The need to identify unknown E&Ls from a risk assessment perspective

Nelson Labs Open House

2020 The Year Of Change for the Medical Device Industry

Leuven, Belgium

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Disclaimers

- I'll be sharing some thoughts on the need to identify unknown E&L compounds released from medical device materials. These approaches are not necessarily valid for compounds released from pharmaceutical packaging or other products.

- I have recently retired from the US FDA, but the thoughts expressed in the presentation are strictly my own and do not necessarily represent the official position of the FDA.

Overview

- What are the implications of not identifying compounds with a high degree of confidence for the toxicological risk assessment?
- What are some recent proposals to evaluate the safety of unidentified and partially identified E&L compounds released from medical device materials?

Overview

- **What are the implications of not identifying compounds with a high degree of confidence for the toxicological risk assessment.**

- **What are some recent proposals to evaluate the safety of unidentified and partially identified E&L compounds released from medical device materials?**

Regulatory Toxicology and Pharmacology 97 (2018) 134–143

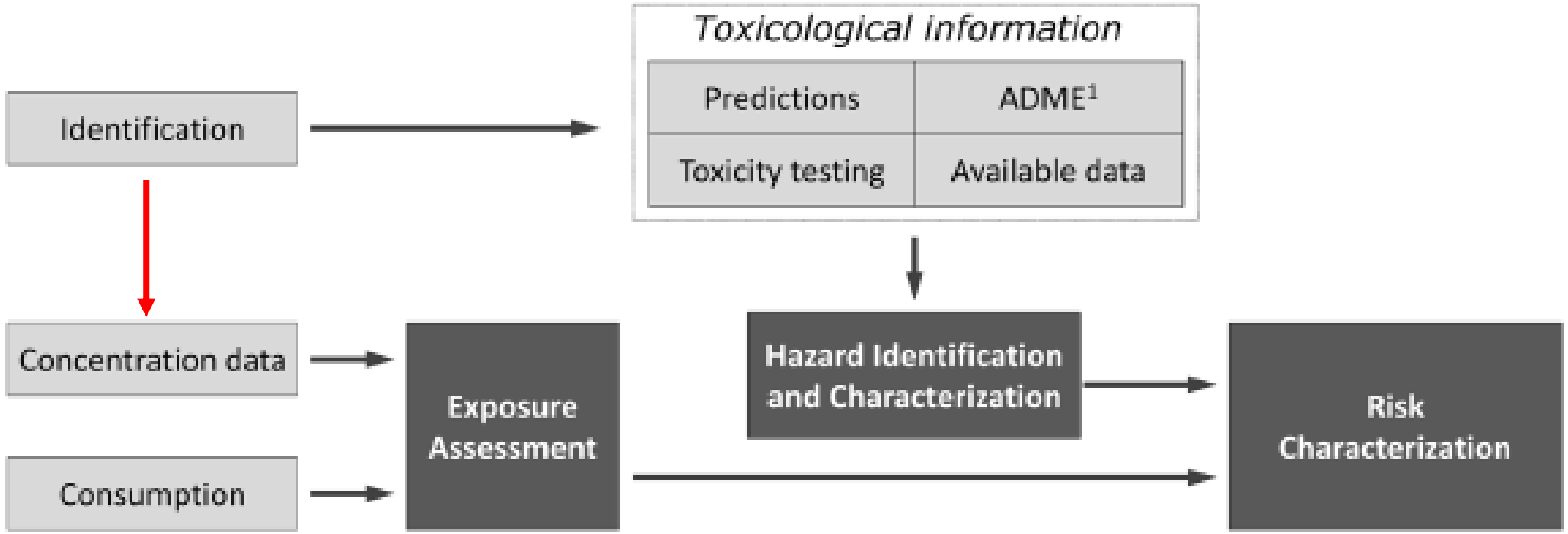
Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Prioritization before risk assessment: The viability of uncertain data on food contact materials☆

Eelco N. Pieke[a,*], Kit Granby[a], Bruno Teste[b], Jørn Smedsgaard[a], Gilles Rivière[b]



Impact on the toxicological risk assessment

- Implications of not identifying compounds with a high degree of confidence.
- Implications of misidentifying compounds.
- Implications of not uniquely quantifying compounds.

Implications of not identifying compounds with a high degree of confidence

PDA Journal
of Pharmaceutical Science and Technology

Identifying and Mitigating Errors in Screening for Organic Extractables and Leachables: Part 2—Errors of Inexact Identification and Inaccurate Quantitation

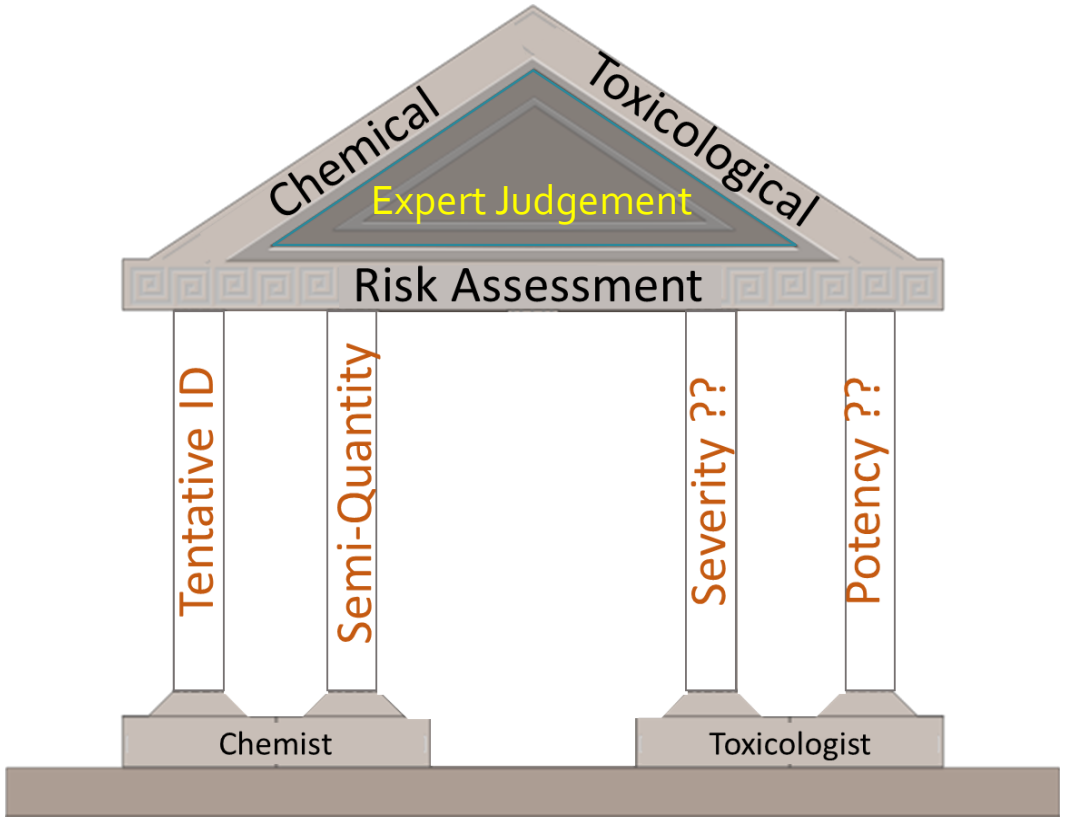
Piet Christiaens, Jean-Marie Beusen, Philippe Verlinde, et al.

PDA J Pharm Sci and Tech **2020**, *74* 108-133
Access the most recent version at doi:10.5731/pdajpst.2018.009779

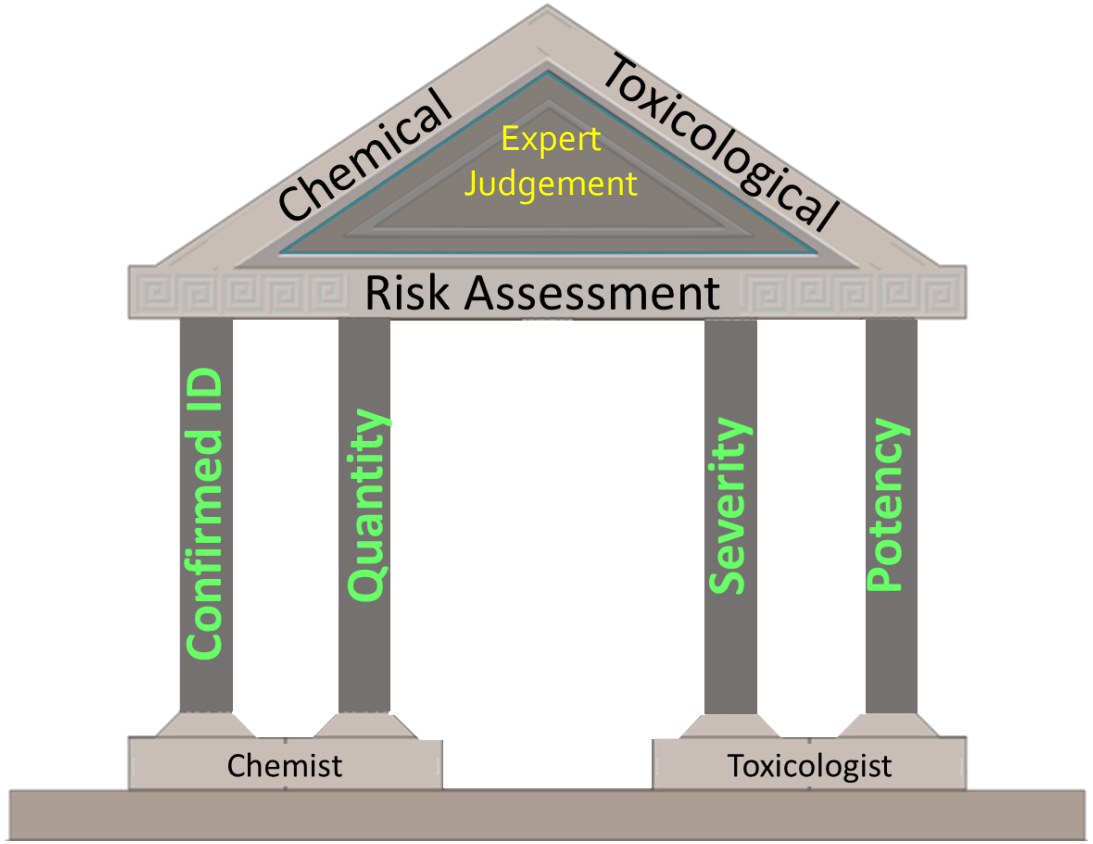
Considering safety, for example, it is the extractable's identity that links the extractable to its relevant toxicological safety information. Clearly, if an identity cannot be secured or if the secured identity is incorrect (errors of inexact identification), then either the assessment cannot be performed or the assessment that is performed is faulty.

Clearly, inaccurate quantitations lead to erroneous safety assessments that either underestimate or overestimate the safety hazard.

Identification, Expert Judgement and Toxicological Risk Assessment

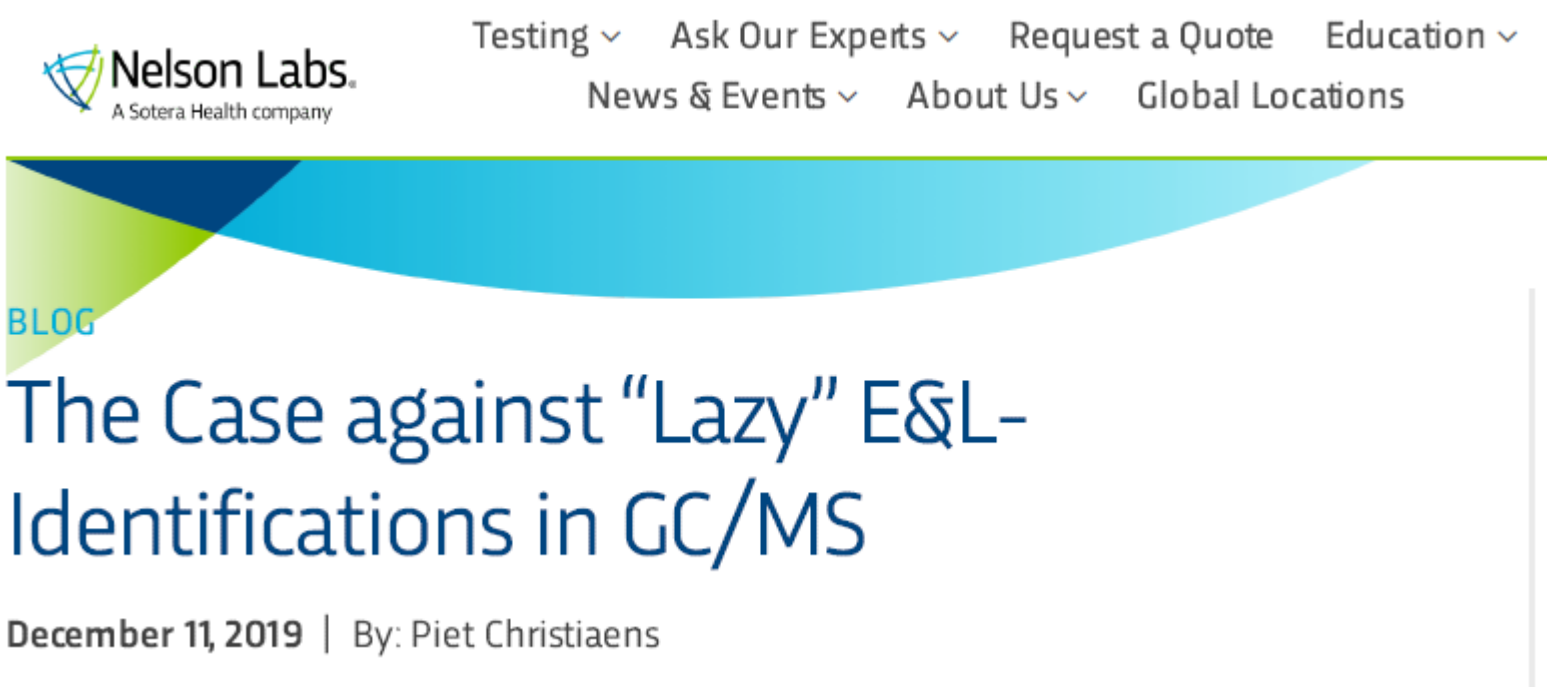


Less work, more uncertainty



More work, less uncertainty

Slide courtesy of Dr. Alan Hood, US FDA



Toxicologists are becoming increasingly aware that chemical analysis is not a trivial procedure.

This paper describes some practical steps to improve the identification and quantification of E&L compounds.

https://www.nelsonlabs.com/the-case-against-lazy-el-identifications-in-gc-ms/

What does the working draft of ISO 10993-17 say about the need to identify compounds?

Utilization of analytical instruments of high sensitivity can result in detection of non-targeted extractables in sufficient number to present a challenge for the analyst to elucidate each extractable's molecular structure, especially when the extract is a complex mixture containing numerous structurally similar extractables (e.g., mineral oil or phthalates), and/or extractable(s) are unexpected). Thus, a toxicological risk assessment of a non-targeted extractable with uncertain identity may be necessary.

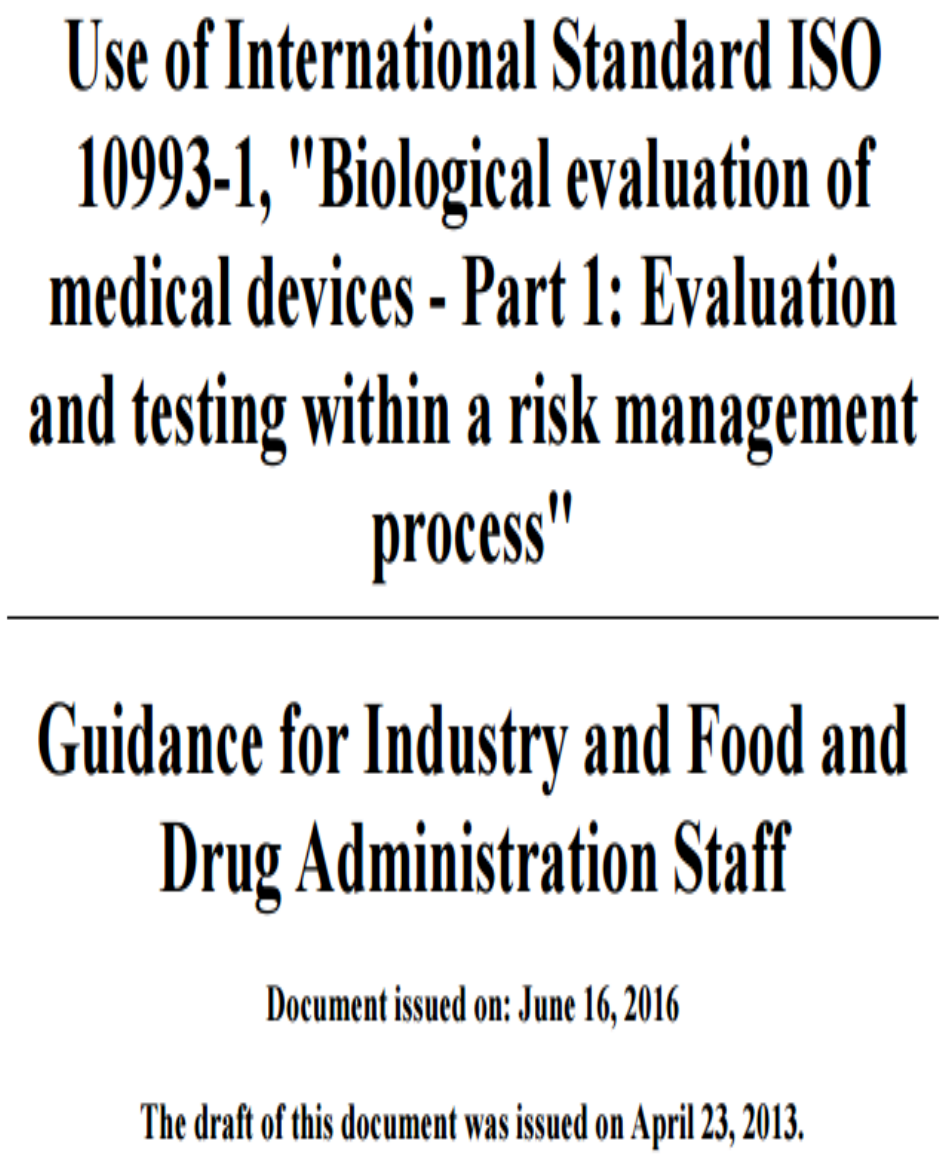
Use of TTC as a screening tool for identifying E&L compounds

TTC – Threshold of Toxicological Concern

Dose below which adverse systemic effects are not expected for most compounds.

Serves as the basis for the AET

- Can be used to prioritize E&L compounds for identification.
- No need to identify compounds released from the device at levels < AET.
- Can also be used as a default Tolerable Intake (TI) for compounds lacking toxicity data to derive a compound-specific TI.



CDRH Biocompatibility Guidance provides FDA's interpretation of the ISO 10993-1 standard on how to conduct a biological safety evaluation of devices.

The TTC approach can be used to determine if quantification without chemical identification is sufficient to assess the toxicity risk of the device. Otherwise, chemical identification is needed.

Section G. Carcinogenicity

https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

What does the working draft of ISO 10993-17 say about the need to identify compounds?

The process described in this Standard is not intended to apply to:

- ***Medical device constituents that do not contact the body (e.g., in vitro diagnostic devices).***
- ***Medical device constituents with unknown identity that are extracted at an amount below an established analytical threshold, see ISO 10993-18:2018***

Information on the following slides comes from a recent FDA webinar

U.S. FOOD & DRUG ADMINISTRATION

CDRH Scientific Perspective on Chemical Analysis and Toxicological Risk Assessment for Medical Devices

Presenters: Berk Oktem, Alan Hood, Jennifer Goode

Co-authors: Eric Sussman, Samanthi Wickramasekara

SOT-MDCPSS Webinar, May 22, 2019

Society of Toxicology Medical Device Combination Products Specialty Section
https://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp

How important is identification in toxicological risk assessment of medical device extractables?

Background

- Textbook toxicological risk assessment method assumes identity of the chemical/compound of interest is known
- When screening for non-targeted extractables, identification of extractables can be challenging for the analytical chemist
  - Especially for extractables unexpected to be present
  - When spectra data of an unexpected analyte does not have a clear library match or no match at all

How important is identification in toxicological risk assessment of medical device extractables?

Background

- Analytical approaches for identifying a non-targeted extractable adequate for toxicological risk assessment is of interest in recent literature

- For medical device extractables, toxicological risk assessments is applied to extractables where molecular structure is elucidated to a confident/confirmed level, less-than-confident level, or not elucidated at all

How important is identification in toxicological risk assessment of medical device extractables?

Scope

Evaluate occurrence of reported MOS values based on identity (i.e., chemical molecular structure) and type of toxicological threshold

Selection Criteria

Submissions (*n*=6) received 2019, prolonged/long-term device contact, adult, non-targeted analysis, maximum exposure dose estimate

Margin of Safety for E&L Compounds

MoS = Tolerable Intake/Daily Dose

Example

TI – 5 mg/kg/day

Dose - 1 mg/kg/day

MoS = 5

MoS > 1 may be acceptable

MoS ≤ 1 may raise toxicological concerns

Use of TTC values as default TIs for compounds lacking the necessary dose-response toxicity data to derive a compound-specific TI will often result in an MoS < 1.

TTC (default TI) – 0.02 mg/kg/day

Dose - 1 mg/kg/day

MoS = 0.00002

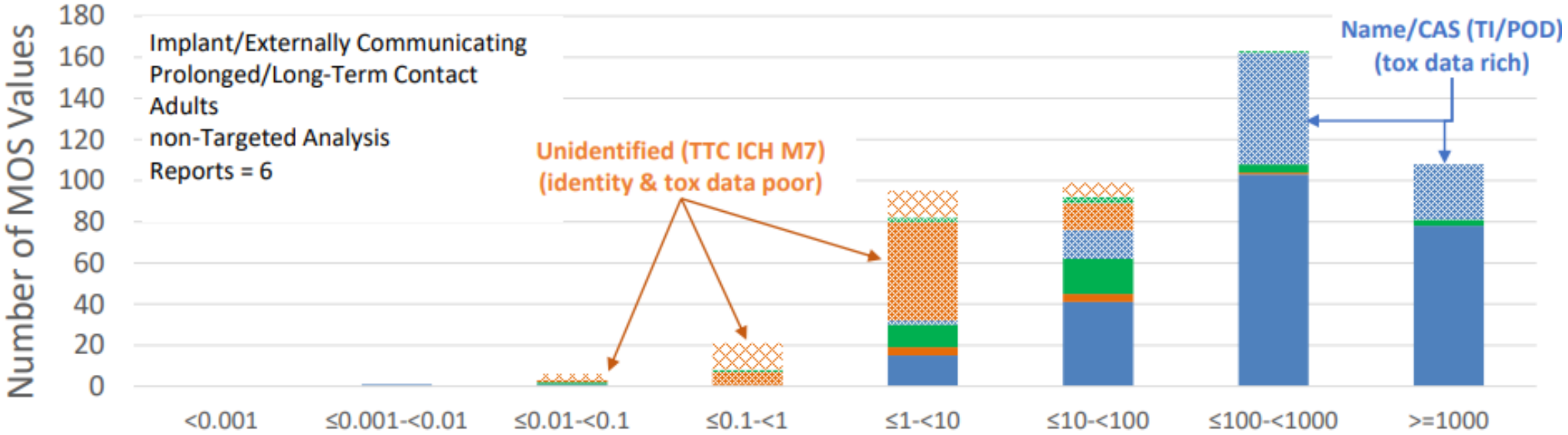
How important is identification in toxicological risk assessment of medical device extractables?

Summary of Reported MOS values

	Molecular Structure	Total
MOS Values	N/A	529
Names/CAS #'s	Complete	191
Other	Incomplete	125
Unidentified	Absent	11

Grouping Reported MOS Values by Identity

Note: Data does not imply risk assessment outcome



Toxicity data rich

- Name/CAS # TI (POD)
- Other TI (POD)

Toxicity data poor
(Suspected mutagenic carcinogen)

- Name/CAS # TTC (ICH M7)
- Other TTC (ICH M7)
- Unidentified TTC (ICH M7)

Toxicity data poor
(Suspected systemic toxicant)

- Name/CAS # TTC (Cramer Class)
- Other TTC (Cramer Class)
- Unidentified TTC (Cramer Class)

Grouping Reported MOS Values by Identity

Summary/Conclusion

>1 MOS values:

almost always occur when complete molecular structure and TI/POD are reported

<1 MOS values:

almost always occur when absence of molecular structure and TTC are reported

Medical device MOS values evaluated support identification is important when assessing whether a non-targeted extractable will not raise a toxicological concern without potential need for additional justification

Implications of using TTC as the basis for a default TI for unknown E&L compounds

- TTC values are intentionally conservative, so use of a TTC as a default TI will result in a number of compounds with MoS values < 1. May unnecessarily raise toxicity concerns.
- May result in the need to perform biocompatibility testing of the device to assess device safety instead of using a chemical characterization/risk assessment approach.
  - Additional biocompatibility testing could result in additional costs, increase animal use, and delay time to market
- May result in rejection of promising and useful devices.
- From a toxicologist's perspective, it is preferable to identify unknown E&L compounds so the use of conservative TTC values is not necessary to derive the TI (for compounds with adequate toxicity data).

What does the working draft of ISO 10993-17 say about the need to identify compounds?

NOTE: When the toxicological risk assessment outcome is critical for establishing the biological risk of the medical device, invasive and long-term body contact duration of the medical device, and high severity of clinically relevant adverse health effect(s), history of safe use might not be sufficient for a constituent with uncertain identity (see Clause 6.5).

Impact on the toxicological risk assessment

- Implications of not identifying compounds with a high degree of confidence
- Implications of misidentifying compounds
- Implications of not uniquely quantifying compounds.

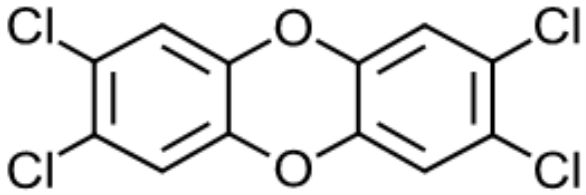
Implications of misidentifying E&L compounds

Tentative ID	Confirmed ID	Implication
Nontoxic (MoS > 10)	Toxic (MoS < 1)	Not sufficiently protective for patient safety
Toxic (MoS < 1)	Nontoxic (MoS > 10)	Can unnecessarily impact device development

Implications Associated with Incorrectly Identifying E&L compounds

IDENTIFICATION CASE STUDY: SIMULATED USE EXTRACT OF DIALYSIS MACHINE

INITIAL IDENTIFICATION

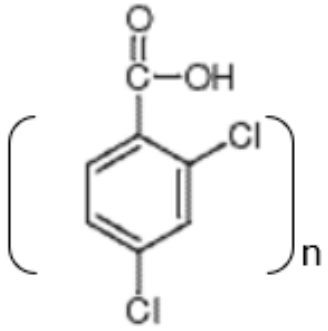


2,3,7,8-Tetrachlorodibenzo-p-dioxin

- Total Quantity: 1065 µg/device
- Daily Exposure Level: 11.41 µg/kg/day
- Tolerable Intake Level: $7x10^{-8}$ µg/kg/day

→ Margin of Safety: **Unacceptable**

FINAL IDENTIFICATION



2,4-Dichlorobenzoic acid

- Total Quantity: 1065 µg/device
- Daily Exposure Level: 11.41 µg/kg/day
- Tolerable Intake Level: 1000 µg/kg/day

→ Margin of Safety: **Acceptable**

Case study presented by Taryn Meade from Fresenius Medical Care at the Biocompatibility for Medical Devices US meeting, October 24, 2019, Chicago, USA

Overview

- **What are the implications of not identifying compounds with a high degree of confidence for the toxicological risk assessment.**

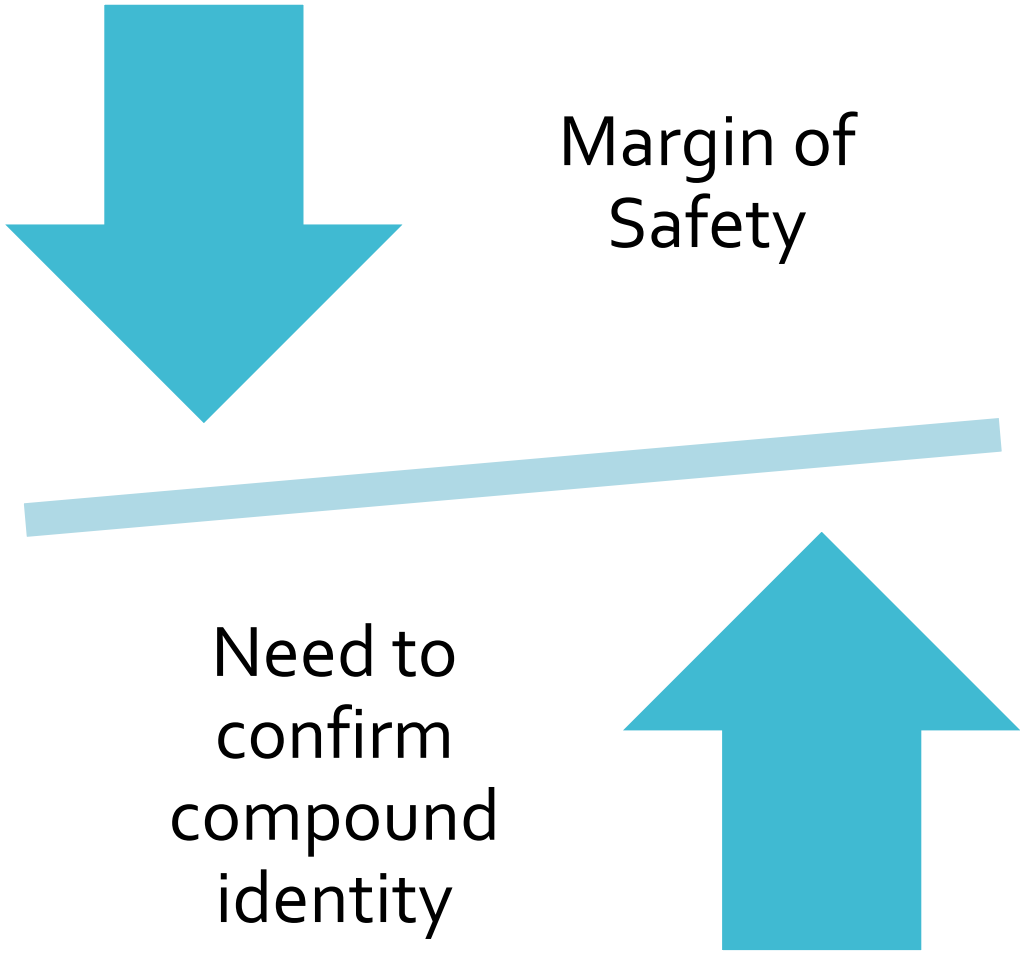
- **What are some recent proposals to evaluate the safety of unidentified and partially identified E&L compounds released from medical device materials?**

What does ISO 10993-17 Working Draft (2019) tell us to do?

When a constituent's identity is uncertain, prioritization of the constituent for further toxicological risk assessment shall be justified and documented. Guidance on prioritizing a medical device constituent is described in Annex E.

NOTE: Uncertainty of a constituent's molecular structure exists when analytical data suggest multiple possible molecular structures, or partial molecular structure is elucidated, and false positive/false negative identity is not addressed. Addressing uncertainty in a constituent's estimated quantity is described in Clause 8.

Relationship between MoS and need to confirm compound identity



Need to confirm identity of compounds above AET as a function of MoS

PDA Journal of Pharmaceutical Science and Technology

IDENTIFICATION AND QUANTITATION CLASSIFICATIONS FOR EXTRACTABLES AND LEACHABLES

Dennis Jenke

PDA Journal of Pharmaceutical Science and Technology **2019**,
Access the most recent version at doi:10.5731/pdajpst.2019.010538

In circumstances where the interpretation of the MoS is definitive (for example, either MoS > 10 and it is definitely concluded that the patient safety risk is negligible or MoS < 0.1 and it is definitely concluded that the patient safety risk is possibly considerable), uncertainty in the identity may be irrelevant to the assessment outcome. ***That is to say that even if the tentative identity were incorrect, it is likely that the true identity is structurally similar to the incorrect initial identity and thus that the toxicity of the compound with the true identity is similar to the toxicity of the compound with the incorrect identity. If this is the case, then it is unlikely that the toxicity of the incorrectly and correctly compound differ by as much as a factor of ten and the conclusion of the assessment remains valid.***

Similar guidance is found in the Working Draft of ISO 10993-17

Annex I. Evaluating a margin of safety value near one

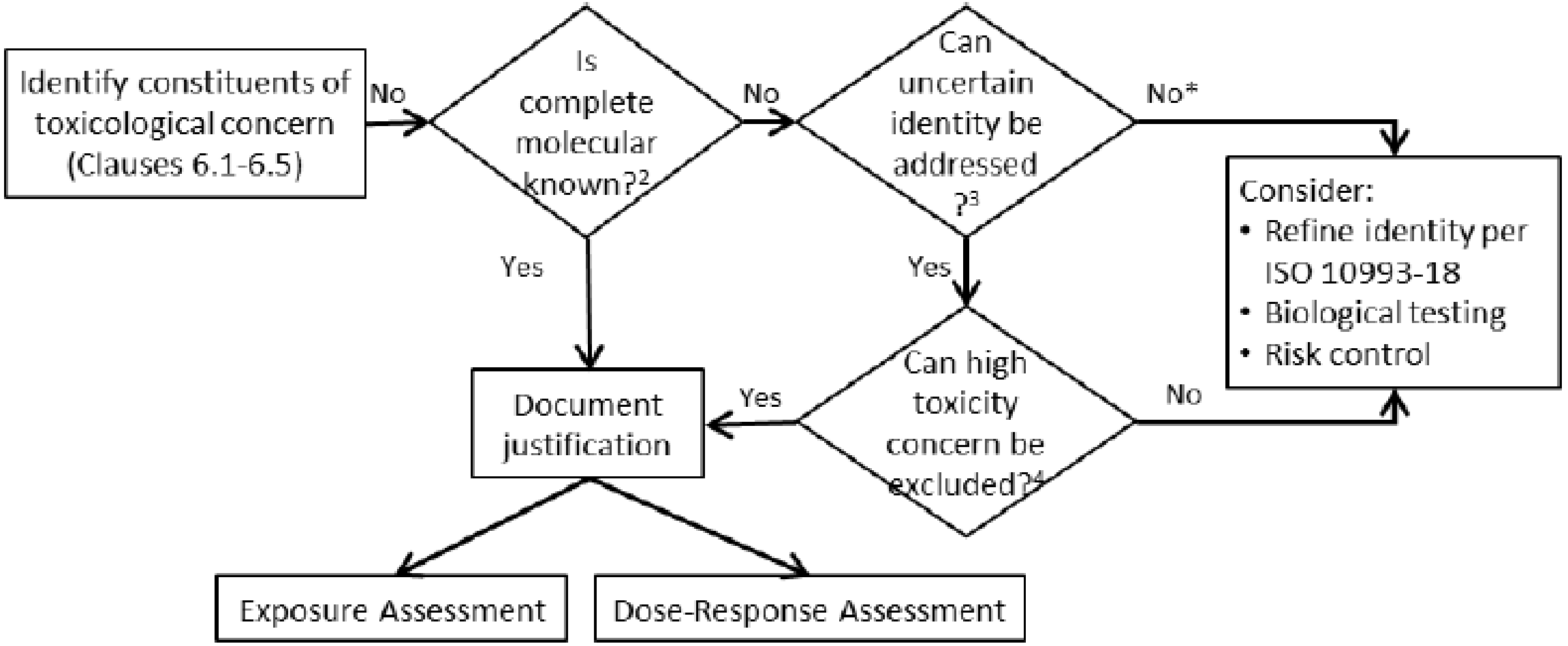
When a medical device constituent's toxicity profile indicates high potency and high severity (i.e., highly toxic), then the toxicological risk assessor should recommend refinement of the constituent's identity (if uncertain and lower toxicity potential is plausible), maximum exposure dose (if not representative of clinical use), or risk control.

What does the working draft of ISO 10993-17 say about the need to identify compounds?

When severe toxicity cannot be excluded and constituent identity is uncertain, alternative approaches should be considered (e.g. refinement of identity/quantity per ISO 10993-18, biological testing if appropriate for the high severity endpoint, or risk control per Clause 11).

Annex E, ISO 10993-17 Working Draft (September, 2019)

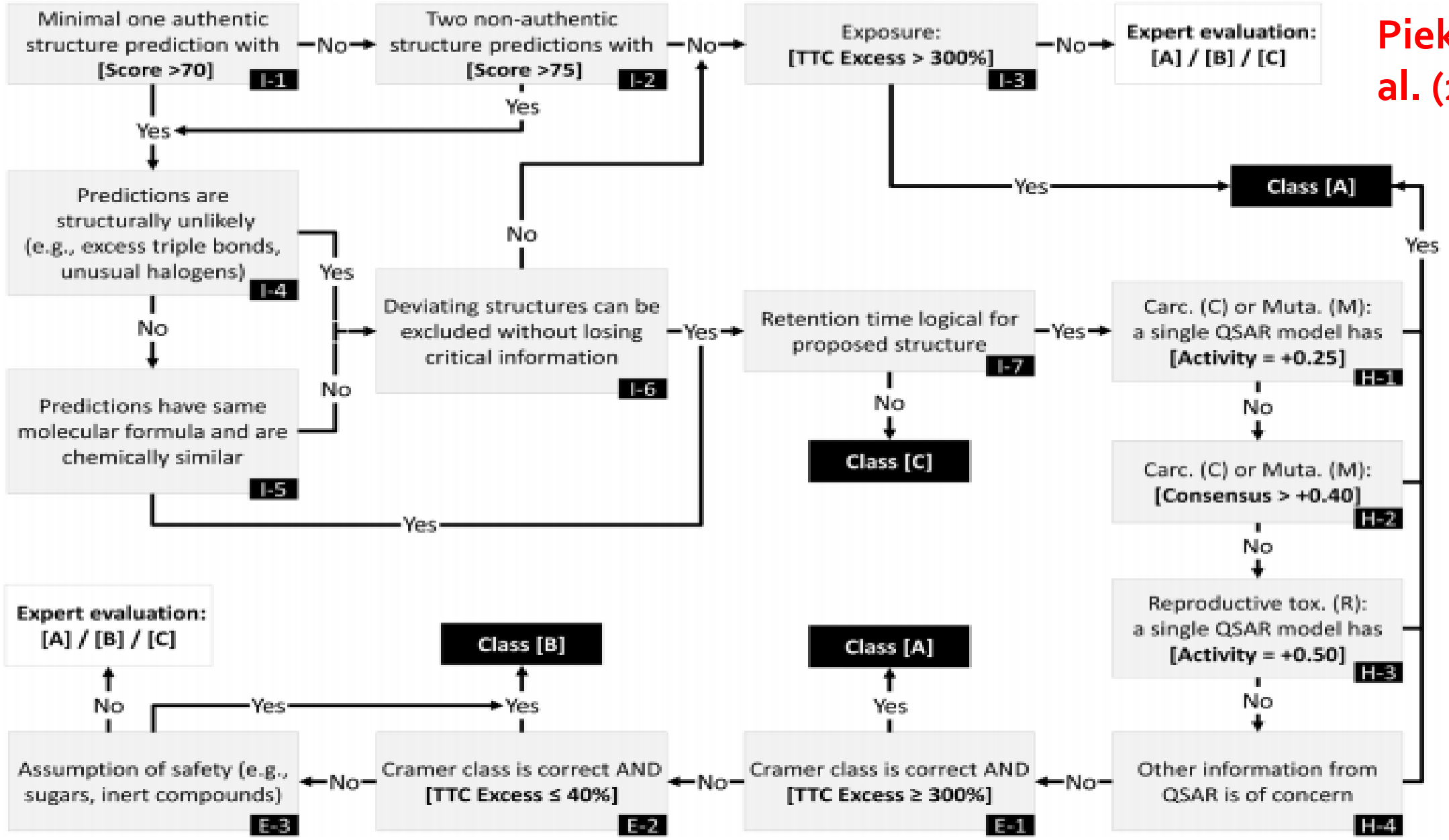
Figure 7. Prioritization of Medical Device Constituents



What does the working draft of ISO 10993-17 say about the need to identify compounds?

Strategies for prioritizing non-targeted extractables for further toxicological risk assessment are emerging; however, a standardized practical method for analytical elucidation of a non-targeted constituent's complete molecular structure has not been established. Consensus from numerous literature reports indicates the extent of analytical data to elucidate a constituent's molecular structure is inversely proportional to the presence of the substance based on a priori knowledge and available molecular structure reference data (Milman 2011; de Vijlder et al. 2017).

- *NOTE: Pieke et al., (2017; 2018) describe analytical approach for prioritizing non-targeted extractables of non-intentionally added substances in food contact materials*



Pieke et al. (2018)

Fig. 3. Implementation of a decision unit for risk prioritization. The decision unit is designed as a decision tree that is evaluated by an expert for each node. The result from the decision unit is risk profile class: [A] high priority, [B] low priority, or [C] insufficient data. The risk profile can be determined either data-driven or via expert decision, in which an experienced assessor decides the class based on all available data.

Food and Chemical Toxicology 49 (2011) 1643–1660

Contents lists available at ScienceDirect

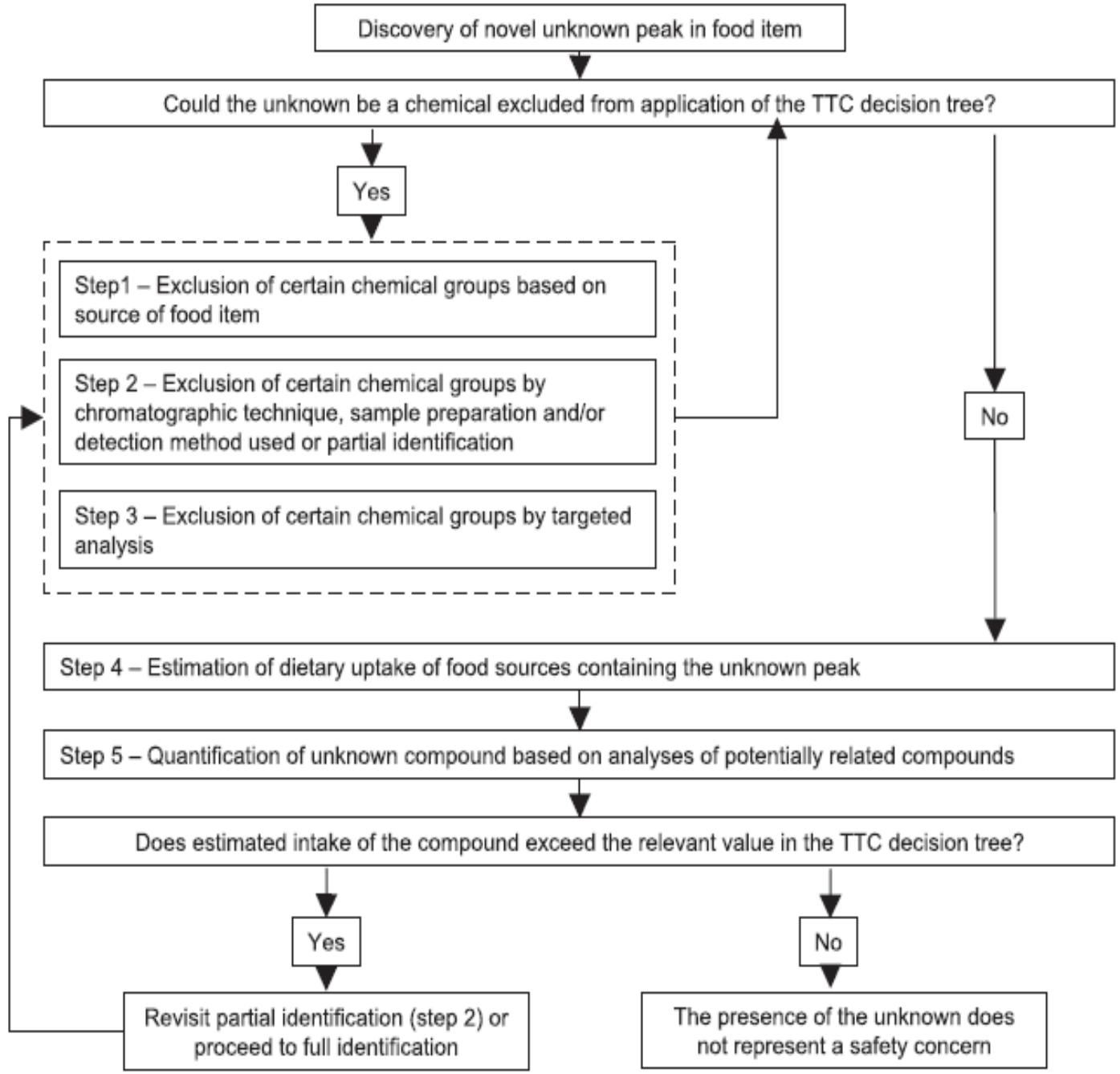
Food and Chemical Toxicology

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]



ILSI Europe
Report Series

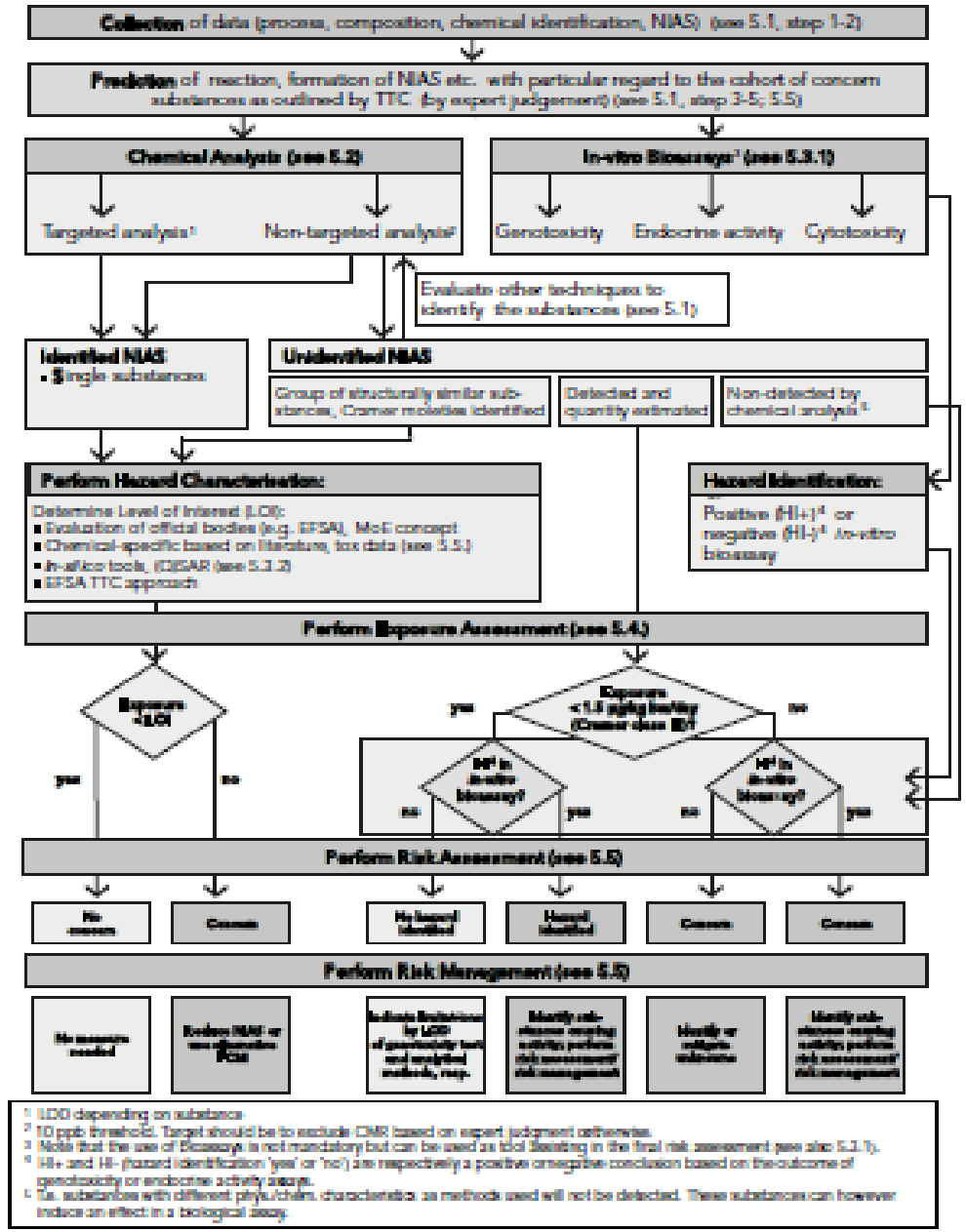
GUIDANCE ON BEST PRACTICES ON THE RISK ASSESSMENT OF NON INTENTIONALLY ADDED SUBSTANCES (NIAS) IN FOOD CONTACT MATERIALS AND ARTICLES

REPORT

ILSI Europe
International Life Sciences Institute

Commissioned by the ILSI Europe Packaging Materials Task Force

Figure 1: Flowchart for the risk assessment of NIAS (may also apply to substances other than NIAS).



1 LOD depending on substance
2 10 ppb threshold. Target should be to exclude CMR based on expert judgment otherwise.
3 Note that the use of Bioassays is not mandatory but can be used as tool assisting in the final risk assessment (see also 5.3.1).
4 HI+ and HI- (hazard identification 'yes' or 'no') are respectively a positive or negative conclusion based on the outcome of genotoxicity or endocrine activity assays.
5 I.e. substances with different phys./chem. characteristics as methods used will not be detected. These substances can however induce an effect in a biological assay.

Approach for Partially Identified Compounds

Although clearly a rigorous toxicological safety assessment cannot be based on a partial identity, partial identities may be sufficient to facilitate some level of safety assessment. For example, quantitative structure–activity relationship QSAR) analysis of a compound's structural characteristics (e.g., via DEREK or SARAH), can be used to establish whether the structural characteristics are associated with an increased risk of an adverse safety effect (e.g., mutagenicity). Compounds without QSAR-alerting structures represent less of a safety hazard than do compounds with QSAR-alerting structures.

Christiaens et al. (2020) PDA J Pharm Sci and Tech 74: 108-133

What does the working draft of ISO 10993-17 say about the need to identify compounds?

NOTE: In silico analysis might not be feasible when uncertainty in a constituent's identity precludes assessment of the model's applicability.

Approach for Partially Identified Compounds

- "Give this to the toxicologist. They may be able to do something with it."
- If there are structural alerts for mutagenicity or carcinogenicity in the fragment, then it may be possible to assign a carcinogenicity based TTC to serve as a default TI for a partially identified compound.
- However, if no alerts are found in the fragment, then we can't be sure that alerts won't be present in the unidentified fragment of the molecule. Therefore, we can't assign a TTC value.
- It may be possible to assign partially identified compounds to a structural group, especially if multiple related compounds/fragments belonging to the same class are found in the extract. May be possible to assign a group TI for the class.

transatlantic think tank for toxicology

t4 report*

Toward Good Read-Across Practice (GRAP) Guidance

Ball et al. (2016) *ALTEX* 33(2)

Can Read Across be used to provide default TI or PDE values for compounds with unknown structures?

Consequently, where the composition of a substance is unknown or variable and the structures of the constituents are not well characterized, it is very difficult to demonstrate that two such substances are structurally similar and to address the questions about how differences in composition and differences in structure between constituents could impact the toxicity.

If a partially identified compound can be placed in a structural group, it may be possible to derive a group TI using Read Across

Impact on the toxicological risk assessment

- Implications of not identifying compounds with a high degree of confidence
- Implications of misidentifying compounds
- Implications of not uniquely quantifying compounds.

Hypothetical Example

Need to uniquely quantify co-eluting compounds reported in a group

Tentatively Identified Compound	TI (µg/day)[1]	Amount extracted from device (µg/device)	Margin of Safety
Oligomer	1000	1	10
Oligomer	1000		
Oligomer	1000		
1-Dodecene	10		
Oligomer	1000		

[1]Hypothetical TI values for illustration purposes

Hypothetical Example

Need to uniquely quantify co-eluting compounds reported in a group

Tentatively Identified Compound	TI (µg/day)[1]	Amount extracted from device (µg/device)	Margin of Safety
Oligomer	1000	20	0.5
Oligomer	1000		
Oligomer	1000		
1-Dodecene	10		
Oligomer	1000		

[1]Hypothetical TI values for illustration purposes

Summary

- What are the implications of not identifying compounds with a high degree of confidence for the toxicological risk assessment.
- What are some recent proposals to evaluate the safety of unidentified and partially identified E&L compounds released from medical device materials?

Take home message

What are the implications of not identifying compounds with a high degree of confidence for the toxicological risk assessment?

- **Sources of analytical uncertainty are well known to chemists.**
- **Medical device toxicologists are becoming increasingly aware that there are challenges associated with the identification and quantification of E&L compounds.**
- **Useful to continue a dialog on this issue at this and similar meetings.**

Take home message

What are the implications of not identifying compounds with a high degree of confidence for the toxicological risk assessment?

- While it is often possible to conduct a toxicological risk assessment on compounds with unknown or partially characterized structures, the approaches used to assess the safety of the compound often result in conservative assumptions being made about the potential toxicity of the compound, and as a result, there is an increased chance for the Margin of Safety (MoS) between the estimated patient dose of the compound and the default TI value to be < 1.

- MoS values < 1 could result in the need for biocompatibility testing or risk mitigation measures.

Take home message

What are some recent proposals to evaluate the safety of unidentified and partially identified E&L compounds released from medical device materials?

- Methods for the safety assessment of unknowns in food contact materials have been published (e.g., Koster *et al.*, Pieke *et al.*).
- This issue is being addressed in Working Draft of ISO 10993-17 for medical device extractables, but it is an evolving issue in the medical device community.
- Proposals have been advanced for using MoS to determine need to identify E&L compounds above the AET (ISO 10993-17; Christiaens *et al.* 2020; Jenke, 2019; Pieke *et al.* 2018)
- It may be possible to evaluate the safety of partially identified compounds, especially if there are many structurally related fragments in the extract.

Recommended follow-up activities

1. Read the following papers

- Christiaens P, Beusen JM, Verlinde P, Baeten J, Jenke D. (2020) *PDA J Pharm Sci Technol*. 74(1):108-133.
- Jenke (2019). *PDA J Pharm Sci Technol*. Aug 16. Epub ahead of print.
- Pieke EN, Granby K, Teste B, Smedsgaard J, Rivière G. (2018) *Regul Toxicol Pharmacol*. 97:134-143.
- Koster S, Rennen M, Leeman W, Houben G, Muilwijk B, van Acker F, Krul L. (2014) *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. 2014;31(3):422-43.

2. Review slides from the FDA/CDRH webinar:

https://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp

3. Review CD of ISO 10993-17 when it becomes available

Acknowledgements

- Thor Rollins and Piet Christiaens, Nelson Labs
- Alan Hood, US FDA
- Taryn Meade, Fresenius Medical Care
- Kelly Coleman, Medtronic

Questions

Ron Brown
riskscienceconsortium@gmail.com

Discussion question

Do you agree with this approach?

I.2.2 Over-estimation of maximum exposure dose

Over-estimating maximum exposure dose can address uncertainty in a constituent's identity and/or quantity. The extent of over-estimating a constituent's exposure dose should reflect the amount of uncertainty in a constituent's identity and/or quantity. When the actual maximum exposure dose is unknown, methods used to quantify a medical device constituent should not represent an under-estimate.