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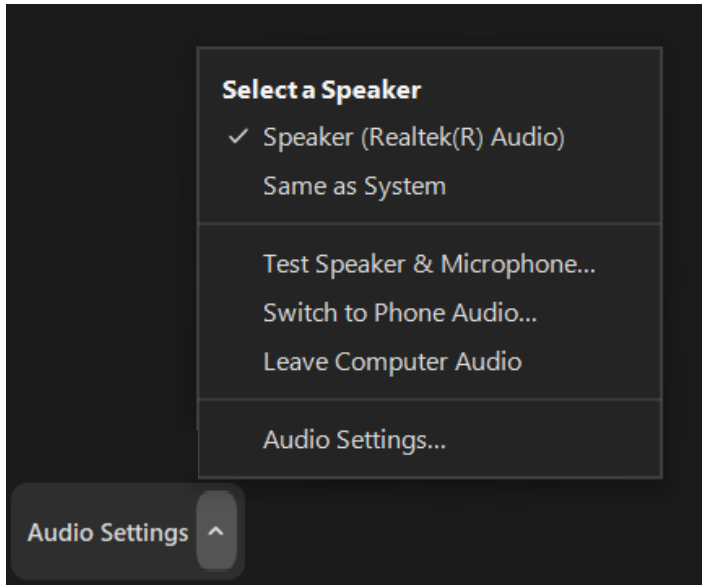

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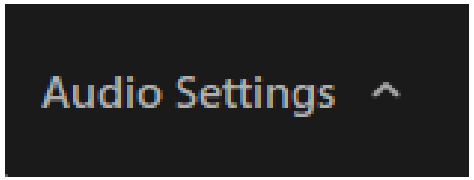

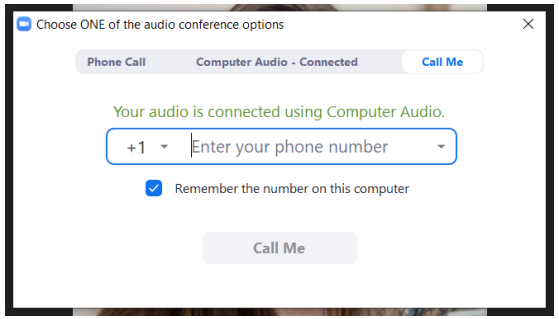

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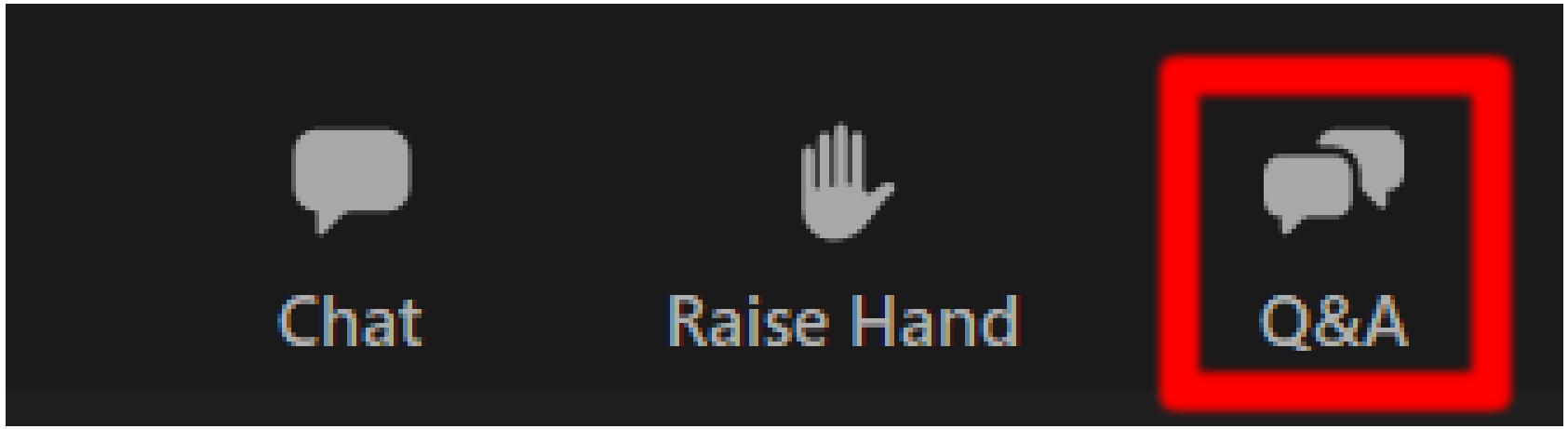


The Q&A will be held after the presentation.

Part 2

Biological Risk Management: Calculating Estimated Exposure Dose and Margin of Safety Values

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

Presenters: Todd Kennedy, Sherry Parker, Alan Hood

January 24, 2024

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

Part 2 Topics

A - Exposure Dose Estimation (Clause 8 and Annex E)

B - Margin of Safety (Clause 9)

C – Toxicological Risk Acceptance Criteria (Clause 10)

Topic A
Exposure Dose Estimation (Clause 8 and Annex E)

Todd Kennedy, PhD DABT

WL Gore & Associates, Inc

Roles in ISO Standard Development Process
US AAMI BE WG 11 Expert
ISO TC 194 WG11 Expert

Exposure Dose (3.7)

exposure dose
quantity of a *constituent* (3.4) that does or can contact the body by an exposure route over a specified time period

Note 1 to entry: The exposure dose is expressed in microgram per kilogram of body mass per day (µg/kg/d) or in microgram per centimetre squared (µg/cm^2).

Note 2 to entry: The exposure dose is different from the absorbed dose. The absorbed dose is the quantity of the constituent that traverses the portal of entry, which is dependent on the absorption rate of the constituent.

Exposure Dose Estimation (8)

- Requirement for each constituent (if not excluded using TSL)
- Two methods described

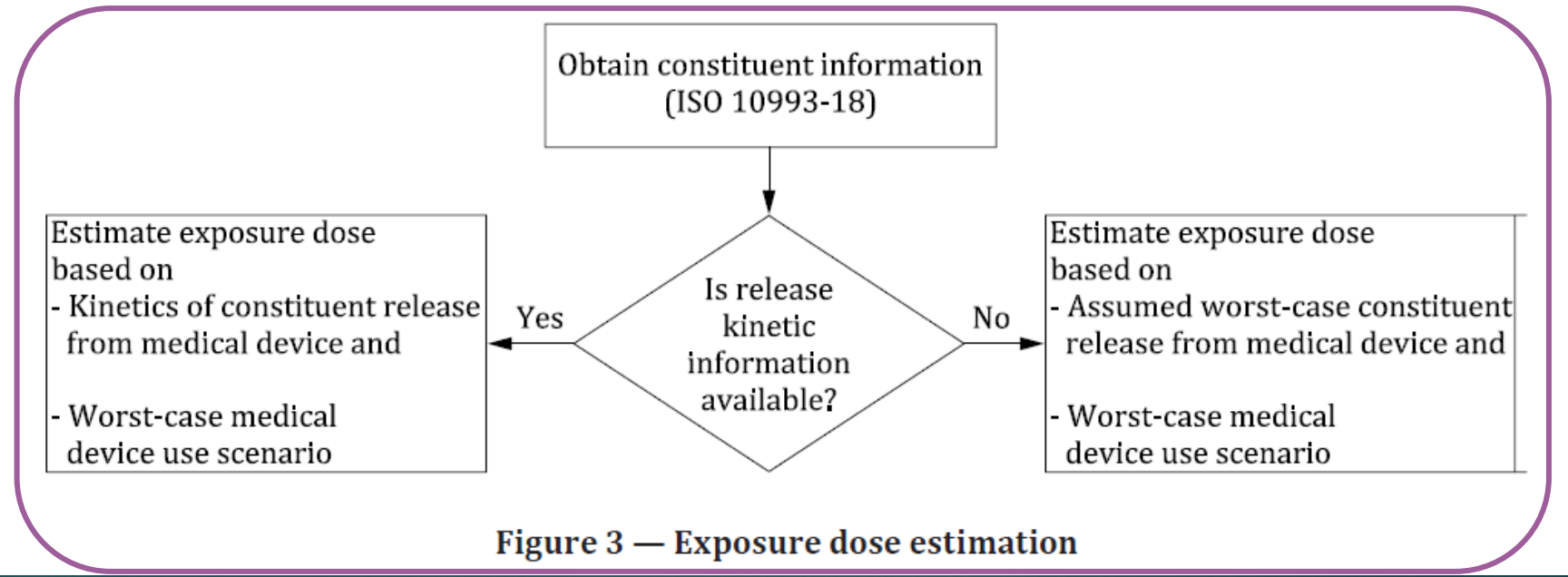


Figure 3 — Exposure dose estimation

Worst-case Exposure Dose

- Worst-case exposure dose is required to be "based on worst-case conditions of the use of the medical device."
  - the type of chemical exposure information relevant to the medical device intended use
  - the largest possible number or quantity of the medical device to which an individual can be exposed in accordance with the medical device intended use, unless otherwise justified
  - the lowest body mass of individuals who can be exposed to the constituent

Worst-case Exposure Dose

- If applicable to the device, requirement to use body mass specific to individuals with unique susceptibilities (e.g. neonates)

- Requirement to account for the maximum number and quantity of medical devices that simultaneously contact the body relative to the chemical characterization data.

Exposure Dose

- The specific medical device use assumptions that are used to calculate an exposure dose shall be justified and documented.

- The method used to calculate an exposure dose shall be in accordance with Annex E. The application of additional assumptions and calculations used in the calculation shall be justified and documented.

NOTE 3 The exposure dose is expressed in the same unit as the TI (i.e. as µg/kg/d) or TCL (i.e. µg/cm^2).

NOTE 4 Exposure on a day can occur intermittently, continuously for a portion of the day or continuously for the entire day. In all these cases, the exposure dose is reported on a per day basis.

Estimation of an exposure dose (Annex E)

A worst-case estimated exposure dose, EEDmax, for each reportable constitutent shall be estimated in accordance with this annex, based on ISO 10993-18 constituent data, unless otherwise justified with supporting evidence.

ISO 10993-18 constituent data includes:

- Information gathered from suppliers and literature
- Exaggerated, exhaustive, or simulated-use extractions

All can be used to represent the Total Quantity of a constituent as long as it is conservative relative to the medical device intended use and justified.

Estimation of an exposure dose (Annex E)

- When not using TSL, calculate EEDmax for the following time periods based on device contact category:

Device Contact Category	Time Period			
	< 1 d	2 d – 30 d	31 d – 365 d	≥ 366 d
Limited	X	NA	NA	NA
Prolonged	X	X	NA	NA
Long-term	X	X	X	X

Estimation of an exposure dose (Annex E)

- When using TSL and the $TSL_{\leq 30\ d}$ is exceeded but $TSL_{>30\ d}$ is not, then calculate EEDmax for the following time periods based on device contact category:

Device Contact Category	Time Period			
	< 1 d	2 d – 30 d	31 d – 365 d	≥ 366 d
Limited	X	NA	NA	NA
Prolonged	X	X	NA	NA
Long-term	X	X	NA	NA

Estimation of an exposure dose (Annex E)

- When using TSL and the both TSLs are exceeded, then calculate EEDmax for the following time periods based on device contact category:

Device Contact Category	Time Period			
	< 1 d	2 d – 30 d	31 d – 365 d	≥ 366 d
Limited	X	NA	NA	NA
Prolonged	X	X	NA	NA
Long-term	X	X	X	X

Estimation of an exposure dose (Annex E)

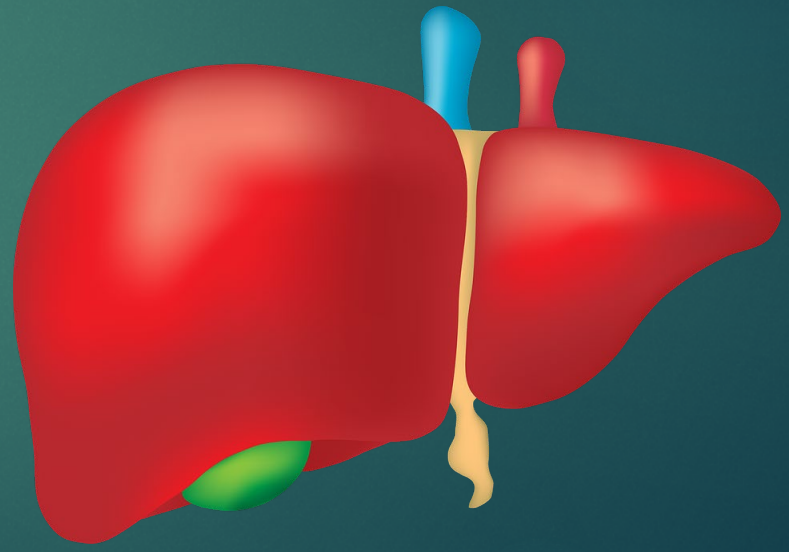
- "When two or more constituents elicit the same harm at the same target organ or system and have the same TI, the individual estimated exposure doses for each of the applicable constituents shall be summed."

Constituent A
TI = 20 µg/kg/day

cholestasis

Constituent B
TI = 20 µg/kg/day

cholestasis



Exposure Dose Estimation (8)

- Requirement for each constituent (if not excluded using TSL)
- Two methods described

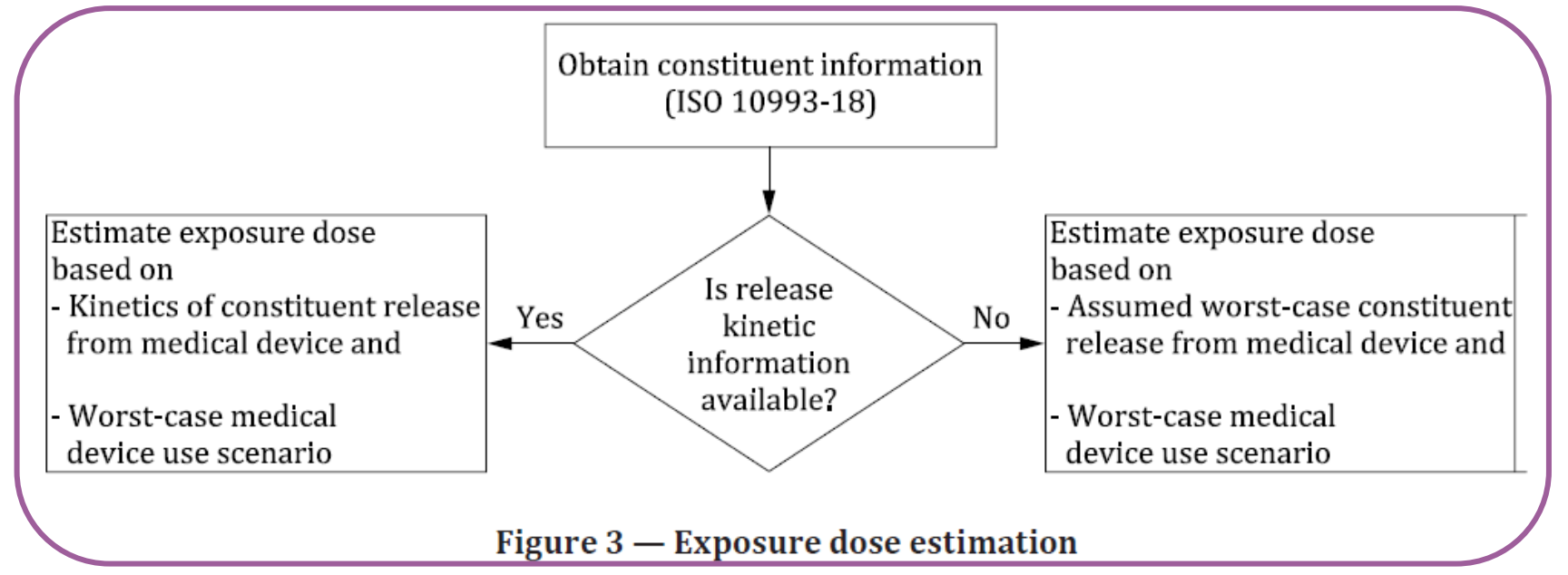


Figure 3 — Exposure dose estimation

Exposure dose estimation based on release kinetics information (E.2)

Exposure dose estimation based on release kinetics information shall be applied to identified constituents using a reference standard suitable for accurate quantification and targeted chemical analysis.

$$(E.1)\ EEDmax = (HQ_{r.k.} \times SF_{r.k.}) / BW_L$$

$HQ_{r.k.}$ is the highest measured quantity, in µg/d, released in a day during a release kinetics study

$SF_{r.k.}$ is the ratio of the number or quantity (in cm^2, g or ml) of medical devices that are in contact with the body divided by the number or quantity of medical devices used in the extraction study

BW_L is the lowest body mass, in kg, of an individual in contact with the medical device

Exposure dose estimation based on release kinetics information (E.2)

- The selection of specific time periods used for $HQ_{r.k.}$ evaluation shall be documented and justified with the medical device category and applicable time periods in accordance with Table E1:

Device Contact Category	**Time Period**			
	< 1 d	2 d – 30 d	31 d – 365 d	≥ 366 d
Limited	X	NA	NA	NA
Prolonged	X	X	NA	NA
Long-term	X	X	X	X

Example of Exposure Dose Estimation based on release kinetics

Constituent release is quantified for multiple days (i.e. same device is repeatedly extracted for 24 h using fresh solvent). The medical device intended use information includes the following:
— externally communicating and prolonged contact;
— body contact is daily for 25 d;
— a single medical device is in contact with the body of a patient;
— the test article extracted is a single final medical device of largest configuration;
— used in adults only (BWL = 60 kg, unisex);
— SFr.k. = 1 (i.e. 1 device is used per patient and 1 device was used in the extract)

Time Period, d	Extraction Day	$HQ_{r.k.}$, µg	EEDmax, µg/kg/d	Formula (E.1)
≤ 1	1	12,000	200	200 = (12,000 x 1)/60
2 to 25	2	1,500	25	25 = (1,500 x 1)/60
	3	200	3.3	3.3 = (200 x 1)/60
	4	< LOD	NA	NA

EEDmax = 200 µg/kg/d for ≤ 1 d time period
EEDmax = 25 µg/kg/d for 2 – 25 d time period

Exposure dose estimation based on release kinetics information (E.2)

The number of time points within an exposure period shall be sufficient to address late bolus release of the constituent(s), unless justified with supporting evidence that late bolus release will not occur.

NOTE 2 Late bolus release of a chemical constituent is the release of a higher quantity after the initial or steady-state release. For example, late bolus release of a chemical constituent can occur when the medical device degrades (e.g. wear/corrosion of a material of construction) over multiple days (e.g. prolonged or long-term).

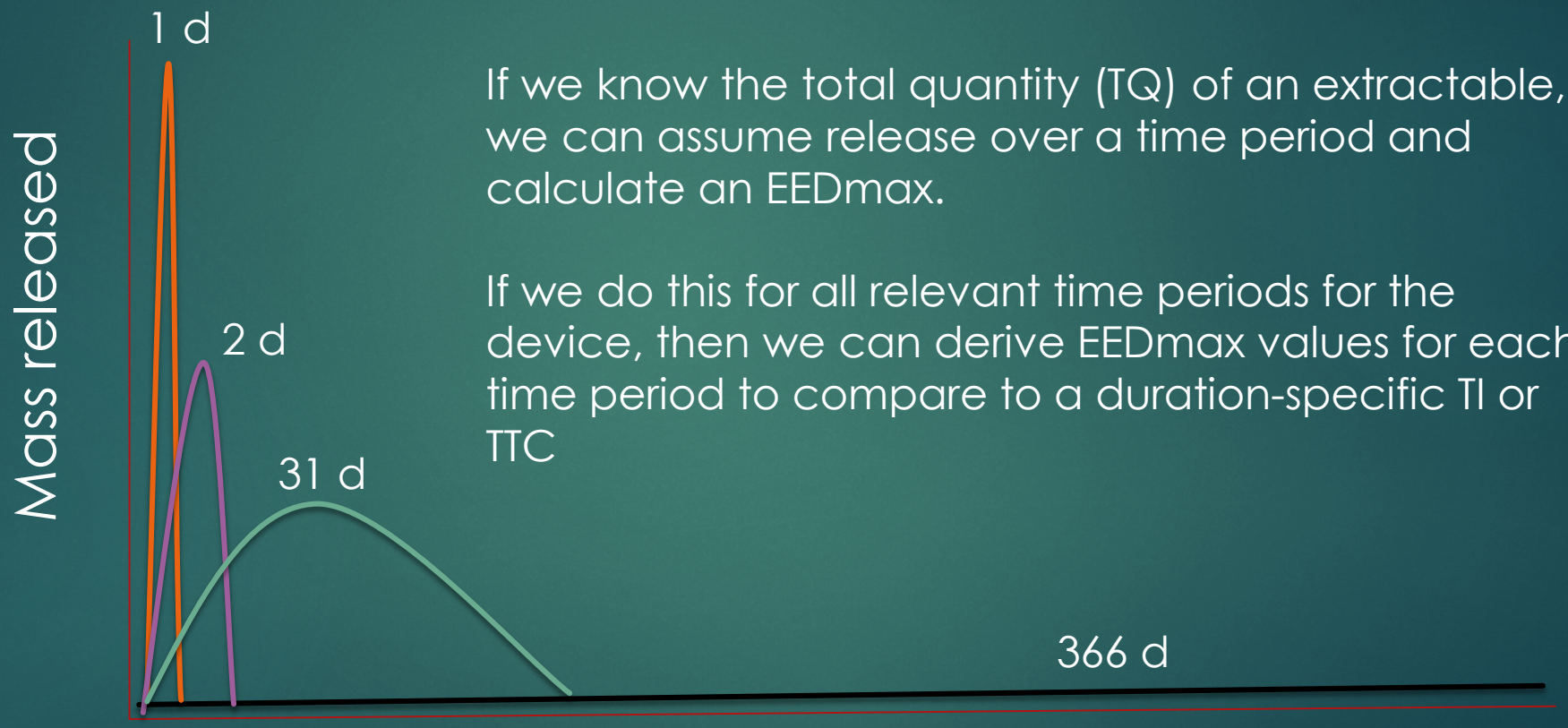
Worst-case exposure dose estimation based on maximum release (E.3)

For many medical devices, it is much easier to measure the total quantity (TQ) of an extractable than it is to measure EEDmax (µg/kg/day).

Problem statement:

How to calculate EEDmax from TQ without knowing the duration of exposure to an extractable?

Worst-case exposure dose estimation based on maximum release



If we know the total quantity (TQ) of an extractable, we can assume release over a time period and calculate an EEDmax.

If we do this for all relevant time periods for the device, then we can derive EEDmax values for each time period to compare to a duration-specific TI or TTC

Worst-case exposure dose estimation based on maximum release (E.3.1)

When the medical device contact is categorized as prolonged or long-term contact and release kinetics data are not available, the exposure dose can be calculated using Formula (E.3).

(E.3) $EEDmax = (TQ \times SF_{a.r.}) / BW_L / R_d$

TQ is the total quantity, in µg, present in or on, or extracted from the medical device (e.g. from an exaggerated or exhaustive extraction study);

$SF_{a.r.}$ is the scaling factor applied when the assumed release is used;

BW_L is the lowest body mass, in kg, of an individual in contact with the medical device;

R_d is the assumed release duration, in d, (i.e. lowest number of medical device exposure days), considering the ISO 10993-1 exposure category applicable to the medical device.

For limited contact medical devices, calculation of the worst-case estimated exposure dose shall be performed in accordance with Clause E.2.

Worst-case exposure dose estimation based on maximum release (E.3.1)

Assumed (i.e. default) release durations, R_d, shall be applied based on the shortest duration of constituent exposure of each period of assumed exposure, unless otherwise justified with supporting evidence.

Device Contact Category	**R_d for each time period of assumed constituent exposure**			
	≤ 1 d	2 d – 30 d	31 d – 365 d	≥ 366 d
Limited	1	NA	NA	NA
Prolonged	1	2	NA	NA
Long-term	1	2	31	366

Example 1 Long-term Implant (E.3.1)

The medical device information includes the following:

— implanted, tissue or bone, and long-term contact;
— body contact is daily for more than 10 years;
— used in adults only (BW_L = 60 kg)
— up to 2 medical devices can be implanted during a patient's life;
— the medical device configuration with the largest surface area is 150 cm2;
— the test article extracted is representative of the final device with a surface area of 100 cm^2;
— $SF_{a.r.}$ is 3 (i.e. 3 = 2 × 150 / 100);
— TQ present or extracted is 10,000 µg.

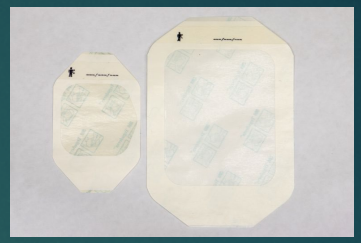
Time Period, d	TQ, µg	R_d, d	EEDmax, µg/kg/day	Formula
≤ 1 d	10,000	1	500	500 = 10,000 x 3/ 60/ 1
2 d – 30 d	10,000	2	250	500 = 10,000 x 3/ 60/ 2
31 d – 365 d	10,000	31	16	500 = 10,000 x 3/ 60/ 31
≥ 366 d	10,000	366	1.4	500 = 10,000 x 3/ 60/ 366

Example 1 (E.3.1)

Time Period, d	TQ, µg	R_d, d	EEDmax, µg/kg/day	Formula
≤ 1 d	10,000	1	500	500 = 10,000 x 3/ 60/ 1
2 d – 30 d	10,000	2	250	500 = 10,000 x 3/ 60/ 2
31 d – 365 d	10,000	31	16	500 = 10,000 x 3/ 60/ 31
≥ 366 d	10,000	366	1.4	500 = 10,000 x 3/ 60/ 366

Each EEDmax value is used to assess toxicological risk for the corresponding time period

Example 2 Single-use device with long-term cumulative exposure (E.3.1)



The medical device information includes the following:

— body contact is in a breached or compromised surface;
— body contact duration of a new medical device is limited (≤24 h);
— cumulative exposure duration from repeat use is more than 30 days (i.e. long-term);
— used in adults only (BW_L = 60 kg);
— five new medical devices are used each day;
— $SF_{a.r.}$ is 1 (5 devices extracted)
— TQ of a constituent present or extracted from the five medical devices is 900 µg.

Time Period, d	TQ, µg	R_d, d	EEDmax, µg/kg/day	Formula
≤ 1 d	900	1	15	15 = 900 x 1/ 60/ 1
2 d – 30 d	900	1	15	15 = 900 x 1/ 60/ 1
31 d – 365 d	900	1	15	15 = 900 x 1/ 60/ 1
≥ 366 d	900	1	15	15 = 900 x 1/ 60/ 1

Example 3 Single-use device with long-term cumulative exposure (E.3.1)

The medical device information includes the following:

— body contact is in a breached or compromised surface;
— body contact duration of a new medical device is 3 days;
— cumulative exposure duration from repeat use is more than 30 days (i.e. long-term);
— used in adults only (BW_L = 60 kg);
— one new medical device per procedure;
— $SF_{a.r.}$ is 1 (1 devices extracted)
— TQ of a constituent present or extracted from one medical device is 1200 µg.

Time Period, d	TQ, µg	R_d, d	EEDmax, µg/kg/day	Formula
≤ 1 d	1200	1	20	20 = 1200 x 1/ 60/ 1
2 d – 30 d	1200	2	10	10 = 1200 x 1/ 60/ 2
31 d – 365 d	1200	2	10	10 = 1200 x 1/ 60/ 2
≥ 366 d	1200	2	10	10 = 1200 x 1/ 60/ 2

Example 4 Single-use device with long-term cumulative exposure (E.3.1)

The medical device information includes the following:

— single-use (disposable) medical device in a breached or compromised surface;
— contact duration of a new medical device is 60 days (i.e. long-term);
— cumulative exposure duration from repeat use is more than 2 years;
— used in adults only (BW_L = 60 kg);
— 1 new medical device is used per procedure;
— $SF_{a.r.}$ is 1 (1 devices extracted);
— TQ of a constituent present or extracted is 10,400 µg.

Time Period, d	TQ, µg	R_d, d	EEDmax, µg/kg/day	Formula
≤ 1 d	10,400	1	173	173 = 10,400 x 1/ 60/ 1
2 d – 30 d	10,400	2	87	87 = 10,400 x 1/ 60/ 2
31 d – 365 d	10,400	31	5.6	5.6 = 10,400 x 1/ 60/ 31
≥ 366 d	10,400	31	5.6	5.6 = 10,400 x 1/ 60/ 31

Alternative method to calculating an EEDmax based on maximum release (E.3.2)

A common, very conservative method of calculating EEDmax is still allowed.

For example, prior to the 2023 standard you might have calculated:

Exposure = TQ x # of devices / BW_L

Which is equivalent to:

$EEDmax = (TQ \times SF_{a.r.}) / BW_L / R_d$

Where R_d = 1 d for all time periods

Exposure dose estimation of an irritant (E.4)

(E.5) $EEDmax = HQ_i / SA_{ext}$

EEDmax is expressed as µg/ cm^2

HQ_i is the highest quantity, in µg, of an irritant, i, released during a day when release kinetics data are available or assuming release occurs in one day;

SA_{ext} is the body contacting surface area, in cm^2, of the medical device used in the extraction or in the release kinetics study.

Topic B
Margin of Safety (Clause 9)

Sherry Parker, PhD

SParker Toxicology Consulting LLC

Roles in ISO Standard Development Process
US AAMI BE WG 11 Co-Chair
ISO TC 194 WG11 Expert

9.2.1 General Requirements

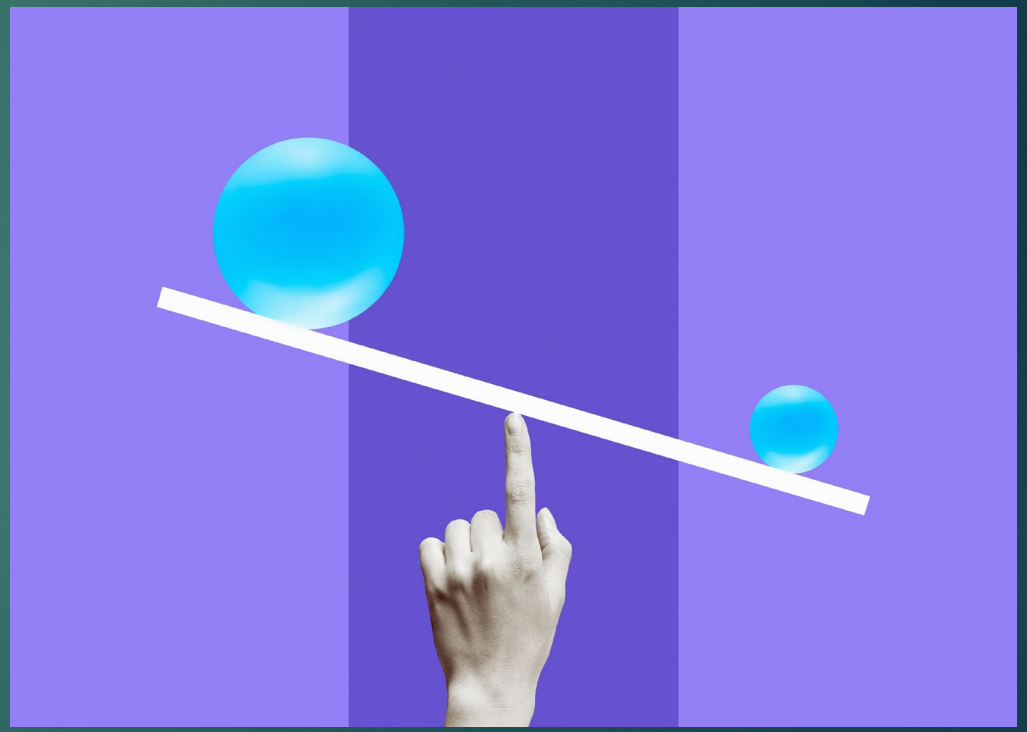
- For each constituent, the estimated exposure dose shall be assessed to be either
  - Without appreciable harm to health, or
  - A harmful dose
- For this toxicological assessment process, a MoS approach shall be used as described in 9.2

An estimated exposure dose can be a harmful dose when the TCL or TI or EEDmax are not conservative

MoS does not apply to biological risks associated with physical interactions of the medical device with the body

Margin of Safety: MoS= $\frac{TI\ or\ TCL}{EEDmax}$

- MoS shall be calculated based on the TI or TCL in accordance with Clause 7; and worst case EEDmax in accordance with Clause 8
  - Note: TCL applies to irritation; TI applies to systemic toxicity (acute, subacute, subchronic or chronic), genotoxicity, carcinogenicity or reproductive/developmental toxicity



Clause 9 Considerations

- The toxicological risk assessment shall address the quantity **as a function of duration of exposure** to the constituent and associated risks.
  - For example, the ratio of a worst-case estimated exposure dose to a life-time TI is generally protective for acute, subacute, subchronic and chronic systemic toxic effects
- When release kinetics data are available, then the worst-case estimated exposure dose, as described in Clause E.2, shall be used in the derivation of the MoS
  - For example, is the highest measured quantity, in µg/d, released in a day during a release kinetics study for the relevant time periods

MoS Values when release kinetics data are not available

Period of assumed exposure to constituent	Calculation of MoS value for toxicological endpoints to be addressed			
	Acute	Subacute	Subchronic	Chronic
≤ 1 d	X	Not applicable	Not applicable	Not applicable
2 d to 30 d	X	X	Not applicable	Not applicable
31 d to 365 d	X	X	X	Not applicable
≥ 366 d	X	X	X	X

When release kinetics data are not available, MoS values that correspond to acute, subacute, subchronic, and chronic exposure shall be calculated based on worst case exposure (fewest number of exposure days) in each of these exposure periods (unless assumed Rd of 1 regardless of category/duration, which is a worst-case assumption, E.3.2)

NOTE 3 When a POD is unavailable to derive a TI for limited or prolonged exposure (i.e. acute or subacute exposure), a TI that applies to long-term exposure (i.e. subchronic and chronic exposure) can be used to address limited or prolonged exposure duration

Example of MoS Based on Assumed Release Kinetics (Table 2)

Long-term implant with tissue/bone contact (adults); example from Table E.5

Table 2 — Calculation example of MoS based on assumed release for a long-term implant and two TI values

Time period d	TI[a] µg/kg/d	EED_{max}[b] µg/kg/d	MoS	Formula (1)
≤1	60	500	0,12	0,12 = 60 / 500
2 to 30	60	250	0,24	0,24 = 60 / 250
31 to 365	10	16	0,625	0,625 = 10 / 16
≥366	10	1,4	7,14	7,14 = 10 / 1,4

[a] TI values of 60 µg/kg/d and 10 µg/kg/d are derived based on a NOAEL obtained from a constituent specific subacute and chronic, respectively, systemic toxicity studies. Because constituent specific POD data from acute (<1 d) and subchronic (90 d) systemic toxicity studies are unavailable, the TI value applicable to the longer time periods is used (i.e. subacute TI for 2 d to 30 d and chronic TI for >366 d of assumed exposure, respectively).

[b] EED_{max} values are based on the assumed worst-case estimated exposure from Annex E.

The MoS values in Table 2 are evaluated according to Clause 10.

When Release Kinetics Data Not Available (i.e exposure based on assumed release kinetics)

- MoS values that correspond to acute, subacute, subchronic, and chronic exposure shall be calculated based on worst case exposure (fewest number of exposure days) in each of these exposure periods (**unless assumed Rd of 1 regardless of category/duration**, which is a worst-case assumption, E.3.2)
- NOTE 3 When a POD is unavailable to derive a TI for limited or prolonged exposure (i.e. acute or subacute exposure), **a TI that applies to long-term exposure (i.e. subchronic and chronic exposure) can be used to address limited or prolonged exposure duration**

Combining MoS Values to address additivity of harm (adapted from hazard index)

- MoS values, MoS_i, of two or more constituents shall be combined when the following apply:

— exposure to each constituent can occur simultaneously (e.g. Constituents are present in or on, or released from the same medical device);

— the constituents elicit the same harm in the same target organ or system and the same mode of action applies.

$$MOS_{\text{com}} = 1 / \sum_{i=1}^{n} \frac{1}{MOS_i}$$

where

MoS_{com} is the result from the summation of reciprocal MoS_{i} (unitless) values;

MoS_i is the MoS for each (i.e. individual) constituent that results from Formula (1).

When the constituent's critical adverse health effect is not known, then combining MoS values is not required and the MoS value for each constituent is calculated and used individually for toxicological risk assessment.

Topic C

Toxicological Risk Acceptance Criteria (Clause 10)

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ISO TC 194 WG11 Convenor

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Topic C

Toxicological Risk Acceptance Criteria (Clause 10)

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

- **10.1 General**
- **10.2 Further risk analysis or risk evaluation or risk control**

10.1 General

10.1 General

An exposure dose of a constituent is without appreciable harm to health (i.e. tolerable toxicological risk) when the following apply:

— MoS exceeds 1;

— contributing values to the MoS are demonstrated to be conservative.

NOTE 1 Conservative means the estimation of toxicological risk is deliberately higher (i.e. lower MoS) than the probable true risk.

Examples when the values contributing to the MoS are conservative include, but not limited to:

— The method used in the calculation of EED_{max} represents an overestimate of the probable true worst-case estimated exposure dose;

— For each uncertainty factor used in the derivation of the TI (C.2.2 or C.3.2) or TCL (C.4.3), the default value is used.

When the TCL, TI or EED_{max} are not demonstrated to be conservative, the evaluation of the MoS shall be addressed in accordance with 10.2.

When the TCL, TI or EED_{max} are demonstrated to be conservative and when the MoS does not exceed 1 (i.e. a possible toxicological risk), the toxicological risk shall be further evaluated in accordance with 10.2.

MoS values shall be assessed based on expert judgement when exposure dose is based on assumed release as described in Clause E.3 (i.e. release kinetics data are not available).

For a toxicological risk to be judged acceptable, it shall be supported by evidence that assumed release is conservative in relation to the intended use of the medical device.

NOTE 2 Expert judgement can include assessment of the nature of the harm to health as described in Clause 5 and Clause 6.

MoS values, including how each was calculated, and the conclusion of each exposure dose evaluation shall be justified and documented, in accordance with Clause 11.

ISO 10993-17:2023 includes considerations that can help users demonstrate the inputs are conservative (e.g., Clause 7/Annex C and Clause 8/Annex E). ISO 10993-18 also plays a role into the determination that the inputs are conservative as described in E.1 of ISO 10993-17:2023.

10.2 Further risk analysis or risk evaluation or risk control

10.2 Further risk analysis or risk evaluation or risk control

Toxicological risk shall be further addressed by other means in accordance with ISO 10993-1 and ISO 14971 when any of the following apply:

— the MoS is below 1 based on release kinetics in Clause E.2, and TI or TCL are used,

— the cancer risk of a human carcinogen or suspected human carcinogen exceeds 1 in 100 000, or

— the MoS is judged to represent possible toxicological risk.

NOTE 1 When constituent exposure is understood, an MoS below 1 generally indicates a possible or probable toxicological risk.

Further risk analysis, risk evaluation or risk control can consider information that addresses:

— the dose of a constituent that will elicit harm (e.g. LOAEL),

— the relevance of the exposure dose to the intended use of the medical device (e.g. refinement of the EED_{max}), or

— if risk control is not practical and information is available that demonstrates the expected benefit of the medical device outweighs the toxicological risk.

For example, exposure is reduced as low as reasonably practicable and cancer risk is actively managed using risk management procedures as described in ISO 14971.

Outcomes of further risk analysis or risk evaluation or risk control shall be documented in accordance with ISO 10993-1 and ISO 14971.

1st Bullet – indicates that the dose-response curve (if available) can be useful for further estimating or evaluating toxicological risk.

2nd Bullet – indicates that additional analytical chemistry data can address issues related to relevance of the EED_{max} value.

3rd Bullet – indicates when benefit-risk analysis can be helpful.

QUESTIONS?

Thank you for participating!

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

END
(PART 2)