 year)	540 µg/day (Cramer Class II)	0.33	9	2	54	5.7	154
10 µg/day (long-term > 1 year)	90 µg/day (Cramer Class III)	0.17	1.5	1	9	2.9	26

ISO/TS 21726 is in revision

- Ideas for updates:
  - Reducing use of 1.5 µg/day as it isn't practical threshold for TTC of many medical devices (unless single-use, repeated daily exposure for lifetime).
  - Proposed non-cancer MD TTC Values
  - Greater Guidance on "Excluded" compounds including clarifications and definitions of the categories



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Characterization of medical device constituents and development of duration-based non-cancer threshold of toxicological concern values

Taylor Builee[1]*, Todd A. Kennedy[2], Valériane Levelut[3], Megan A. Hahn[4], Stephen Bond[5], Michael K. Peterson[6], Frances K. Hsia[7], Alessia Stornetta[7], Kristin J. Erickson[8], Kimberly D. Ehman[8], Bindu Prabhakar[8], Bradford D. Bagley[9] and Sherry P. Parker[10]

[1]Toxicology Consultant, Princeton, NJ, United States, [2]WIL Corp and Associates, Inc., Flagstaff, AZ

MD Non-Cancer TTCs

- Effort involved 24 Medical Device Toxicologists
- Actual Medical Device Constituents Identified in studies conducted under ISO 10993-18:2020 requirements
- > 15,000 Total Medical Device Constituents
- Studies selected for POD included Reproductive and Developmental Toxicity NOAELs

Builee et al., 2025; Front. Toxicol. 7:1600127

Inclusion/Exclusion Criteria

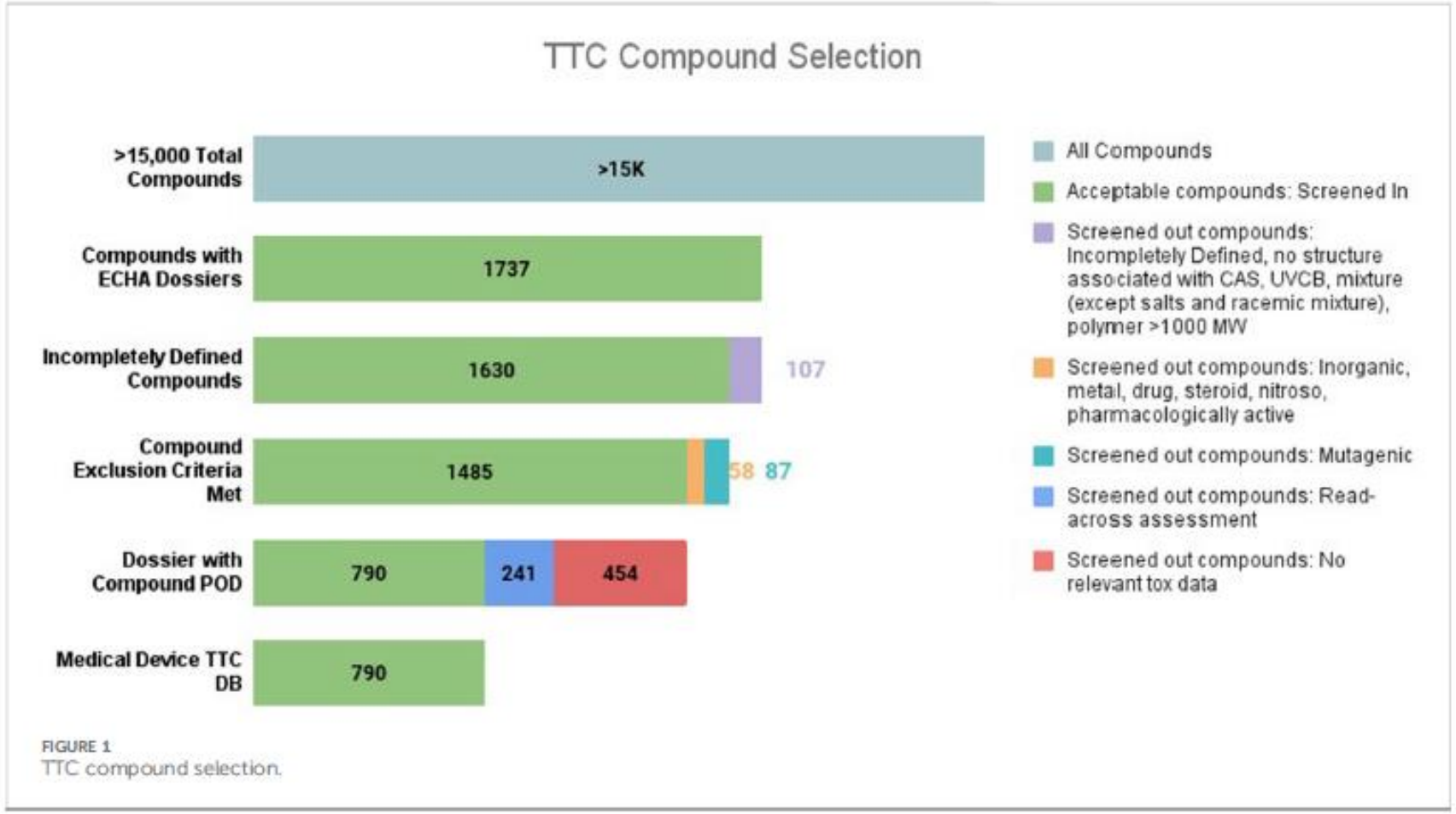


FIGURE 1
TTC compound selection.

Builee et al., 2025; Front. Toxicol. 7:1600127

Results of Analysis

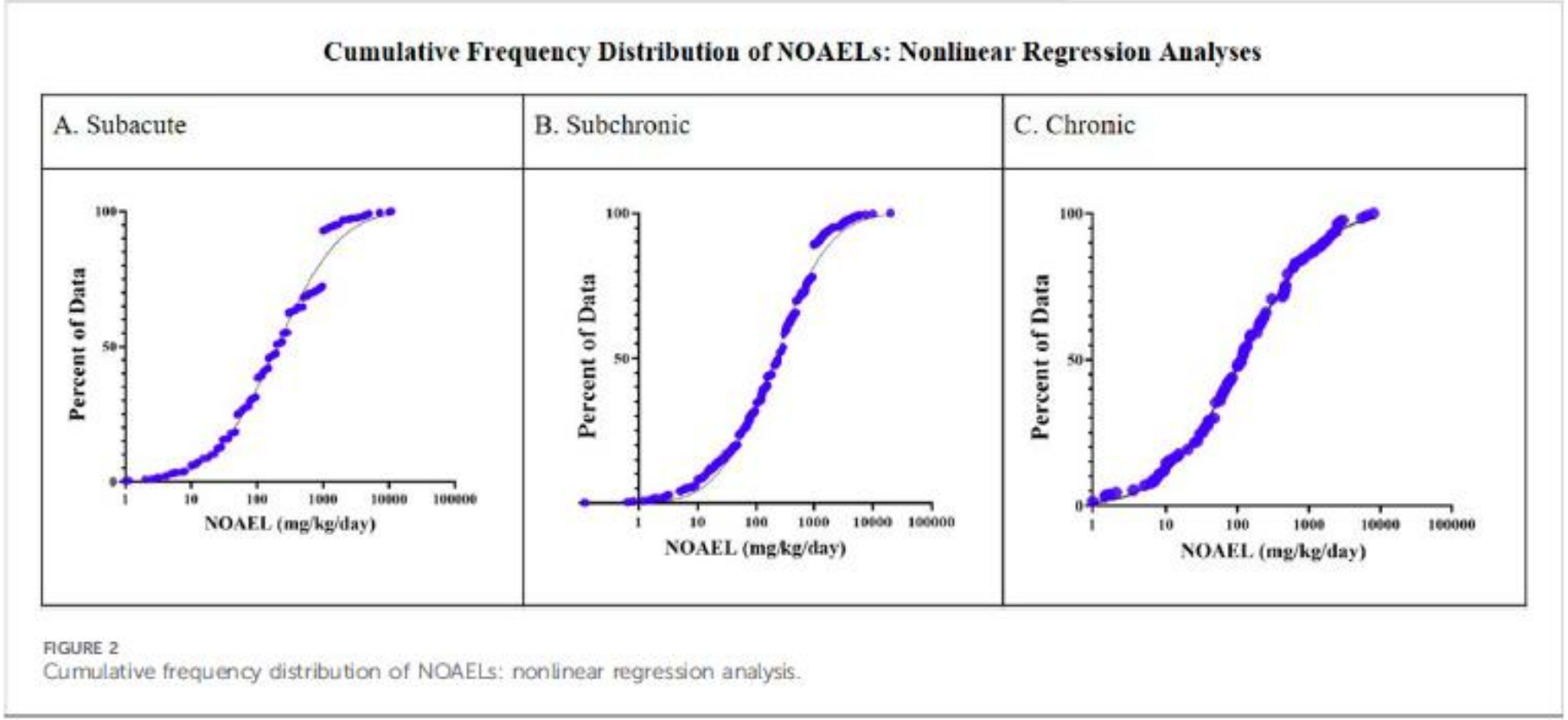


FIGURE 2
Cumulative frequency distribution of NOAELs: nonlinear regression analysis.

Builee et al., 2025; Front. Toxicol. 7:1600127

Proposed MD Non-Cancer TTCs

TABLE 4 Medical device non-cancer TTC values and comparison to established TTC values.

Device categorization (ISO 10993-1)	Limited (≤24 h)	Prolonged (>24 h to 30 days)	Long-term (>30 days)	
Patient/User constituent exposure duration (ISO 10993-17:2023)	≤ 1 day	2–30 days	31–365 days	≥ 366 days
MD Non-Cancer TTC (μg/kg/day)	112	112	111	41
Munro 1996 Cramer Class I TTC (μg/kg/day)	NA	NA	NA	30
Munro 1996 Cramer Class II TTC (μg/kg/day)	NA	NA	NA	9
Munro 1996 Cramer Class III TTC (μg/kg/day)	NA	NA	NA	1.5

NA: not applicable.
Note: Proposed TTC, Values are based on the lowest fifth percentile NOAEL ÷ MF, of 100.

Discussion ongoing about need for bioavailability adjustments for non-oral route

Currently considered protective for all patient populations

Builee et al., 2025; Front. Toxicol. 7:1600127

New FDA EDT for Non-Cancer TTC

Expanded Decision Tree: FDA's Food Chemical Toxicity Screening Tool

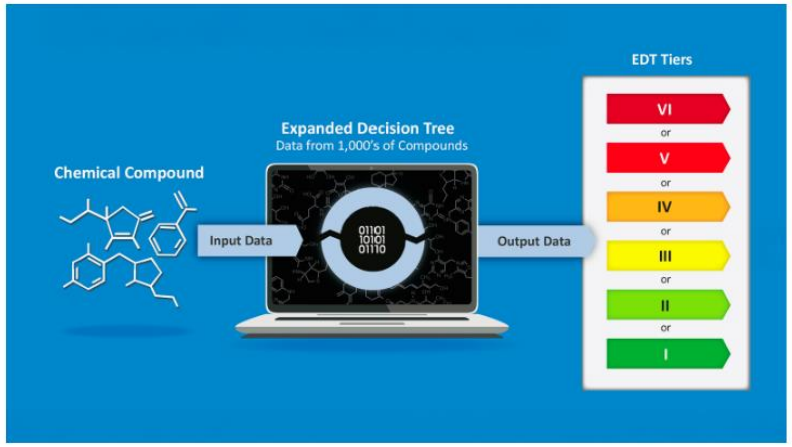


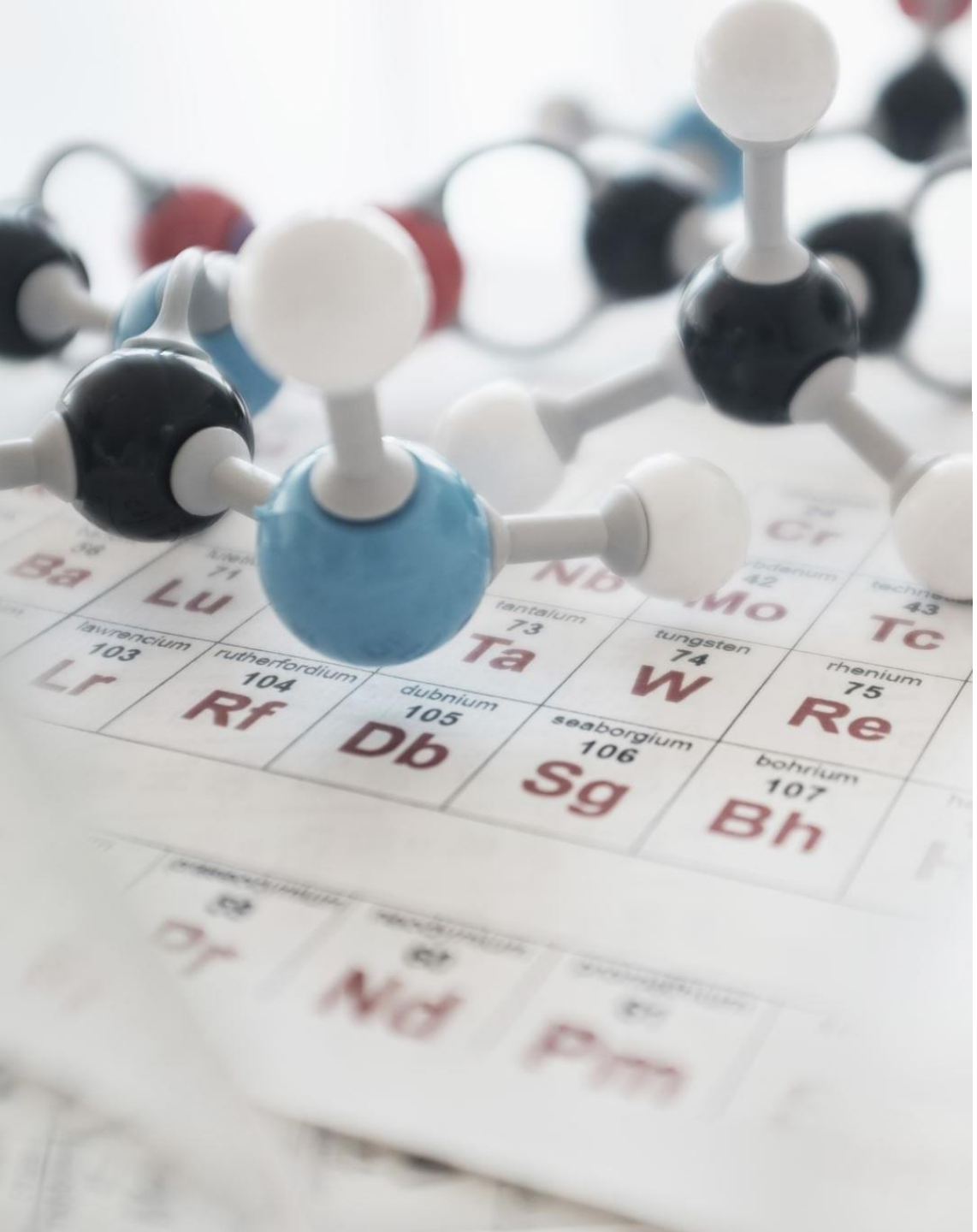
Table 2

Summary of TTC values for EDT subset compared with the Munro dataset. Only substances associated with a study with a minimum duration of 84 days were used to derive TTCs, which accounts for the lower number of chemicals with NEL vs all substances assigned to its respective EDT class.

Cramer class	TTC EDT (μg/kg bw/day)	TTC Munro (μg/kg bw/day)	No. EDT Chem (with relevant NEL values)	No. Munro Chem
I	34	30	571 (360)	137
II	13.68	9	78 (58)	28
III	1.54	1.5	1312 (922)	448

Patelwicz and Milhalchick, Computational Toxicology 39 (2026)

Patlewicz et al. further evaluated FDA EDT by applying Kroes workflow, and found Class I, II and III to be similar.
Proposed a EDT class 0, yielding a TTC of 1387 μg/kg/day that could be applied to non-toxic substances like carbohydrates



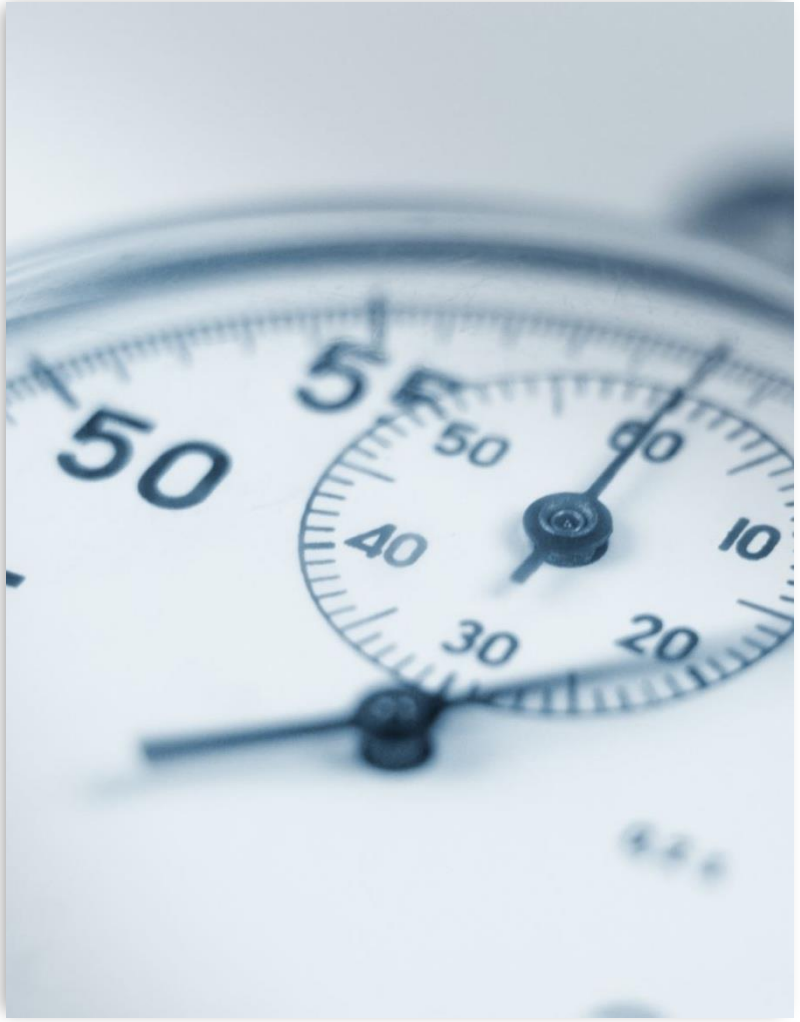
If MoS < 1 when TTC (ISO/TS 21726) is used as TI:

- Consider targeted analysis for the chemical to refine chemical characterization
- Consider more clinically relevant extraction conditions to refine chemical characterization
- Risk Management (ISO 14971)

- Note: Biological Testing (e.g., genotoxicity testing) may not be accepted to mitigate risk

Summary

- Use caution when applying TSL
- It is time to transition to ISO 10993-17:2023 for FDA Submissions
- Consider physical and chemical properties when estimating bioavailability
- Watch for developing guidance on Sources of Hazard Information and Read-Across
- Non-weight adjusted TTC (with exception of Clause 7.2) may be challenged
- Biological testing may not mitigate risks identified in TRA



Thank You!!

Questions?