



Practical Application of the TTC Approach for Compounds Released from Device Materials

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SOT Medical Device and Combination Products webinar
November 16, 2015



Progress on development of ISO Technical Specification

- ISO TC194 WG11 met in Lund, Sweden in June, 2015
- Delegates participated in a significant discussion of issues relating to revision of: *Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of extractable substances from medical devices*



Biocompatibility testing approaches for medical devices

Toxicity testing of extracts



Chemical characterization



Major limitations to implementing the chemical characterization/risk assessment approach are: 1) the lack of toxicity data for many of the compounds released from medical devices, 2) need for toxicologically relevant limits of detection for analytical techniques.



Issues discussed in Lund

- **How can we use TTC values for the safety assessment of compounds released from device materials?**
- **Are TTC values derived from distributions of oral toxicity/carcinogenicity appropriately protective for other routes of exposure?**
- **Should we use one set of TTC values to assess both cancer- and noncancer effects?**
- **Are TTC values applicable for constituents of a mixture?**



How can we use TTC values for the safety assessment of compounds released from device materials?

(Lund draft, June 2015)

- *as default Tolerable Intake (TI) values when adequate toxicity data are not available to derive a TI value for a compound using the approach outlined in ISO 10993-17,*
- *as a screen to determine the need for additional chemical characterization and toxicological evaluation of compounds extracted from a device or materials, including unknown compounds,*
- *to establish toxicity-based thresholds for determining appropriate analytical limits for compounds extracted from medical devices or materials, and*
- *to establish the toxicological equivalence between two devices or materials.*

[illegible]



Applicability of TTC to assess various toxicological endpoints (Lund draft, June 2015)

This document does not apply to the evaluation of local effects that may occur in tissues at the site of contact between a device and the body. In addition, the values do not apply to the evaluation of endpoints such as cytotoxicity, irritation, implantation, [sensitization], and hemocompatibility that may need to be assessed as part of the biological evaluation of a device, per ISO 10993-1.



Issues discussed in Lund

- How can we use TTC values for the safety assessment of compounds released from device materials?
- Are TTC values derived from distributions of oral toxicity/carcinogenicity appropriately protective for other routes of exposure?
- Should we use one set of TTC values to assess both cancer- and noncancer effects?
- Are TTC values applicable for constituents of a mixture?

ICH M7 Draft Consensus Guidance (2013)

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

The above risk approaches are applicable to all routes of administration and no corrections to acceptable intakes are generally warranted. Exceptions to consider may include situations where data justifies route-specific concerns that need to be evaluated case-by-case. These approaches are also applicable to all patient populations based upon the conservative nature of the risk approaches being applied.



Route of exposure considerations (Lund draft)

- *The TTC values described in Table 1 are based on potency values derived from oral carcinogenicity studies; nevertheless, these values are applicable for other routes of exposure, including parenteral routes such as intravascular exposure.*
- *Although route-to-route extrapolation of dose is typically necessary when oral toxicity data are used to establish TI values for parenteral routes exposure, in the absence of toxicity data from a clinically relevant route, such an extrapolation technique is not necessary to convert the TTC values in Table 1 to equivalent parenteral TTC values. Adjusting the TTC values in Table 1 for oral bioavailability would add little additional safety to these already conservative values, as a result, they are intended to be protective for patient exposure to the compounds by both oral and parenteral routes of exposure.*
- *Separate TTC values are under development for inhalation exposure to compounds released into the gas pathway of respiratory devices. The values in Table 1 are not intended to be protective for patient exposure by dermal, intraocular, or intracranial exposure to compounds released from devices.*

Internal threshold of toxicological concern values: enabling route-to-route extrapolation

Falko Partosch · Hans Mielke · Ralf Stahlmann ·
Burkhard Kleuser · Susan Barlow ·
Ursula Gundert-Remy

Table 3 Internal TTC values ($\mu\text{g/kg bw/d}$) derived from the merged databases (Munro, ELINCS, FCM)

Origin of TTC value	Internal TTC value for Cramer class I ($n = 287$) in $\mu\text{g/kg bw per day}$	Internal TTC value for Cramer class II/III ($n = 1,289$) in $\mu\text{g/kg bw per day}$
Based on 5th percentile of the distribution of the NOAELs (corrected for bioavailability)	6.9 3.8–11.5	0.1 0.08–0.14
Based on 10th percentile of the distribution of the NOAELs (corrected for bioavailability)	38.6 31.5–40.5	1.5 1.2–1.9

	Cramer class I ($\mu\text{g/day}$)	Cramer class II/III ($\mu\text{g/day}$)
5th percentile	483 (1800*)	7 (90*)
10th percentile	2702	105

* Munro et al. (1996)

Development of inhalation TTC values for volatile compounds released from respiratory devices



- Patients can be exposed to volatile organic compounds (VOCs) released from plastic materials used in the breathing circuit of respiratory devices, like ventilators.
- Efforts are underway to develop inhalation TTC values for volatile compounds released from device materials.



Derivation of inhalation TTC values

Regulatory Toxicology and Pharmacology 58 (2010) 259–274



Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



Evaluation of inhalation TTC values with the database RepDose

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Table 3

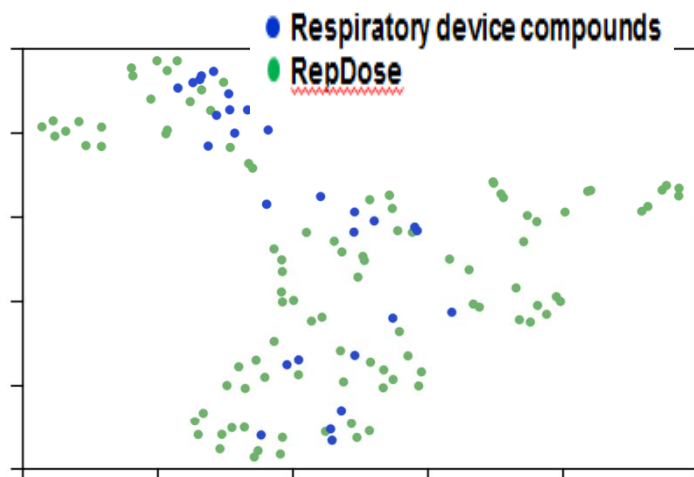
Overview on current TTCs derived for consumer.

Dataset	Route	Type	Unit	N	TTC for Cramer class	
					1	3
RepDose	Inhalation	General	ppm [*] mg/m ^{3*} µg/person/d	136 [*] (203)	3.6×10^{-3} (1.5×10^{-3}) 8.9×10^{-3} (3.6×10^{-3}) 180 (71)	2.4×10^{-5} (2.2×10^{-5}) 1.8×10^{-4} (1.8×10^{-4}) 4 (4)
Carthew et al. (2009)	Inhalation	Local	µg/person/d	92	200	67
		Systemic	µg/person/d	92	980	170
Munro et al. (1996)	Oral	General	µg/person/d	611 ^{***}	1800	90

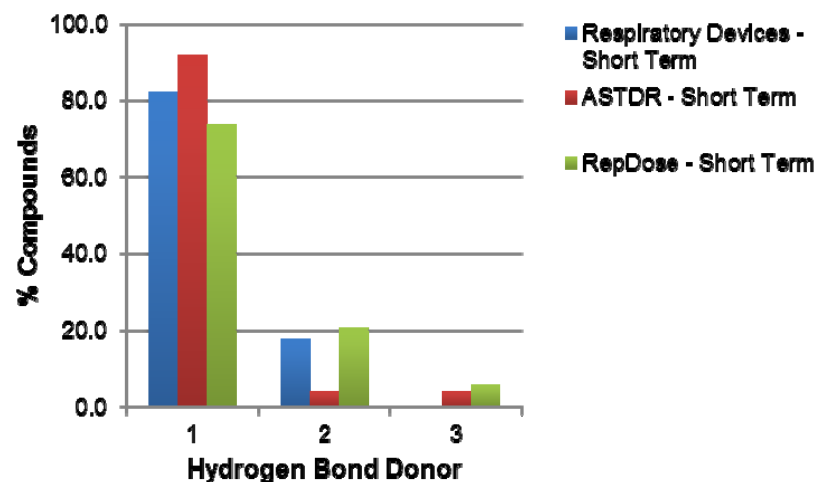
Chemical space analysis of inhalation data sets

Chemical space analysis of compounds used in respiratory devices vs. compounds in RepDose database (modified to exclude pesticide, drugs)

Structural comparison using StarDrop software



Physicochemical property comparison





Proposed inhalation TTC values for compounds released from device materials

Short-term TTC values (< 30 days)

Exposure Population	RepDose ($\mu\text{g/day}$)	ATSDR acute MRL ($\mu\text{g/day}$)	Texas ESL ($\mu\text{g/day}$)	OEHHA REL ($\mu\text{g/day}$)
Adult	279.4	317.2	48	20
Child	20	34.9	5.3	3.6
n	108	27	55	5

Long-term TTC values (≥ 30 days)

Exposure Population	RepDose Escher et al. ($\mu\text{g/day}$)	EPA RfC ($\mu\text{g/day}$)	ATSDR MRL ($\mu\text{g/day}$)	Texas ESL ($\mu\text{g/day}$)	OEHHA REL ($\mu\text{g/day}$)
Adult	4*	9.6	43.3	10.4	14.0
Child		1.1	4.8	2.1	2.8
n	203	67	23	55	52

Exposure Population	Long-term noncancer based TTC ($\mu\text{g/day}$)	Short-term noncancer based TTC ($\mu\text{g/day}$)
Adult	10	300
Child	1	20



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- **Should we use one set of TTC values to assess both cancer- and noncancer effects?**
- Are TTC values applicable for constituents of a mixture?



Should we use one set of TTC values to assess both cancer- and noncancer effects? (Lund draft, June 1025)

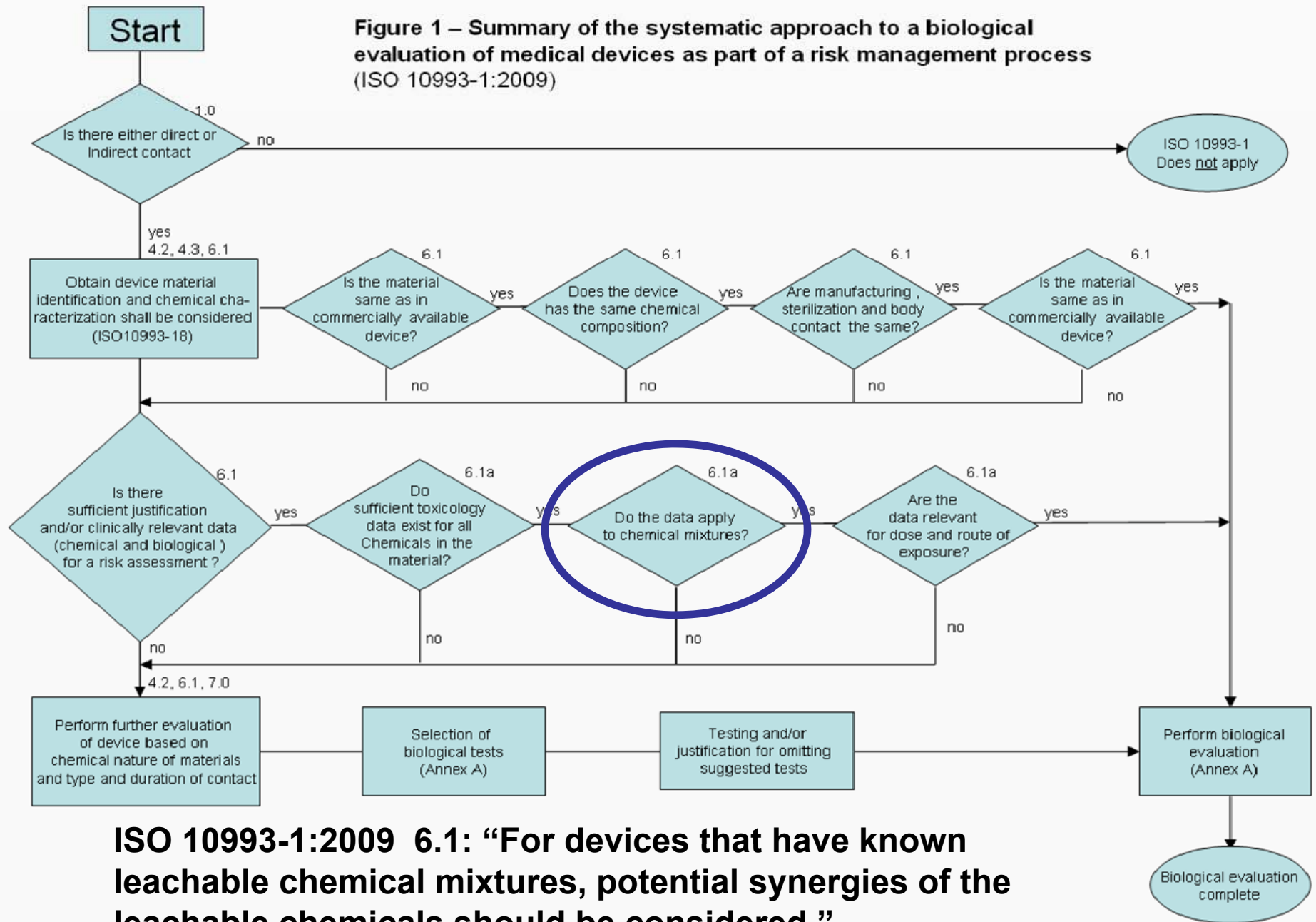
- *The TTC values defined in this Technical Specification are based on the Acceptable Daily Intake values derived by the ICH (2015) for individual mutagenic impurities in pharmaceuticals. The threshold value derived by ICH for mutagenic impurities in the longest exposure duration category (1.5 µg/day) is lower than the threshold value assigned to the most conservative and protective Cramer Class of noncarcinogenic compounds (90 µg/day), which is also intended to be protective for lifetime exposure. Therefore, use of the threshold values established by ICH for mutagenic impurities is presumed to be protective for both the potential carcinogenic and noncancer effects that may occur following patient exposure to compounds released from medical devices.*
- *Alternately, if experimental data or model-derived predictions suggest that the compound is not likely to have carcinogenic effects (e.g., negative genotoxicity data or negative results in at least two computational models that operate using different approaches – expert system-based and statistically based), then the user of the Technical Specification can categorize their compound into its appropriate Cramer Class and use the threshold value for that category as the noncancer-based TTC value for the compound.*



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Figure 1 – Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process (ISO 10993-1:2009)



ISO 10993-1:2009 6.1: “For devices that have known leachable chemical mixtures, potential synergies of the leachable chemicals should be considered.”

Chemical Mixtures: Current Risk Assessment Methodologies and Future Directions

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Limited, yet compelling, data are reviewed that suggest that for noncancer endpoints, adverse effects are unlikely to occur when the individual components in the mixture are present at levels well below their respective thresholds. Synergistic or antagonistic effects, not readily predicted from the mechanisms of action of the individual components, are possible when the mixture components are present at levels equal to or above their individual thresholds. Finally,



Assumption of low dose additivity

Feron et al. *Toxicology* 105 (1995) 415-427

“Although generalizations may be scientifically not fully justifiable, a most important practical lesson from these studies is that exposure to a combination of chemicals compared with exposure to the single chemicals does not constitute an evidently increased hazard provided each individual chemical is administered at a level similar to or slightly lower than its own NOAEL.”



Applicability of TTC to compounds in a mixture (Lund draft, June 1025)

Since multiple compounds are used to manufacture, process, and disinfect/sterilize medical devices, the extracts obtained from medical devices and their materials are likely to contain complex mixtures of compounds. The TTC values defined in this document are applicable to individual compounds whether they exist singly in the extract or are components of a complex mixture extracted from the device. Additional steps are not needed to account for the aggregate effects of multiple compounds in a mixture, since toxicological interactions are not expected at the low doses that correspond to the TTC values. However, mixtures risk assessment approaches may be needed if the concentration of the compounds in the extract exceeds their TTC (or TI) value. In that case, guidance on how to conduct a mixtures risk assessment is provided in ISO 10993-17.



ISO 10993-17, Annex B

Annex B (informative)

Risk assessment for mixtures of leachable substances

If the compounds being leached from a device exert their effects via a common toxicological mechanism of action or are structurally similar to one another (e.g., phthalate esters, acrylates, methacrylates), and the dose of these compounds received by a patient is well below the respective TI value for each compound, it can be assumed that any effects will occur in an additive fashion; that is, the combined effects of two or more agents is equal to the sum of the effects of each agent given alone. As a result, a hazard index (HI) approach can be used to estimate the likelihood that adverse effects will occur following exposure to the mixture. An HI can be calculated as follows:

$$HI = \sum_{i=1}^n \frac{dose_i}{TI_i}$$

(B.1)

← Replace with TTC if necessary

where

n is the number of components of the mixture;

$dose_i$ is the dose of each compound received by the patient, in milligrams per day;

TI_i is the tolerable intake, in milligrams per day, of each compound.



TTC values for mixtures ICH M7 Draft Guidance

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	$>1 - 12$ months	$>1 - 10$ years	>10 years to lifetime
Daily intake [$\mu\text{g}/\text{day}$]	120	20	10	1.5

Table 3: Acceptable Intakes for Total Impurities

Duration of treatment	≤ 1 month	$>1 - 12$ months	$>1 - 10$ years	>10 years to lifetime
Daily intake [$\mu\text{g}/\text{day}$]	120	60	10 (30*)	5



Additional issues discussed in Lund related to the application of TTC to compounds released from device materials

- **Application of TTC to unknown compounds**
- **Use of TTC values to assess the safety of compounds extracted using exhaustive or exaggerated extraction conditions**

Application of TTC concept to unknowns

Certain highly potent compounds (nitrosamines, polycyclic aromatic hydrocarbons, etc.) are exempt from the TTC.

Proposal was discussed in Lund for application of a step-wise approach to screen unknowns for their likelihood to be members of excluded classes, similar to Koster et al.

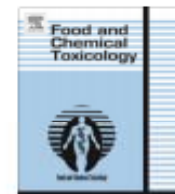
Food and Chemical Toxicology 49 (2011) 1643–1660



Contents lists available at [ScienceDirect](#)

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox



Review

Application of the TTC concept to unknown substances found in analysis of foods

Sander Koster^a, Alan R. Boobis^b, Richard Cubberley^c, Heli M. Hollnagel^d, Elke Richling^e,
Tanja Wildemann^{f,*}, Gunna Würtzen^g, Corrado L. Galli^h



Use of TTC values when exaggerated or exhaustive extraction is performed (Lund draft, June 2015)

- Use existing TTC value in units of $\mu\text{g}/\text{day}$ if clinically relevant 24-hour extraction is performed.
- *Alternately, it is possible to use the TTC approach when exaggerated or exhaustive extraction of the device provides information on the total amount of the compound(s) present on the device. It is possible to derive a TTC value for the total amount of compound on the device using the TTC values for each duration category in Table 1 by identifying the most conservative (lowest) value that is the product of the TTC in units of mass/day and the lowest number of days in the exposure category. When this exercise is performed, the lowest cumulative TTC value is $120 \mu\text{g}/\text{device}$. This value is obtained from the product of the TTC value for Limited Exposure Devices ($120 \mu\text{g}/\text{day}$) and the smallest number of days in that exposure category (1 day).*



Summary

Issues discussed in Lund

- How can we use TTC values for the safety assessment of compounds released from device materials?
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