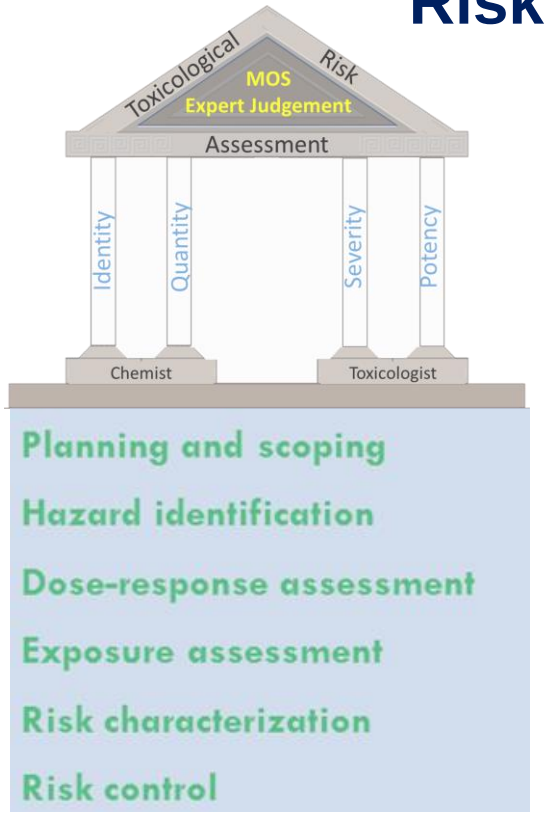
Risk Assessment Applied to Medical Devices:

Recent and proposed advancements



Source: ISO WD 10993-17:2019

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FDA

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Peri-operative medicine, critical care and pain

Association of Anaesthetists

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Aluminium release by coated and uncoated fluid-warming devices

T. Perl, N. Kunze-Szikszay, A. Bräuer, M. Quintel, A. L. Röhrig, K. Kerpen, U. Telgheder

First published: 21 February 2019 | https://doi.org/10.1111/anae.14601 | Cited by: 6

ACTA PÆDIATRICA
NURTURING THE CHILD

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Using isopropyl alcohol impregnated disinfection caps in the neonatal intensive care unit can cause isopropyl alcohol toxicity

Charlotte Sauron, Philippe Jouvet, Geneviève Pinard, Danielle Goudreault, Brigitte Martin, Bastien Rival, Ahmed Moussa

First published: 24 June 2015 | https://doi.org/10.1111/apa.13099 | Cited by: 3

Outline

Part 1 Role of chemical characterization (ChemChar) and toxicological risk assessment (TRA) when evaluating medical device biocompatibility

Part 2 Advancing analytical/toxicological risk assessment approaches/methods for medical device extractables

Part 3 Advancing approaches to estimate maximum exposure dose of medical device chemical constituents

Note: ChemChar is pronounced 'Chem Care'

Part 1

Role of chemical characterization and toxicological risk assessment when evaluating medical device biocompatibility

Medical Device Chemical Characterization

- Devices are not Drugs
- Devices are not Pharmaceutical Packaging
- Devices are not Food Containers
- Analytical approaches that generate chemical identity/quantity data adequate for toxicological risk assessment can be useful for medical devices

Material characterization of medical devices require unique approaches

Background: Why chemical characterization and toxicological risk assessment?

2016 CDRH Biocompatibility Guidance (Section VII Chemical Assessment, page 42)

- "Inherent in the review of medical devices is an understanding of the body's entire exposure to the medical device, including all chemical entities contained within the device."

- "chemical analyses can be used to assess the toxicological risk of the chemicals that elute from devices. For example, chemical analysis using exhaustive extraction techniques (per ISO 10993-12) can also be helpful to evaluate long-term toxicity endpoints such as potential carcinogens…In addition, the outcomes of chemical analyses are often sensitive to the parameters of the test. Extraction solvents should be selected to optimize compatibility with the device materials "

Why conduct a toxicological risk assessment?

Can be useful for determining whether a chemical/compound present or released from a medical device presents a systemic toxic, genotoxic, carcinogenic, reproductive, or developmental toxicological risk (other biological endpoints on a case-by-case basis).

"For devices where the patient-contacting portions may contain potentially toxic chemicals, the evaluation of safety should include both chemical risk (i.e., the level of toxicological concern) and the type and duration of exposure." – Section VII Chemical Assessment, page 42 of CDRH (2016) Biocompatibility Guidance

Note: "*However, chemical analysis is usually insufficient to identify all of the risks of the device in its final finished form, because it will not consider aspects of the finished device such as surface properties (e.g., rough versus polished surface) or device geometry that could affect the biological response in certain scenarios (e.g., thrombogenicity, implantation).*" – Section B Identification of Potential Risks, page 8 of CDRH (2016) Biocompatibility Guidance)

What chemical characterization standards are used?

A standardized method for complete chemical analysis of medical device materials does not currently exist.

- CDRH partially recognizes ANSI AAMI BE83:2006/(R)2011 (there are differences between ISO 10993-18: 2005 and BE83)

- CDRH does not recognize PQRI recommendations (2006)

The "ISO FDIS 10993-18:2019 (recently balloted) includes additional details on analytical instruments, quantification methods, etc."

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm

Expanded information in ISO FDIS 10993-18:2019

Concepts that do not appear in ISO 10993-18:2005

- AET: Analytical Evaluation Threshold, a pre-determined concentration above which an extractable is expected to be identified, semi-quantified, and further assessed toxicologically (definitions)
- The importance of identification (not new as concept but….)
- Expansion of reporting requirements

….and more

Part 2

Advancing analytical/toxicological risk assessment approaches/methods for medical device extractables

Chemical characterization approaches

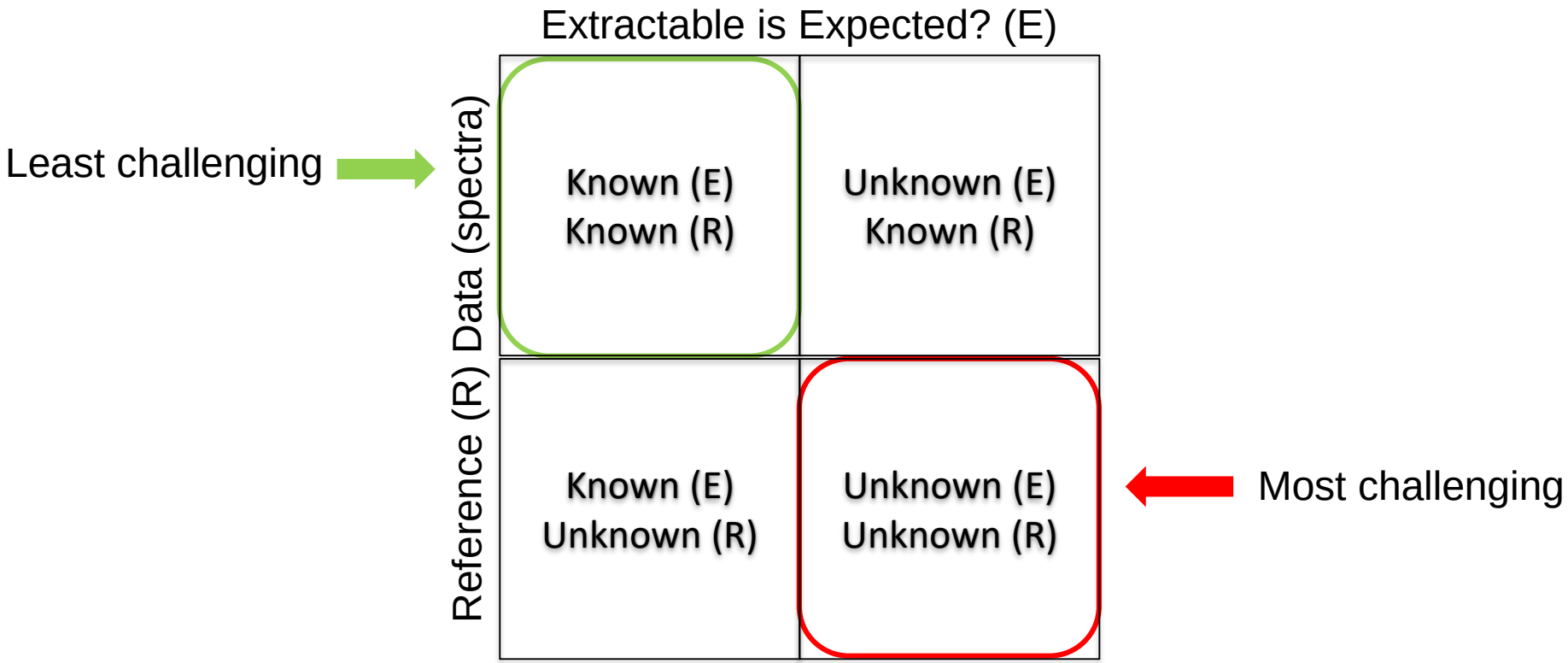
MDCPSS-SOT Webinar (May 22, 2019) CDRH Scientific Perspective on Analytical Testing and Toxicological Risk Assessment for Medical Devices http://www.toxicology.org/groups/ss/MDCPSS/pastevents.asp

Non-targeted screening:

- Extraction: Exhaustive (long-term body contact) or Exaggerated (limited body contact) Extraction
- Data Generation: Multiple Analytical Methods
- Detect, Identify and Quantify: To provide data to support Toxicological Risk Assessment

Medical device analytical chemist

Identification of non-targeted extractables



Adapted from: Stein (2012) *Analytical Chemistry* 84:7274-7282; de Vijlder et al. (2018) Mass Spectrometry Reviews 37:607–629

Impact of identification levels on Margin of Safety (MOS) values of non-targeted medical device extractables

Scope

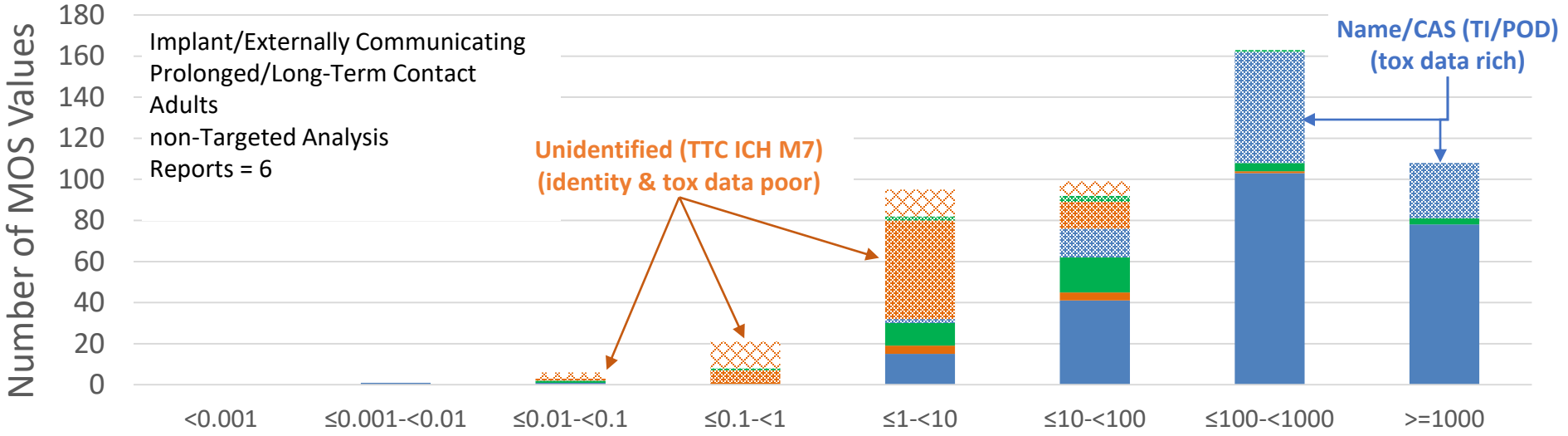
Evaluate occurrence of reported medical device extractable MOS values based on identity (i.e., chemical molecular structure) and toxicological threshold

Selection Criteria

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

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)

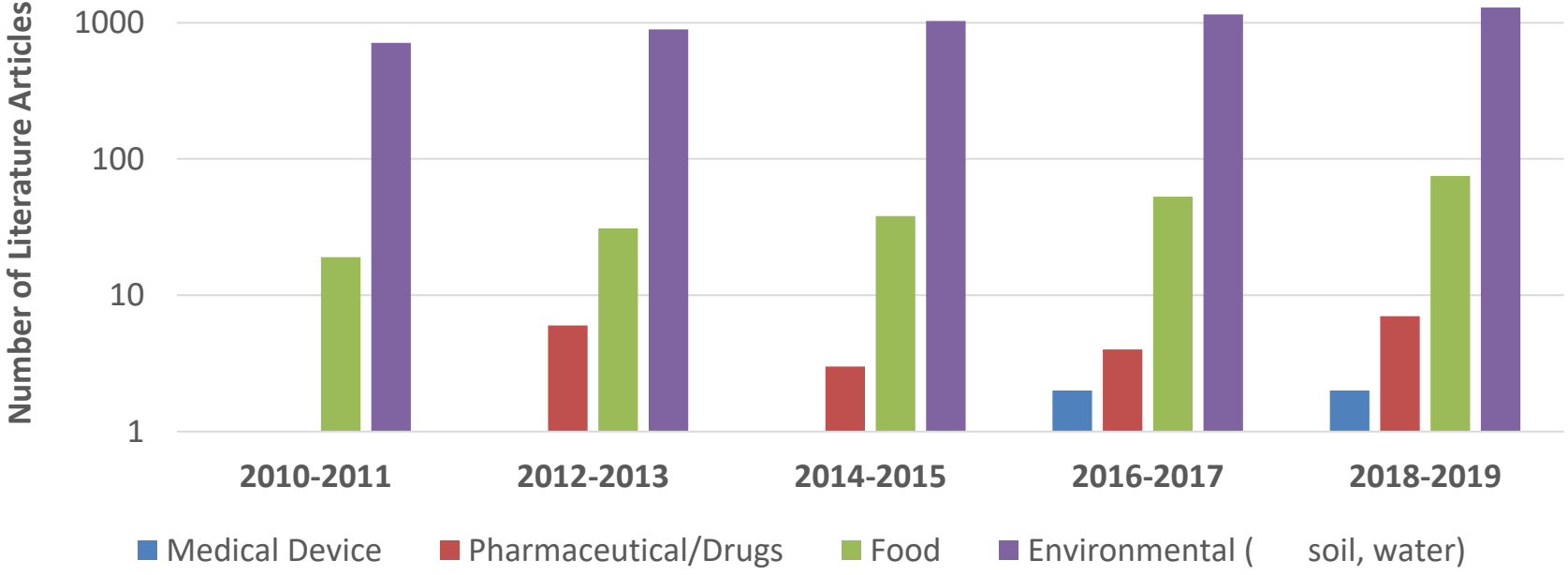
- Name/CAS # TTC (ICH M7)
- Other TTC (ICH M7)
- Unidentified TTC (ICH M7)

Toxicity data poor

(Suspected systemic toxicant)

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

Emerging Approaches/Methods on Non-Targeted Identification by Spectrometry



Source: Google Scholar (https://scholar.google.com)
Common Search Terms: ("screening" OR "non-targeted") "identification" spectrometry "risk assessment" -forensic -peptide –metabolomics
Subject Specific Terms: “medical device”; (“drug” OR “pharmaceutical”); “environmental” (“water” OR “soil”)
Additional Search Terms: (“extractables” OR “leachables”) for medical device & drug; -food for drug, medical device, & environmental

ISO TC 194 10993 Standards

ISO 10993-17 Current (2002(R)2012) vs Working Draft

Current	Working Draft (WD)
ISO 10993-17:2002(R)2012 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances	**ISO WD 10993-17 (current) Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents**
1. Scope	1. Scope
2. Normative references	2. Normative references
3. Terms and definitions	3. Terms and definitions
4. General principles for establishing allowable limits	4. Overview of toxicological risk assessment within the biological evaluation process
5. Establishment of tolerable intake (TI) for specific leachable substances	5. Planning and scoping
6. Calculation of tolerable exposure (TE)	6. Hazard identification
7. Feasibility evaluation	7. Dose-response assessment
8. Benefit evaluation	8. Exposure assessment
9. Allowable limits	9. Risk characterization
10. Reporting requirements	10. Risk control
	11. Reporting requirements

Part 3

Advancing approaches to estimate maximum exposure dose of medical device chemical constituents

Exposure model in medical device applications

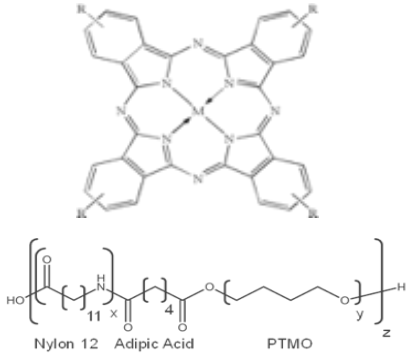
CORRECTED PROOF

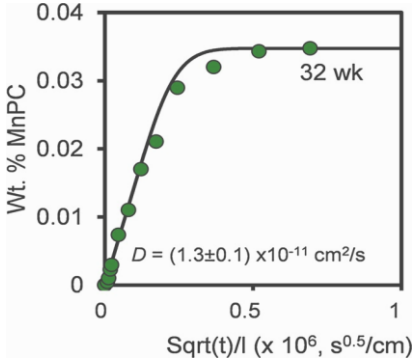
Strategies for Rapid Risk Assessment of Color Additives Used in Medical Devices

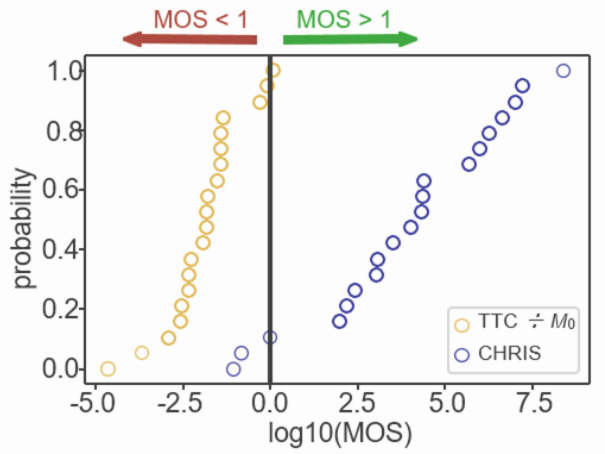
David M Saylor ✉, Vaishnavi Chandrasekar, David D Simon, Paul Turner, Laura C Markley, Alan M Hood

Toxicological Sciences, kfz179, https://doi.org/10.1093/toxsci/kfz179

Published: 06 August 2019







Annals of Biomedical Engineering
January 2018, Volume 46, Issue 1, pp 14–24 | Cite as

Conservative Exposure Predictions for Rapid Risk Assessment of Phase-Separated Additives in Medical Device Polymers

Authors | Authors and affiliations

Vaishnavi Chandrasekar ✉, Dustin W. Janes, David M. Saylor ✉, Alan Hood, Akhil Bajaj, Timothy V. Duncan, Jiwen Zheng, Irada S. Isayeva, Christopher Forrey, Brendan J. Casey

Article
First Online: 25 September 2017

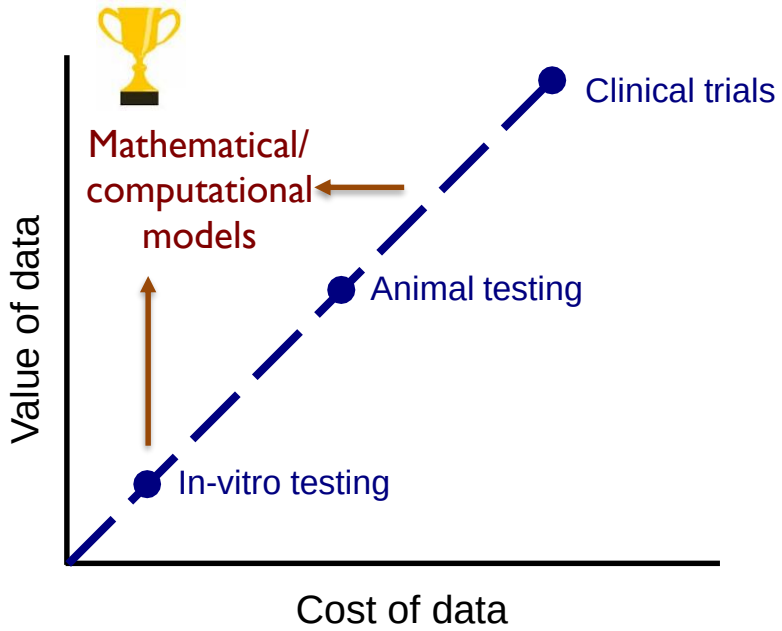
Exposure models in medical device applications

Physics-based exposure models based on conservative assumptions can provide more clinically relevant maximum exposure estimates, in lieu of or supplementary to extraction testing.

- Potential benefit of exposure models to aid toxicological risk assessment
- Challenges with using exposure models in regulatory applications
- Strategy to address challenges in device polymers
- Potential applications

Potential benefits of exposure modeling

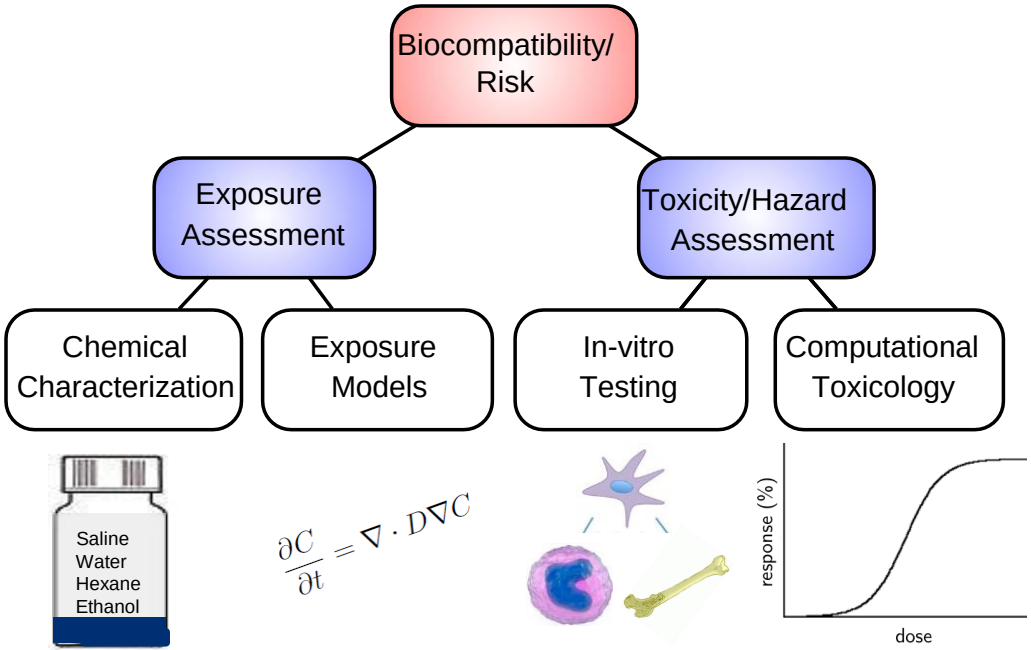
Traditionally, there has been a tradeoff between the cost of collecting data and the value of the data for evaluating medical products.



Adapted from: D. Steinberg, G. Horwitz, D. Zohar, Building a business model in digital medicine, Nature Publishing Group. 33 (2015) 910–920.

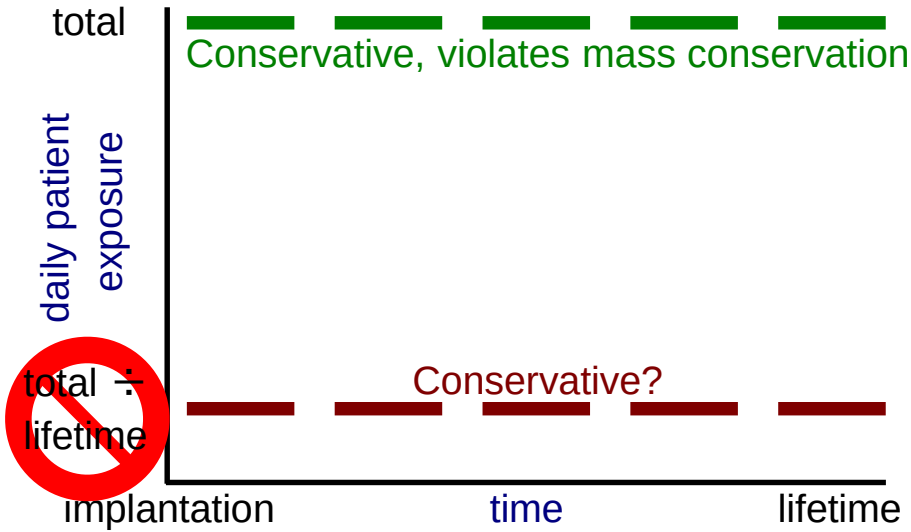
Toxicological risk assessment

Goal: where possible, obviate the need for expensive and time-consuming animal testing by using in-vitro and/or computational capabilities to establish acceptable risk



Current medical device exposure “models”

Once the total amount of an extractable is established, exposure is estimated by:



No physical/physiological basis - significant room for improvement!

Diffusion based mass transport models from polymeric materials

Interactions Between:

- Media
- Additive
- Matrix (e.g., polymer)

Assumptions:

- “durable” matrix
- dilute additive/impurity
- homogeneity (macroscopic)

When assume worst case media/tissue properties - only need diffusion parameter (D^M) of the additive from the polymer matrix

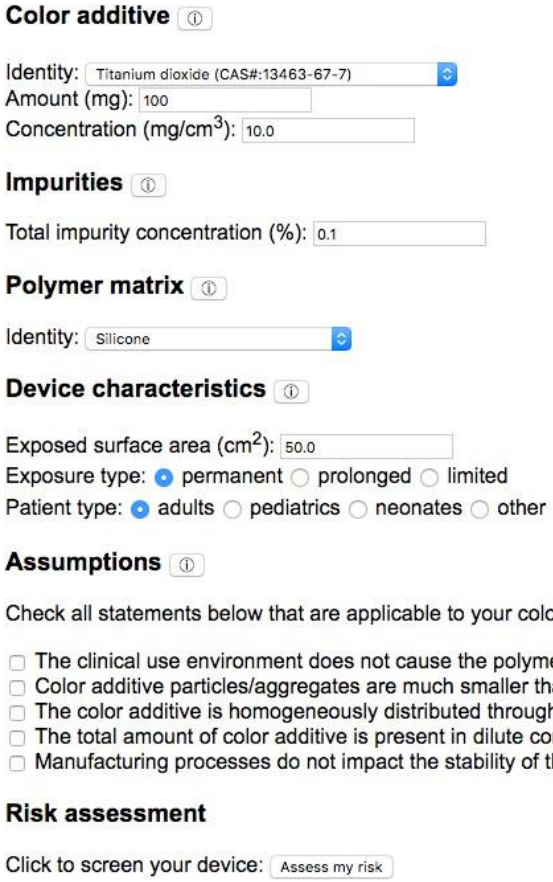
Color additives

Color additives (CA) are used in a wide range of devices to provide differentiation or radiopacity

Typical characteristics of these systems:

- “Durable” polymers that do not swell or degrade in-vivo
- CA are homogeneously distributed
- CA are present in dilute concentrations ($C_0 < 2$ %)

Color Hazard and RISk calculator (CHRIS)

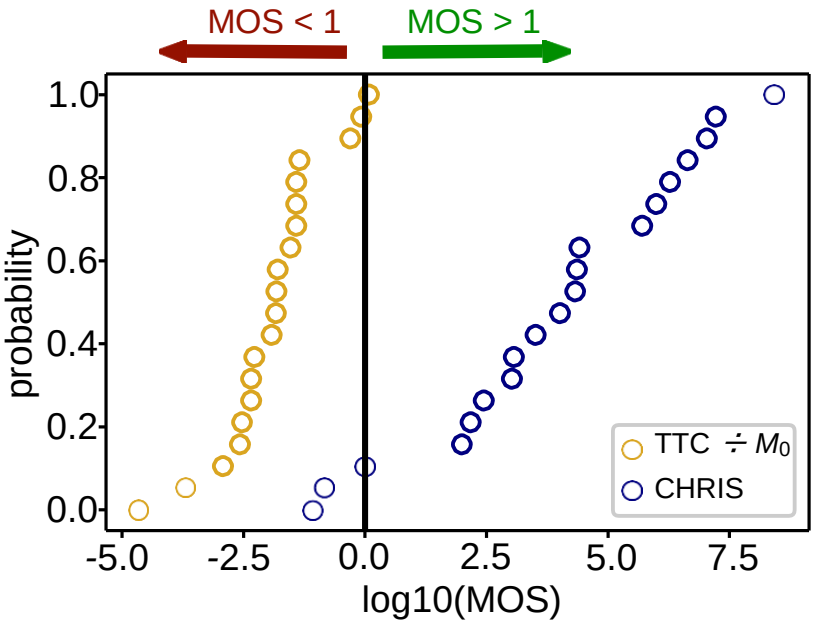


- Rapid (screening level) risk assessments of color additives in medical devices
- Under review for qualification as a Medical Device Development Tool (MDDT)
- Available for evaluation at: https://dsaylor.github.io/CHRIS/

D.M. Saylor, et al., Strategies for rapid risk assessment of color additives used in medical devices, Toxicol. Sci. (2019)

Screening success frequency

Results of initial testing CHRIS model with industry (20 CA-polymer combinations)

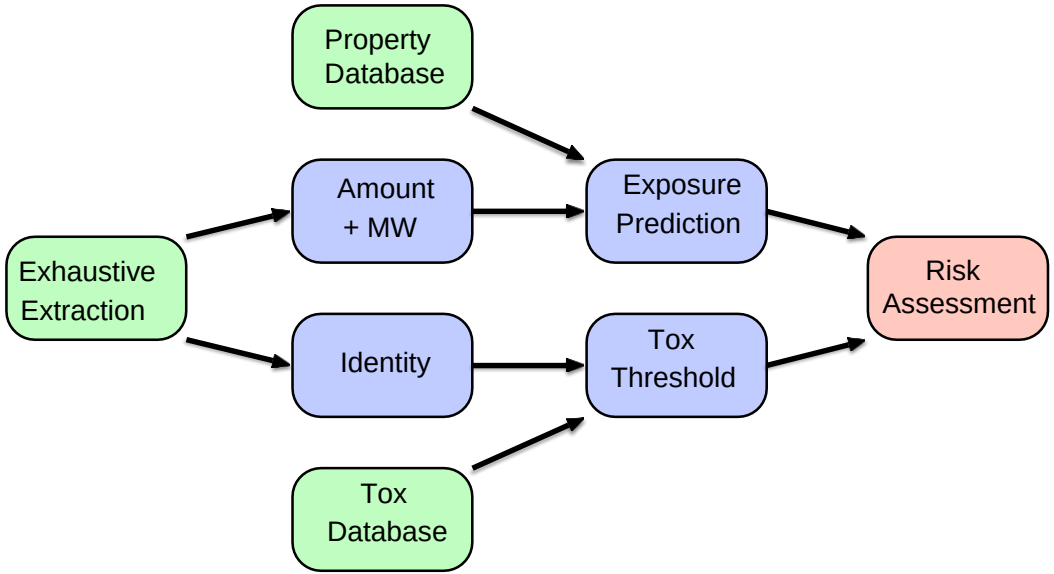


Margin of safety (MOS) =
TI ÷ exposure

Two “failures” - violated an assumption (dilute solution) of the exposure model

Identity independent model

Exploring whether similar concepts can be applied to improve interpretation of extraction test results for (bulk) non-targeted additives/impurities:



Part 1 & 2 Summary

- Chemical characterization can be an approach to address some biological endpoints
- Chemical characterization can be based on multiple data sources (e.g., compositional information, analytical chemistry extractables data, modeling)
- Chemical characterization information is used to support toxicological risk assessment of medical device chemical constituents
- Opportunity exists to advance analytical and toxicological risk assessment approaches/methods that will improve understanding of toxicological risk of medical device extractables

Part 3 Summary

Physics-based exposure models based on conservative assumptions can provide more clinically relevant maximum exposure estimates, in lieu of or supplementary to extraction testing.

- The primary challenge in developing reliable physics-based exposure models is the lack of data to parameterize and validate
- While this largely prohibits exposure models that can be predictive of clinical use scenarios, protective exposure models based on conservative assumptions can be applied when assessing toxicological risk and data is absent/inadequate
- We are developing a conservative model and parameterization for additives/impurities in common device polymers
- Application to additives with known identity and amount is straightforward and we are exploring ways to leverage extractables data to address non-targeted analytes

Acknowledgements

- CDRH Office of Science and Engineering Laboratories (OSEL): technical colleagues and managers
- CDRH Office of Product Evaluation and Quality (OPEQ)*: regulatory colleagues and managers
- Colleagues from industry for valuable conversations
- National Capital Area Chapter of the Society of Toxicology (NCAC-SOT) for hosting this event

* 5/1/2019 reorganization combined Office of Device Evaluation (ODE), Office of Compliance (OC) & Office of Surveillance and Biometrics (OSB)

Thank you!

Questions?