Part 1

Biological Risk Management: Hazard Identification and Derivation of Tolerable Intake Values

ISO 10993-17:2023
Toxicological Risk Assessment of Medical Device Constituents

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ISO 10993-17:2023
Toxicological Risk Assessment of Medical Device Constituents

Part 1 Topics

A - Toxicological risk assessment within the biological evaluation process

B - Toxicological Information, Hazardous Constituents, TSL, Carcinogens

C - Derivation of Tolerable Intake Values

Topic A

Toxicological risk assessment within the biological evaluation process

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Topic A

Toxicological risk assessment within the biological evaluation process

Parts of ISO 10993-17:2023 that are covered in this presentation

- **Process of revising ISO 10993-17**
- **Clause 3. Terms and Definitions**
- **Clause 5. Toxicological risk assessment within the biological evaluation process**

Note: FDA/CDRH partially recognizes ISO 10993-17:2023. For specific text not recognized, see https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=44811

Process of revising ISO 10993-17:2023

Phase	Year	Description
WD Study	2016	In October 2016, ISO TC 194 WG11 experts met in Annapolis, Maryland and discussed the need to expand the scope of the current ISO 10993-17 to include toxicological risk assessment of medical device constituents. Because ISO TC 194 WG14 update of 10993-18 includes when a toxicological risk assessment should be conducted, WG11 agreed that expansion of ISO 10993-17 is needed and formed a writing group to create the framework that describes the new revision.
NWIP	2018	In April 2018, ISO TC 194 WG11 experts agreed that a proposed working draft (WD) document is adequate for preparing and submitting a new work item proposal (NWIP). The proposal was to update the document to establish a common medical device constituent toxicological risk assessment approach, including common requirements and criteria.
WD	2019	In October 2019, moving the working draft (WD) document to the committee draft (CD) stage was initiated. Project officially began October 2020.
CD	2021	In October 2021, moving CD document to the draft international standard (DIS) stage was initiated.
DIS	2022	In August 2022, moving the DIS document to final DIS (FDIS) stage was initiated.
FDIS	2023	In August 2023, the FDIS document was submitted to ISO/CEN for review and published in September 2023.

Clause 3. Terms and Definitions (key)

Clause	Term	Definition	Related Clauses
3.11	Identified Constituent	constituent (3.4) for which molecular structure information is complete Note 1 to entry: The identity of a constituent can be obtained by information gathering or non-targeted or targeted analytical approaches as described in ISO 10993-18.	6.2.1 (application of *in silico* analysis) 6.2.2 (application of TSL, also see Annex B) 6.2.4 (application of TTC or identification of an analogue) E.2 (exposure dose estimation based on release kinetics information)

Clause	Term	Definition	Related Clauses
3.27	Total Quantity (TQ)	amount of a constituent (3.4) present in, or that can be extracted from, the medical device Note 1 to entry: The total quantity is expressed in microgram (µg). Note 2 to entry: The constituent's total quantity and its release rate (or kinetics) influence the maximum duration that an individual can be exposed to the constituent (3.4)[11].	6.2.2 (when the quantity represents cumulative exposure and compared to TSL) E.3 (when estimating worst-case exposure dose based on maximum release and the quantity represents cumulative exposure)

Clause 3. Terms and Definitions (key)

Clause	Term	Definition	Related Clauses
3.32	Worst-Case Estimated Exposure Dose (EED_{max})	exposure dose (3.7) that is a maximum value for a specified intended clinical-use scenario Note 1 to entry: EEDmax is based on the selection of the full range of intended clinical use scenarios, specific clinical use condition or assumption related to the intended clinical scenario (see Annex E for additional information). Note 2 to entry: Specific clinical use conditions or assumptions used to establish worst-case estimated exposure dose do not include deliberate misuse of a medical device that is not reasonably foreseeable or that results in different harm to health (3.8).	Clause 8 (requirement that worst-case estimated exposure dose is based on worst-case conditions). 9.2 (requirement that MoS is based on worst-case estimated exposure dose) Annex E (how to determine worst-case estimated exposure dose for different types of chemical data)

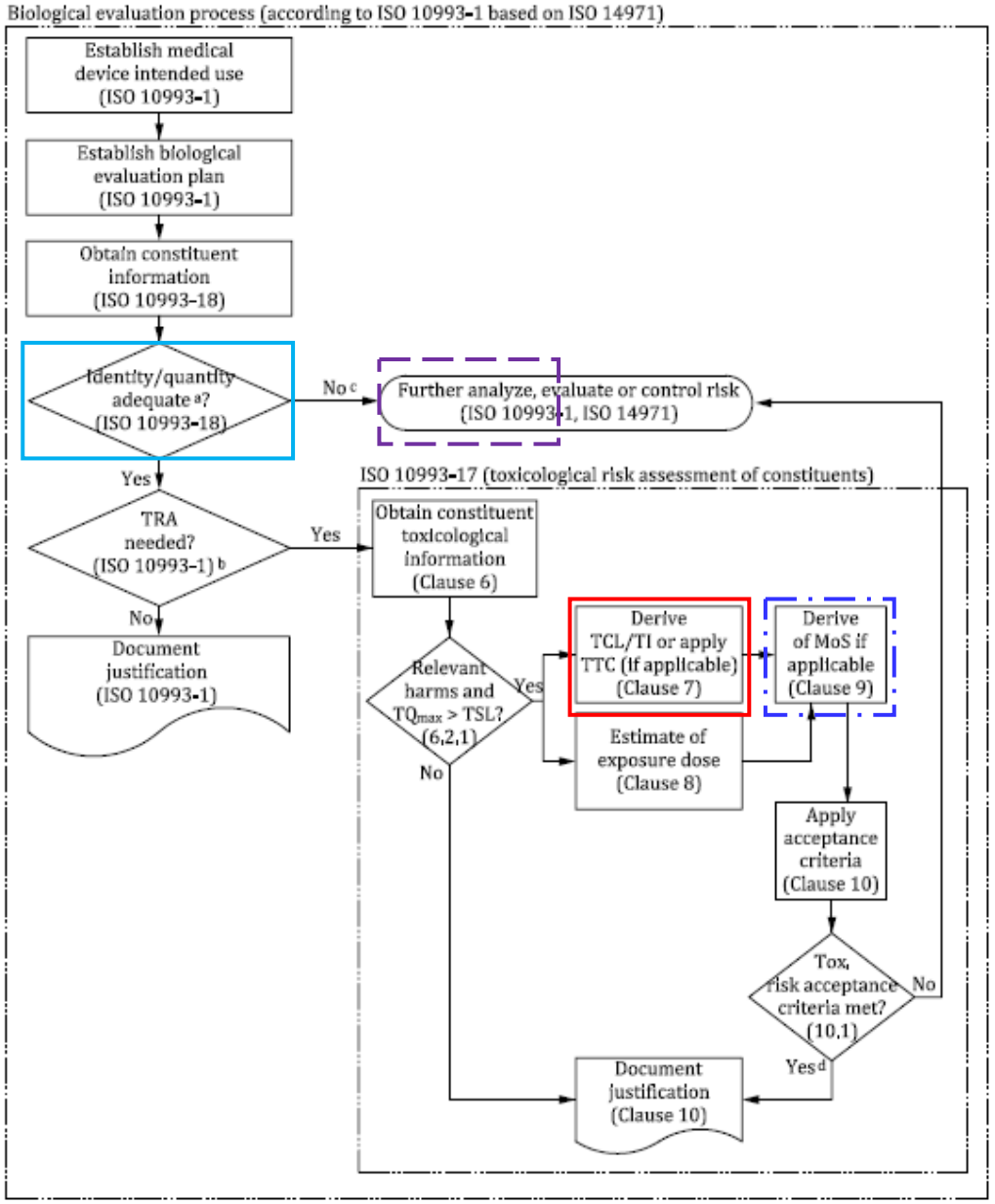
The remaining terms and definitions in Clause 3 are important and necessary to apply the standard as intended by ISO / TC 194.

Clause 5
Toxicological risk assessment within the biological evaluation process

The toxicological risk assessment (TRA) approach should:

- Be systematic (5.1.1)
- Align with applicable risk management principles of ISO 14971
  - Hazard identification (5.1.2)
  - Risk estimation (5.1.3)
- Align with ISO 10993-1 biological evaluation process (5.2)
  - Figure 1. Toxicological risk assessment within the biological evaluation process
  - Figure 2. Critical toxicological risk assessment activities

Figure 1. Toxicological risk assessment within the biological evaluation process



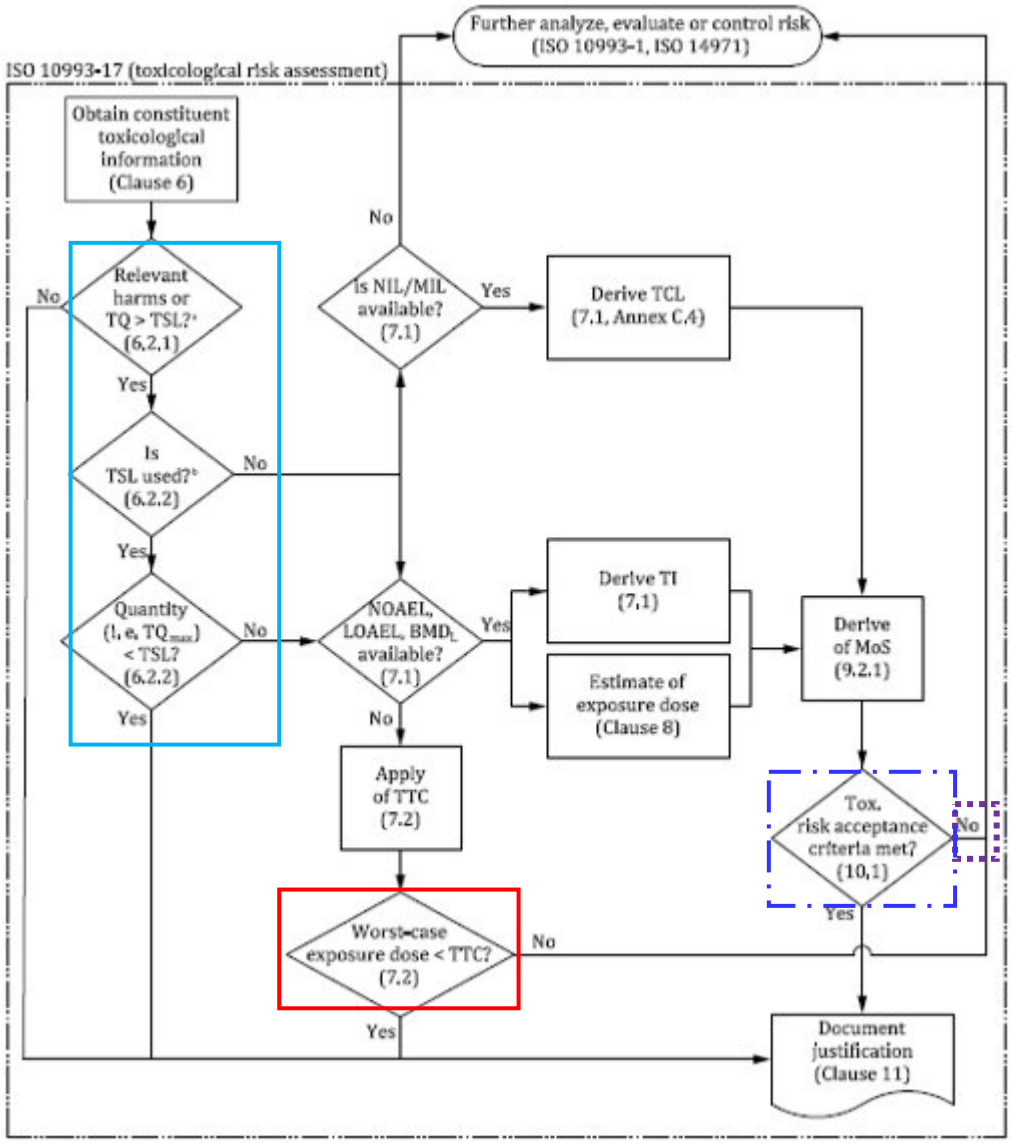
"**Identity/quantity adequate?**" indicates not all constituents could be addressed in the TRA (*e.g.*, a reportable extractable with no identity information), and additional steps in accordance with ISO 10993-1 would be considered, such as: analyze, evaluate or control the risk (*e.g.*, identity information that permits identification of hazardous constituents, see clause 6 for requirements, recommendations and guidance).

"**Derive TCL/TI or apply TTC (if applicable)"** indicates multiple types of thresholds for a constituent may be necessary when the same or different constituents elicit different types of harms that are relevant to device intended use.

"**Derive MoS (if applicable)"** indicates calculating an MoS may not be necessary for all identified constituents, see Figure 2. Calculating and reporting MoS would be necessary when TSL is not used, and a relevant PoD is available. The document requires justifying and documenting in the report how the toxicological risk(s) of constituents are addressed.

"**Further analyze**" indicates additional biological or chemical information may be necessary, for example, conduct applicable biological test or identify whether a medical device constituent is a hazardous substance(s) or demonstrate that exposure to the constituent will be at a tolerable level or control the risk, or if risk control is not practical then consider benefit-risk.

Figure 2. Critical toxicological risk assessment activities



"**Relevant harms or TQ > TSL?", "Is TSL used?", and "Quantity (*i.e.*, TQ_{max}) < TSL?"** indicate when calculating and reporting an MoS for a reportable constituent would not be required, provided that the justification used addresses applicable requirements.

"**Worst-case exposure dose < TTC?**" indicates when the standard does not require calculating and reporting an MoS for a specific constituent.

"**Tox. risk acceptance criteria met?**" means

- the worst-case exposure dose DOES NOT exceed the constituent specific TI value (*i.e.*, MoS >1 where MoS = TI ÷ EED_{max}) **AND**
- the TI and EED_{max} values deliberately overestimate (*i.e.*, lower MoS) the probable true risk.

"**Tox risk acceptance criteria met? No**" indicates the risk management process DOES NOT STOP. Instead, the risk of the identified hazard should be further analyzed (if feasible), or alternatively, evaluated and mitigated. If mitigating the risk is not practicable, then benefit-risk considerations may be useful. The standard requires justification and documentation of the risk management approach that is used.

Clause 5
Toxicological risk assessment within the biological evaluation process

The toxicological risk assessment process requires that[12][13][14]:

a) The following information shall be provided (see Clause 6), in accordance with ISO 10993-1 and ISO 10993-18:

- a description of the device (e.g. an illustration of the device and identification of its materials of construction that contact the body);
- a description of the intended use of the medical device (e.g. indications, contraindications, clinical use conditions, route of exposure, patient population, duration and frequency of use), from which the worst-case intended clinical use scenario shall be determined;
- the identity and quantity of each reportable constituent (e.g. molecular structure or CAS RN) obtained in accordance with ISO 10993-18.

b) The toxicity of each constituent shall be characterized (see 6.1 and 6.2), based on a systematic review of available toxicological information that takes into account:

- the nature of the harm(s) to health;
- the relationship between exposure and harm (i.e. dose-response relationship and the influence of the route and duration of exposure).

c) The toxicological risk shall be assessed for each constituent by either:

- determining that the constituent is not capable of eliciting harm that is relevant to the intended use of the medical device (see 6.2), or
- determining that the total quantity of a constituent is too low to elicit appreciable harm to health (see 6.2.1 or 6.2.2), or
- determining that the worst-case estimated exposure dose for each constituent present in, on, or released from the medical device is below its TCL or TI (see Clauses 7, 8 and 9), or
- determining that the quantity of a constituent released is below the relevant TTC value (if applicable; see 7.2).

ISO 10993-17:2023 - Errors

- Example 6, Annex B,

10 is the *SF* where 50 cm^2 is the maximum device surface area, in cm^2, that is in contact with the body divided by the 50 cm^2 device surface area extracted.

Should read...

10 is the SF where ~~50~~ 500 cm^2 is the maximum device surface area, in cm^2, that is in contact with the body divided by the 50 cm^2 device surface area extracted.

- Table B.1, 2nd Column,

Table B.1 — Default toxicological screening limit *TTC* and *D* for *TSL* calculations

Period of assumed exposure to the constituent d	*TTC* g/d	*D* d	*TSL* µg

Should read...

Period of assumed exposure to the constituent *d*	*TTC* ~~g/d~~ µg/d	*D* d	*TSL* µg

Topic B
Toxicological Information, Hazardous Constituents, TSL, Carcinogens

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Topic B
Toxicological Information, Hazardous Constituents, TSL, Carcinogens

Parts of ISO 10993-17:2023 that is covered in this presentation

- Constituent specific toxicological information (6.1)
- Identification of hazardous constituents (6.2.1)
- Toxicological screening limit (6.2.2)
- Identification of human carcinogens or suspected human carcinogens (6.2.3)

Constituent specific toxicological toxicological Information (6.1)

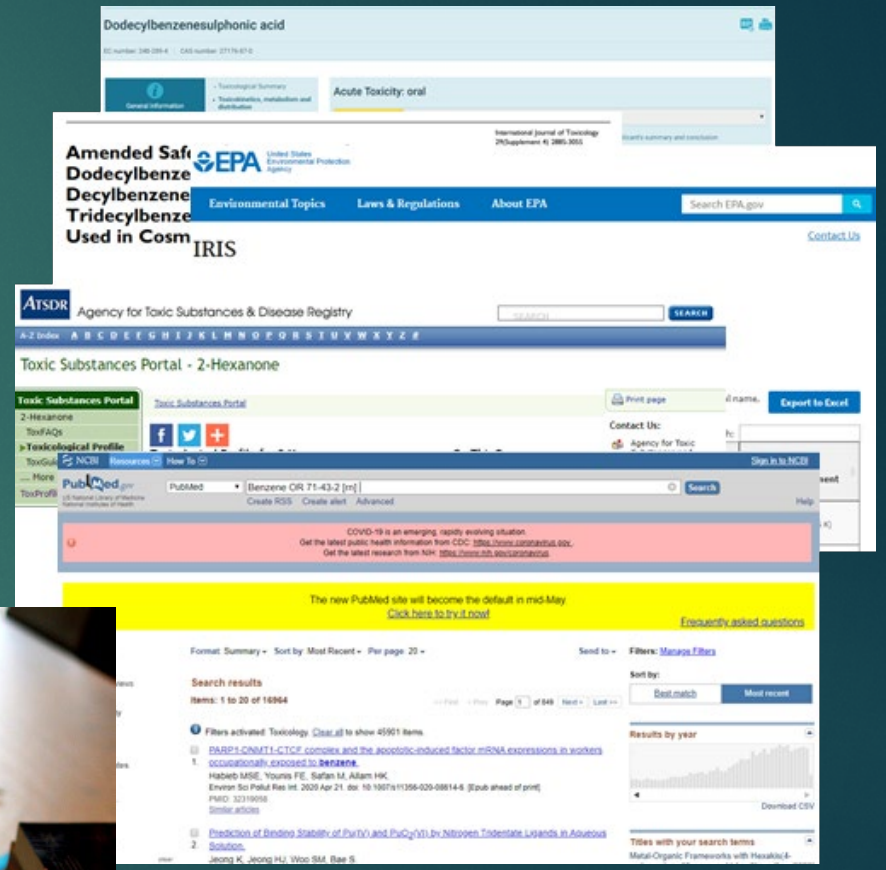
Description of harms to health that can be addressed in the TRA

Harm	TCL	TSL	TI	TTC
Irritation	X			
Systemic toxicity		X	X	X
Genotoxicity		X	X	X
Carcinogenicity		X	X	X
Reproductive Toxicity		X	X	X
Developmental Toxicity		X	X	X

*Other endpoints, such as sensitization, can be addressed but must be justified.

Identification of Hazardous Constituents (6.2)

- Requirements, recommendations, and guidance:
  - Obtaining, evaluating, and documenting toxicological information about constituents
  - Permits *in silico* models for an identified constituent (must be validated)
  - Specific exposures and relevance to medical device use



Toxicological Screening Limit (TSL) (6.2.2 and Annex B)

cumulative *exposure dose* (3.7) to an *identified constituent* (3.11) over a specified time period that is without appreciable *harm to health* (3.8)

Note 1 to entry: TSL is expressed in microgram per individual exposed.

TSL (µg) ≠ AET (µg/ml)

TSL (µg) ≠ TTC (µg/day)

TSL (µg) ≠ DBT (µg/day)

Background of TSL

- TSLs are TTCs expressed as cumulative doses over a specified time period
- TTCs are typically expressed as daily exposure doses, µg/day
- TTCs multiplied by days of exposure duration (TTC x days) give the TTC in cumulative exposure dose, µg
  - Cannot exceed the daily exposure in µg/day if less than corresponding cumulative TTC

Medical Device contact Category	**Limited (<24 h)**	**Prolonged (24 h to 30 days)**	**Long-term (> 30 days)**		
TTC Exposure Duration Category	Limited (<24 h)	Prolonged (24 h to 30 days)	Long-term (> 1 month to 1 year)	Long-term (> 1 year – 10 years)	Long-term (>10 years)
TTC, µg/day	120	120	20	10	1.5
Exposure duration, day	1	2	31	366	3650
Cumulative TTC, µg	120	240	620	3660	5475

TSL = Toxicological Screening Limit TTC = Threshold of Toxicological Concern TQ = Total Quantity

Background of TSL

TTC Exposure Duration Category	Limited (<24 h)	Prolonged (24 h to 30 days)	Long-term (> 1 month to 1 year)	Long-term (> 1 year – 10 years)	Long-term (>10 years)
Cumulative TTC, µg	**120**	240	620	3660	5475

- Lowest Cumulative TTC is 120 µg
- If Total Quantity (TQ in µg) is less than 120 µg, then:
  - the quantity is insufficient to exceed the cumulative TTC for any exposure duration

    AND
  - Therefore, risk of adverse effects is considered negligible
- Therefore, **120** µg is a cumulative threshold below which the risk of adverse systemic effects of the TQ is considered negligible.

TSL = Toxicological Screening Limit TTC = Threshold of Toxicological Concern TQ = Total Quantity

Toxicological Screening Limit (TSL) (6.2.2 and Annex B)

Optional tool to reduce the work required to perform a TRA

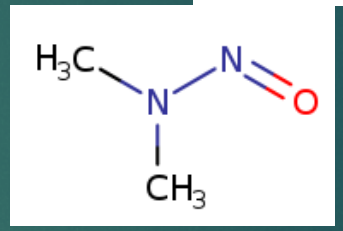
- When TSL can be applied:
  - When total Quantity (TQ) of an identified constituent is reported
  - When the TQ_{max} value represents the cumulative exposure dose, see clause 6.2.2 for guidance
- Key requirements:
  - TSL must be compared to TQ_{max}
  - TQ_{max} accounts for the duration of exposure, number/quantity of devices extract, and number/quantity of devices that contacts the body
  - See clause 6.2.2 for remaining requirements

Chemical Name	CAS #	TQ (µg/device)
Ether, 2-ethylhexyl tert-butyl	83704-03-4	8.4
Cyclohexanecarboxylic acid, hexyl ester	27948-10-3	18
1,1,2-Ethanetricarboxylic acid, triethyl ester	7459-46-3	17
Erucamide	112-84-5	260
Hexadecanedioic acid	505-54-4	5
Irgafos 168 oxidation degradant	95906-11-9	430

Toxicological Screening Limit (TSL) (6.2.2 and Annex B)

TSL is not applicable to the following:

- long-term devices used in patients < 6 months of age
- cohort of concern or excluded substances
- volatile compounds of gas pathways devices
- harms not protected by TTC values
- single-use (disposable) medical devices that are repeatedly used and cumulative duration of body contact is long-term



Toxicological Screening Limits (TSL) (Annex B)

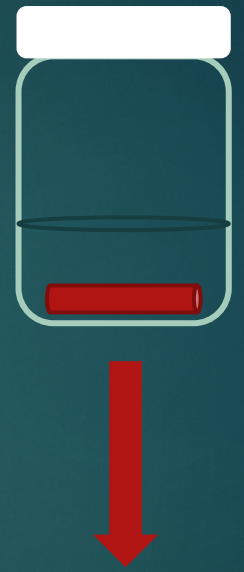
Medical device contact duration	Periods of assumed exposure to constituent		
	1 d	≤30 d	>30 d
Limited	120 µg	NA	NA
Prolonged		120 µg	
Long-term			600 µg

TSL = Toxicological Screening Limit

Calculating TQ_{max} (B.3)

TQ is the reported total quantity of an identified extractable from an exhaustive or exaggerated extractables study

- May need adjustment based on the number or amount of devices in the extractables study compared to worst-case clinical exposure
- Use Scaling Factor (SF) to make adjustment
  - Example – if one device was extracted, but two devices can be used worst-case clinically, then SF = 2
- TQ_{max} = TQ x SF
- TQ_{max} = 50 µg/device x 2 devices = 100 µg



TSL = Toxicological Screening Limit SF = Scaling Factor

Application of TSL (6.2.2, Examples in B.3)

- Compare TSL to TQ_{max}
- If TQ_{max} < TSL, then the toxicological risk is negligible for that extractable

- If TQ_{max} > TSL, then exposure dose shall be estimated and evaluated as described in Clauses 7, 8, 9, and 10

TSL = Toxicological Screening Limit TQ = Total Quantity TI = Tolerable Intake

Examples (Annex B)

Example 1 - Limited or prolonged contact: when 100 µg of an identified constituent is extracted from a single medical device and 1 device contacts the body for less than or equal to 30 d (not repeatedly used).

$TSL_{\leq 30\ d}$ = 120 µg/d x 1 d = 120 µg

TQ_{max} = 100 µg x 1 = 100 µg

Short-term exposure to the constituent is a negligible toxicological risk because TQ_{max} is less than $TSL_{\leq 30\ d}$

Examples (Annex B)

Example 2 – Limited or prolonged contact: when 100 µg of an identified constituent is extracted from a single medical device and 2 devices contact the body for less than or equal to 30 d (not repeatedly used)

$TSL_{\leq 30\ d}$ = 120 µg/d x 1 d = 120 µg

TQ_{max} = 100 µg x 2 = 200 µg

Short-term exposure to the constituent can present a toxicological risk because TQ_{max} is greater than $TSL_{\leq 30\ d}$

Examples (Annex B)

Example 3 – Long-term contact: when 300 µg of an identified constituent is extracted from a single medical device and 1 device contacts the body for long-term (i.e. greater than 30 d)

$TSL_{\leq 30\ d}$ = 120 µg/d x 1 d = 120 µg

$TSL_{>30\ d}$ = 20 µg/d x 30 d = 600 µg

TQ_{max} = 300 µg x 1 = 300 µg

Short-term exposure to the constituent can present a toxicological risk because TQ_{max} is greater than $TSL_{\leq 30\ d}$

Long-term exposure to the constituent is a negligible toxicological risk because TQ_{max} is less than $TSL_{>30\ d}$

Cancer TI Derivation (6.2.3 and C.3)

- Applies to human and suspected human carcinogens
- Acceptable lifetime cancer risk of 1 in 100,000 (10^{-5})
- Two approaches permitted (most appropriate for genotoxic carcinogens)
  - Cancer slope factor approach
    - 1 x 10^{-5}/CSF = TI equivalent to 1 in 100,000 lifetime cancer risk (Cancer Risk Specific Dose (CRSD)

EXAMPLE The lifetime oral cancer risk specific dose for benzene is:

— $SlF = 0{,}015\ (\text{mg/kg/d})^{-1}$[121];

— CRL = 1 in 100 000 (i.e. 1×10^{-5});

— $CRSD = 1 \times 10^{-5} / 0{,}015 = 6{,}667 \times 10^{-4}$ mg/kg/d.

  - TD50 approach
    - TD50/50,000 = TI equivalent to 1 in 100,000 lifetime cancer risk (CRSD)
- Other approaches are permitted if justified and documented.

Topic C
Derivation of Tolerable Intake Values

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Topic C
Derivation of Tolerable Intake Values

Parts of ISO 10993-17:2023 that is covered in this presentation

- Clause 6.2.4. Selection of the point of departure
- Clause 7. Tolerable contact level, tolerable intake and threshold of toxicological concern
- Annex C. Derivation of constituent TI or TCL for select endpoints
- Annex D. Typical Assumptions for Biological Parameters

Requirements

- When a constituent specific POD is available, the selected POD and source (*i.e.*, primary health effect data, supporting data or secondary health effect source) **shall** be documented
- The most critical (*e.g.*, the lowest) clinically relevant POD **shall** be selected.
- When toxicological information is assessed to be inadequate or absent for an identified constituent, the use of TTC (Clause 7.2) or toxicological data from a structural analogue (also known as read-across approach), **shall** be justified and documented

Additional Guidance on Selection of POD included in Clause 7.1

Guidance on Evaluating Data Quality in Annex A

Use of Read-Across: Useful Criteria for Identifying Analogue

When toxicological information is inadequate or absent for identified constituent

Select an analogue based on following

- Similar molecular structure (Tanimoto/similarity score, Fingerprints can be useful)
- Similar physical and chemical properties
- Similar biological properties (*e.g.*, metabolic pathways)

Requirements

- Selection of a structural analogue **shall be justified and documented**. Alternatively, TTC can be used to address genotoxicity, carcinogenicity, systemic toxicity, or reproductive or developmental toxicity as described in 7.2

7 Tolerable contact level, tolerable intake and threshold of toxicological concern

7.1 Derivation of TCL and TI

Deriving a TI or TCL…first determine if POD is available

- When available, a constituent's POD is used to derive a TCL or TI value for each constituent. The TCL (*i.e.*, for irritation) or TI (*i.e.*, for genotoxicity, systemic toxicity, carcinogenicity, or reproductive or developmental toxicity) used **shall account for the duration** for which constituent exposure is assessed.
- When multiple NILs or NOAELs are available that apply to the **same harm and same clinically relevant exposure scenario**, the highest NIL or NOAEL can be used to derive the TCL or TI, respectively. When toxicological data are of mixed quality, the TCL or TI shall be based on the study with the highest quality data
- For different harms, lowest POD shall be used.

Annex C: Derivation of constituent TI or TCL for select endpoints

Annex D: Contains biological information that may be useful (*e.g.*, converting the units of a selected PoD when route-to-route differences exist).

When a threshold for a constituent is available for other applications (*e.g.*, pharmaceutical, food, occupational, environmental).....

1. applicability of the threshold for the duration and type of medical device body contact **shall be** justified and documented
2. additional UF(s) should be applied when the approach used to derive the threshold does not address all of the sources of uncertainty that reflect the circumstances of exposure applicable to the intended use of the medical device

Thresholds for other purposes may not be directly applicable to medical devices

Annex C
Deriving a TI (non-cancer, or cancer) or TCL For Select Endpoints

Non-Cancer TI, Clause C.2

Point of departure (POD)

- Benchmark dose (BMD_L), or a NOAEL or LOAEL or other value

TI **Shall** Account for…

- Most Sensitive Patient Population (for Device Contact)
- Uncertainty of the data and extrapolation to human exposure

In absence of data, use Threshold of Toxicological Concern (TTC); Clause 7.2

- See Technical Specification TS 21726 - 2019

Note: Where relevant dose-based threshold has been determined by an expert committee or regulatory Agency for non-medical device use; it can be adapted by use of uncertainty factors

Application of Uncertainty Factors

Determination of Uncertainty Factors (UF): Clause C.2.2

Value of each UF **shall** be documented, with justification

Default UFs:

- $UF_{(TI)1}$: 10 for Interspecies Differences among humans (unless otherwise justified)
- For preterm, neonate and very young infants (*i.e.*, 6 months or younger), additional UF of 3 **shall** be applied
- $UF_{(TI)2}$: 10 for Intraspecies Differences (unless otherwise justified)

For Intraspecies variation, a UF can be less than 10 when supported by human data

For Interspecies differences, a UF can be less than 10 when toxicity and toxicokinetic data support similarity

Additional Uncertainty Factors: $UF_{(TI)n}$

Table C.1 — Additional uncertainty factors for consideration in the derivation of a TI

Sources of additional uncertainty	Types of additional uncertainty	$UF_{(TI)n}$	Subclause
Route-to-route	Oral data to dermal application or inhalation to dermal application	1	C.2.2.4.1
	Inhalation to parenteral or inhalation to oral application	1 to 10	
	Oral data to parenteral	1 to 100	
Exposure duration	Subchronic to chronic extrapolation	2 to 6	C.2.2.4.2
	Subacute to chronic extrapolation	6 to 10	
Point-of-departure	LOAEL to NOAEL	3 to 10	C.2.2.4.3
Data applicability	Use of an analogue, state of matter (e.g. gas to solid dose)	1 to 10	
Data quality	Reliability and relevance	1 to 10	

Considerations for each is included in text

Additional Uncertainty Factors: Route to Route (C.2.2.4.1)

- For extrapolation from inhalation to parenteral routes, default UF=10
- Lower or higher UFs can be applied when the extent of absorption is known (*e.g.*, higher absorption can be higher for more volatile organic chemicals vs. non-volatile organic chemicals and metals
- For inhalation to oral, UF of 1 can be applied
- For oral to parenteral, oral bioavailability data can be used (shall be justified with supporting data)
  - 100 if oral bioavailability is <1%
  - 10 if oral bioavailability is ≥1% and <50%
  - 2 if oral bioavailability is ≥50% and <90%
  - 1 if oral bioavailability is ≥90%
  - Oral POD can be extrapolated by multiplying by the percent of oral bioavailability
- In absence of bioavailability, default UF of 10 can be used

Additional Uncertainty Factors: Exposure Duration (C.2.2.4.2)

- For subchronic to chronic exposure extrapolation, default UF=6 (unless otherwise justified)
  - For subacute to chronic exposure extrapolation, default UF=10 (unless otherwise justified)
- UF 10 should be applied when dose-response curve is shallow or unknown
- Higher UFs may be considered when toxicity increases over time and constituents bioaccumulate

Additional Uncertainty Factors: POD, Data Applicability, and Data Quality (C.2.2.4.3)

- Consider uncertainty in applying data from an analogue (read-across) based on extent of structural/biological similarity
- Default UF of 1 for high quality studies; 10 for studies with reduced reliability or relevance
- Examples of when default UF 10 for data quality and relevance can be applied
  - Absence of clinically relevant tox data pertaining to patient population, *e.g.*, repro/dev tox for device used in pregnant women
  - POD obtained from underpowered study (limited number/sex/parameters)

Modifying Factor (C.2.3)

$$MF = UF_{(TI)1} \times UF_{(TI)2} \times UF_{(TI)n}$$

The application of a large MF (*e.g.*, >10 000 for the general population) can overestimate a toxicological risk

In these cases, toxicological risk **shall** be assessed by applying TTC in accordance with 7.2, or further analyse or control the toxicological risk

Derivation of a TCL for irritation (C.4)

- TCL ($\mu g/cm^2$)= NIL / MF_{TCL} (NIL=non-irritating level in $\mu g/cm^2$)
- Uncertainty Factors
  - Intraspecies variation $UF_{(TCL)1}$. Default of 10 unless otherwise justified (but UF of 3 to 9 can be used if justified)
  - Interspecies variation $UF_{(TCL)2}$. Default of 10 unless otherwise justified
  - Uncertainty from quality or relevance of experimental data $UF_{(TCL)n}$
    - When a MIL is used, default UF of 3 shall be applied unless otherwise justified
    - UF of 9 applied when conclusions are drawn based on poorly designed or executed study, or when the amount of relevant constituent specific irritation is limited
- In most cases, an overall modifying factor of 30 or less should be sufficient but can be larger when non-irritating concentrations have not been established

Annex D
Typical Assumptions for Biological Parameters

- For Humans (examples)
  - 70-year lifespan
  - 20 m^3/24 h day air intake (adult)
  - 70 kg body mass for adult men; 60 kg for adult women, or unisex (lower body mass, 50 kg or lower can be used if more conservative approach necessary)
  - 10 kg for children (>1 year to ≤16 years of age); 3,5 kg for infants (<1 year); 1,5 kg for very low birthweight infants; or 0,5 kg for very low birthweight neonates (*e.g.*, preterm neonate);
  - NOTE: In the medical devices intended use is for a wide range of general patients, the use of infant mass (3,5 kg) is sufficiently conservative to calculate the EEDmax for infants and the general population.

Assumptions for other species are also included (*e.g.*, can be helpful calculate a NOAEL in mg/kg/day from a POD in drinking water or feed in animals)

QUESTIONS?

Thank you for participating!

Please attend Part 2 of this webinar series on
Wednesday, January 24, at 2:00 PM EST

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Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology