Do We Really Need to Account for Bioaccumulation When Assigning a Medical Device to an Exposure Duration Category?

Biocompatibility Insights, Copenhagen

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Ron Brown
Director and
Principal
Toxicologist

Current requirements in ISO 10993-1:2025

Table 2 — Biological effects for medical devices in contact with intact mucosal membranes

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[e]	Local effects after *tissue* contact (6.5.6)[d]	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E					
B – prolonged (>24 h to 30 d)	E	E	E	E	E	E		
C – long-term (>30 d)	E	E	E	E	E	E	E	

Historically, the extent to which medical devices undergo an evaluation for potential risk depends on the nature and duration of contact of the device with the patient.

What does the standard say?

Section 6.4.3.3 of the ISO 10993-1:2025 standard:

The potential for bioaccumulation of medical device constituents shall be considered for all duration categories. Where bioaccumulation is expected (e.g. a raw material contains perfluoro-heptanoic acid, a substance known to bioaccumulate in humans), the contact duration of the medical device shall be long term unless otherwise justified.

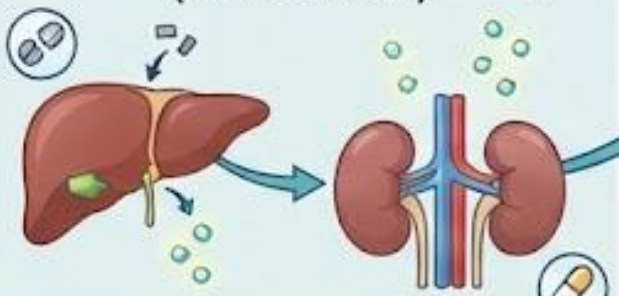
DRUG BIOACCUMULATION:
INPUT EXCEEDING ELIMINATION

DRUG INPUT
(DOSING)



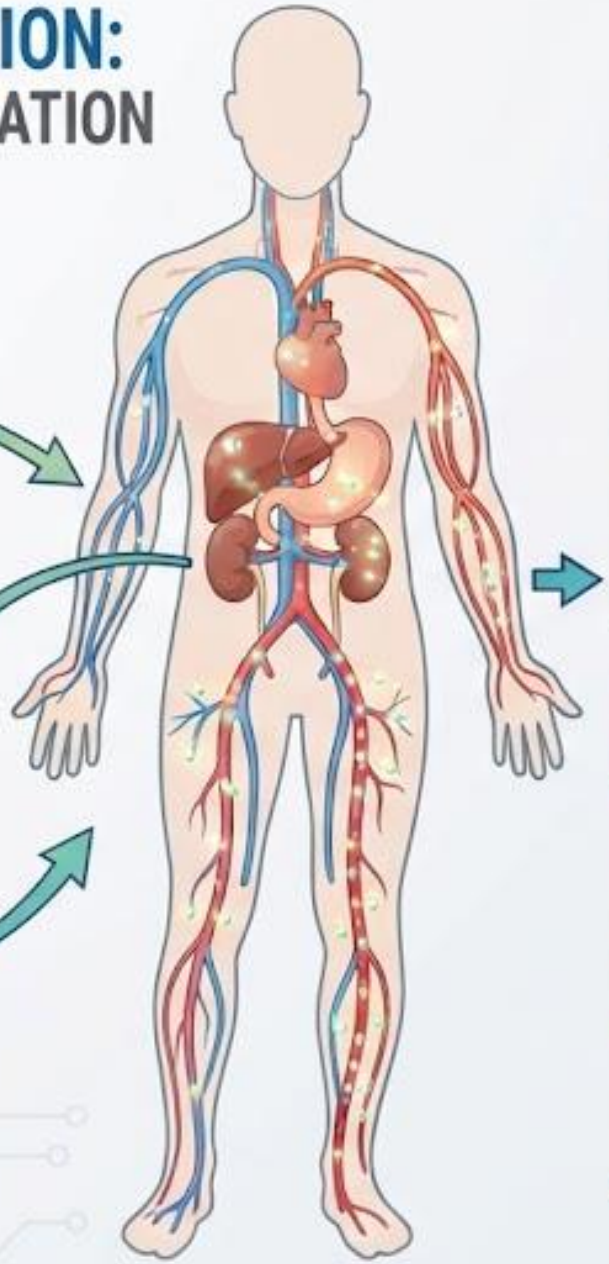
MULTIPLE DOSES
ADMINISTERED OVER TIME

DRUG CLEARANCE
(ELIMINATION)

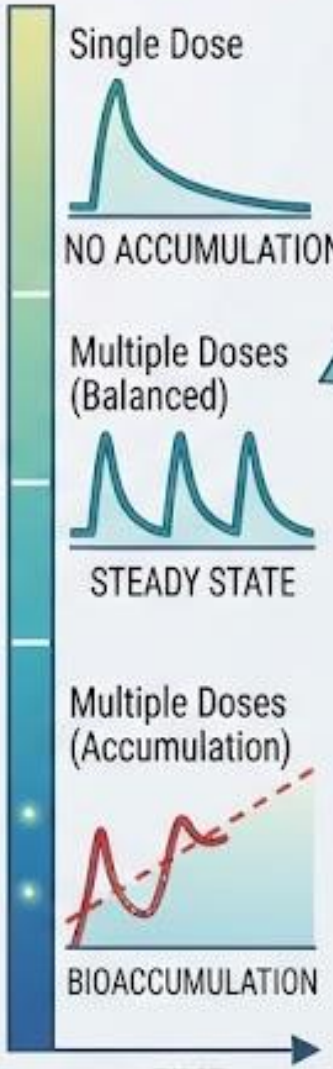


METABOLISM EXCRETION

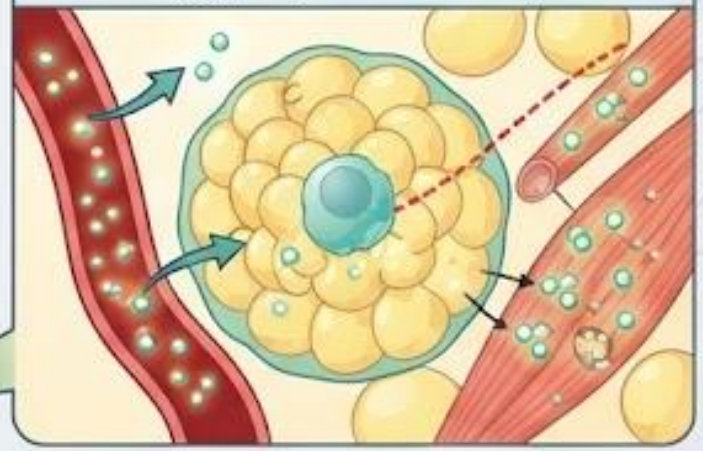
METABOLISM & EXCRETION PROCESSES



DRUG CONCENTRATION IN BODY



TISSUE COMPARTMENT
(e.g., Adipose or Muscle)



DRUG SEQUESTRATION IN TISSUES

RATE OF INPUT > RATE OF CLEARANCE

ACCUMULATION = TOTAL DOSE IN − TOTAL DOSE OUT

CONSEQUENCES OF BIOACCUMULATION



Increased Side Effects | Toxicity Risk | Prolonged Drug Action

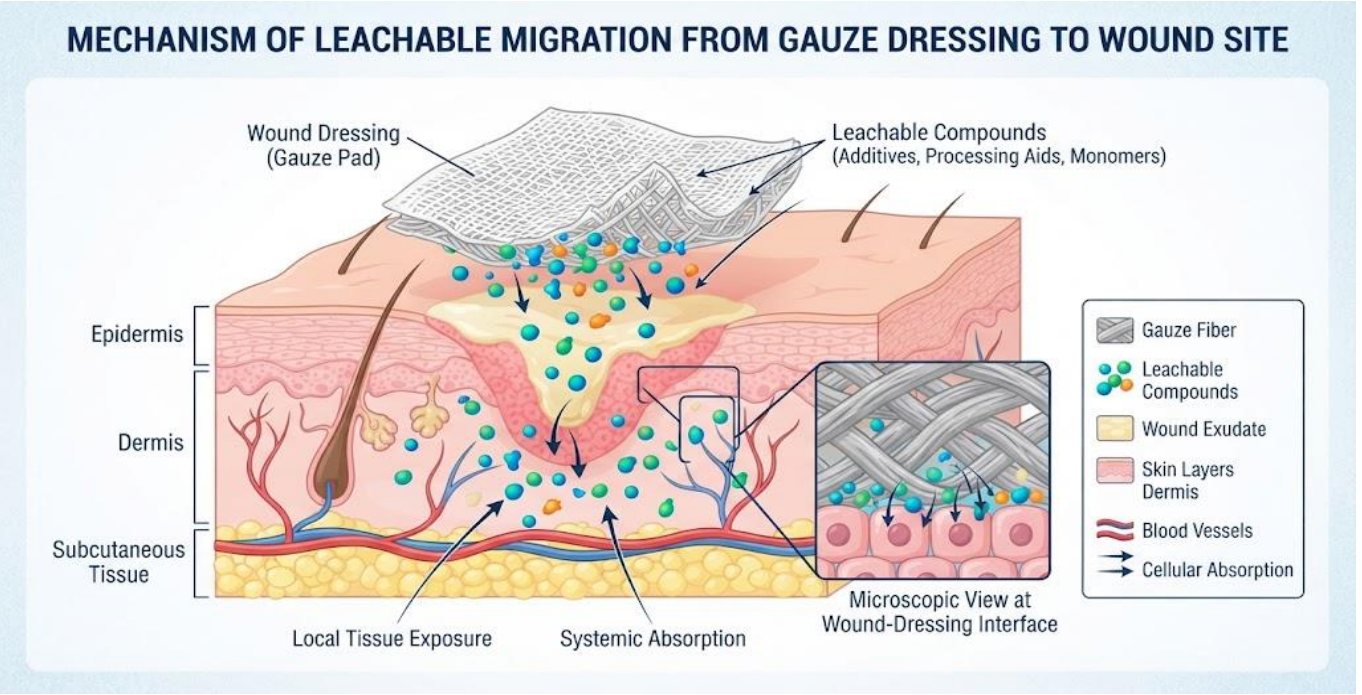
LEADS TO HIGHER STEADY-STATE CONCENTRATION

A new perspective in ISO 10993-1:2025

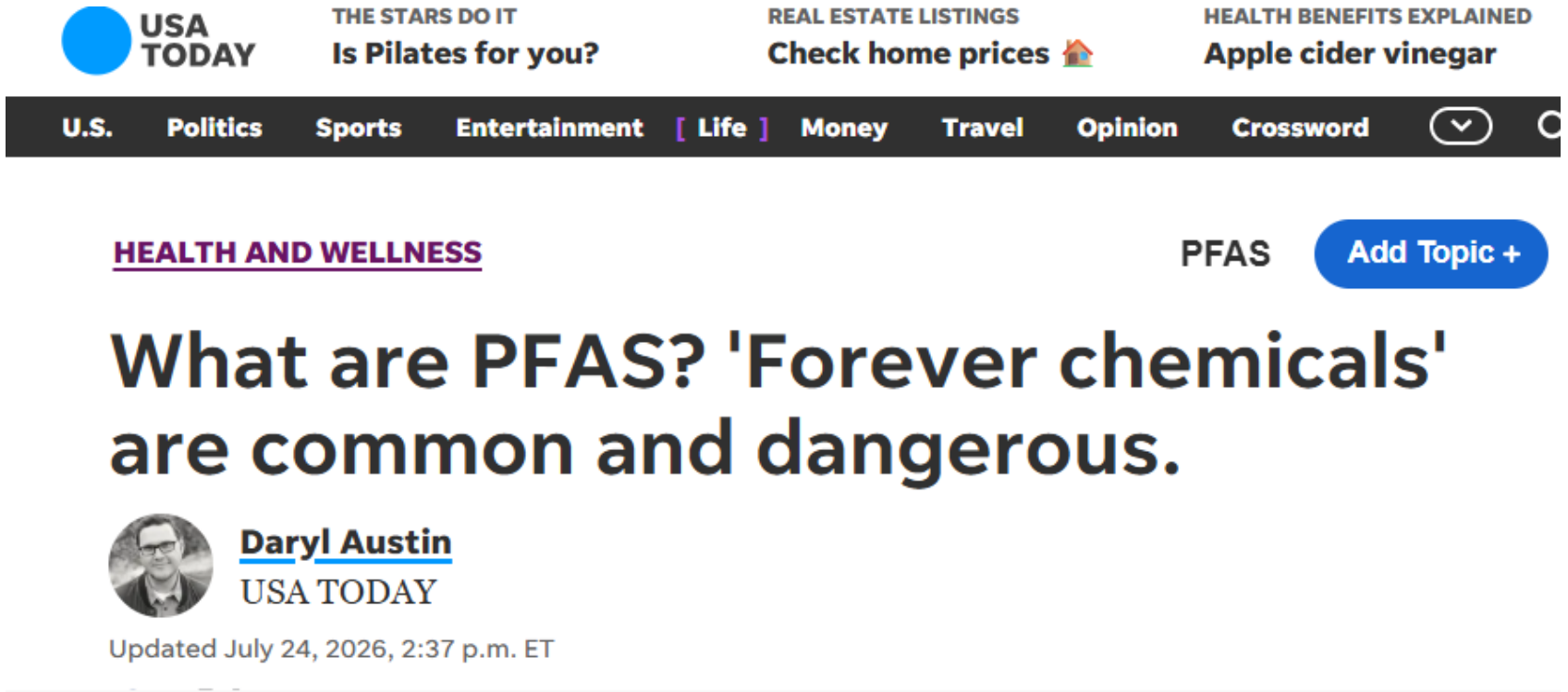
As described in the ISO 10993-1:2025 standard, consideration is now also being given to the **duration of patient contact with the compounds** released from the device as well as the **duration of patient contact with the device**.

Why was this change incorporated into the standard?

The statement in the standard does not say why "the potential for bioaccumulation of medical device constituents shall be considered for all duration categories", but the implication is that release of a compound from a device with short-term exposure to the patient could result in long-term exposure to the released constituent.



What's behind this new language?



As a practical matter, what does this new requirement mean for the biological safety assessment of some short-term exposure devices?

Introduction of this concept now means that a device with short-term patient exposure that contains compounds with a long elimination half-life could be categorized as long-term exposure device with a resulting need for a more rigorous biocompatibility assessment of the device.

Short-term use device
+
compound expected to bioaccumulate



Equivalent to a long-term use device

Implications of moving a limited exposure device to a longer exposure duration category

Table 2 — Biological effects for medical devices in contact with intact mucosal membranes

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C – long-term (>30 d)	E	E	E	E	E	E	E	

Changing the duration category of a device is likely to result in additional biocompatibility testing or chemical characterization.

Let's look more closely at the language in the standard

The potential for bioaccumulation of medical device constituents shall be considered for all duration categories.

- **Does the presence on a device of a compound known to bioaccumulate mean that bioaccumulation is expected or is just possible?**
- **What factors influence the potential for a compound to bioaccumulate?**
  - **Elimination half life (t1/2)**
  - **Interval between exposures**

The new recommendation represents a hazard-based approach

- ***Where bioaccumulation is expected*** ***(e.g. a raw material contains perfluoro-heptanoic acid, a substance known to bioaccumulate in humans)…***

- **It seems that the statement is based on bioaccumulation potential alone, not the resulting levels of the compound in the body or comparing those levels with concentrations associated with adverse effects, as would be expected in a risk-based approach.**

- **A risk-based approach is the cornerstone of the ISO 10993-17:2023 and ISO 10993-1:2025 standards.**

HAZARD vs. RISK: The Shark Analogy



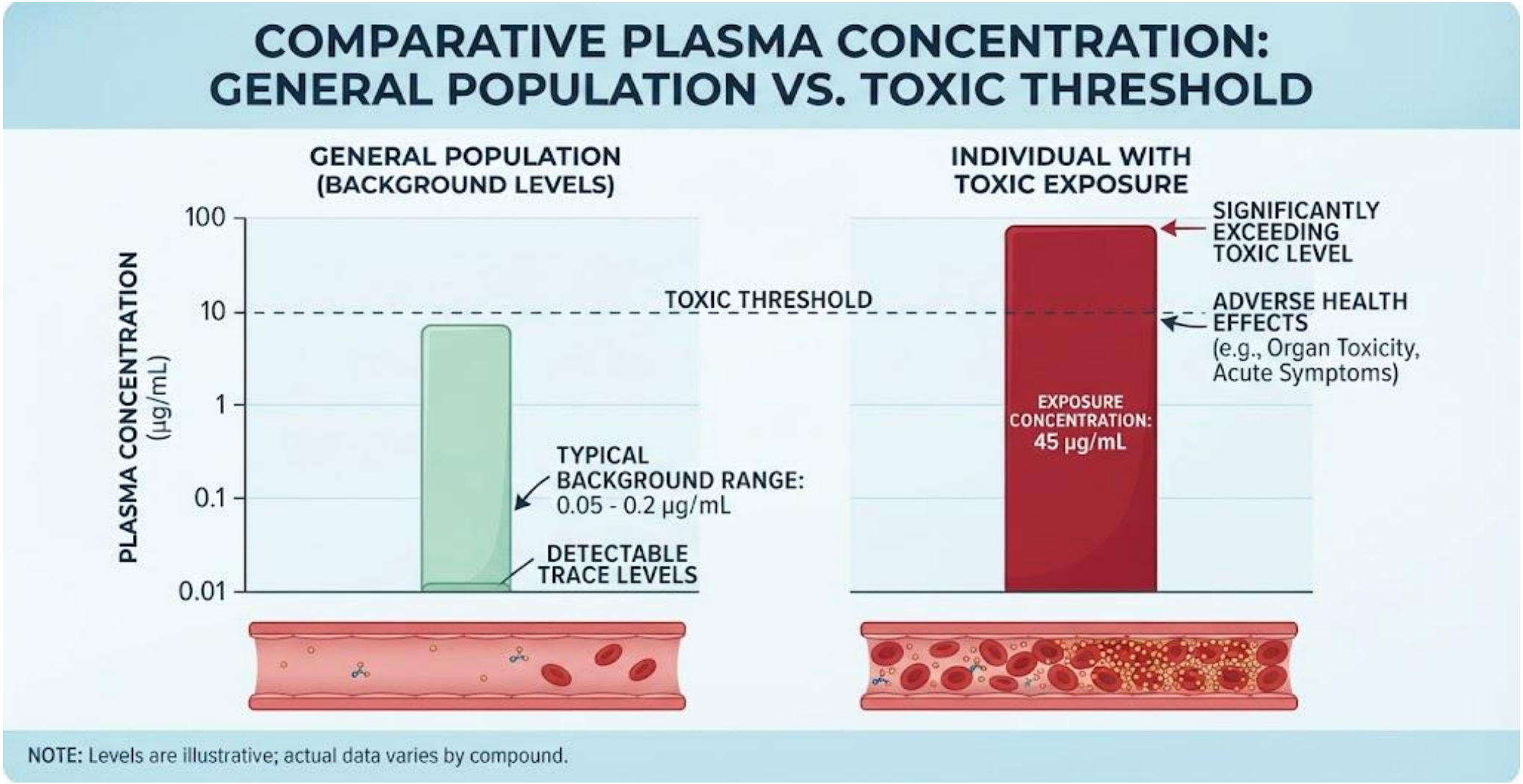


HAZARD + EXPOSURE = RISK

A **Hazard** is an inherent property with the potential to cause harm.
(e.g., A Shark exists)

Risk is the combination of the probability of exposure to a hazard and the **severity** of the outcome.
(e.g., Swimming alone with the Shark)

We need to compare the amount of the compound that bioaccumulates in the body to levels associated with toxicity and with background levels.



Isn't it better to be safe than sorry if one of these compounds is present in a device?

- This is an example of the Precautionary Principle
- Similar to the issue with Material-Mediated Pyrogens (MMP)
- Consequences:
  - May lead to unnecessary biocompatibility testing and chemical characterization for some devices,
  - Will result in increased costs, animal use, and time to market; and
  - Inconsistent with the risk-based approach that is a central theme of the ISO 10993-1:2025 standard.

Do we really need to account for bioaccumulation when determining an exposure category for devices?

We can ask ourselves three questions:

1. Are compounds with long elimination half lives actually found in or on medical devices?
2. If so, do they bioaccumulate device-related exposure scenarios?
3. If they do bioaccumulate, do levels of the compound increase to levels associated with toxicity?

Proposed workflow to address the questions

Step 1: Identification of extractable and leachable (E&L) compounds with long total body elimination half-lives,

Step 2: Estimation of the amount of the long half-life compound released from medical device under clinically relevant use scenarios,

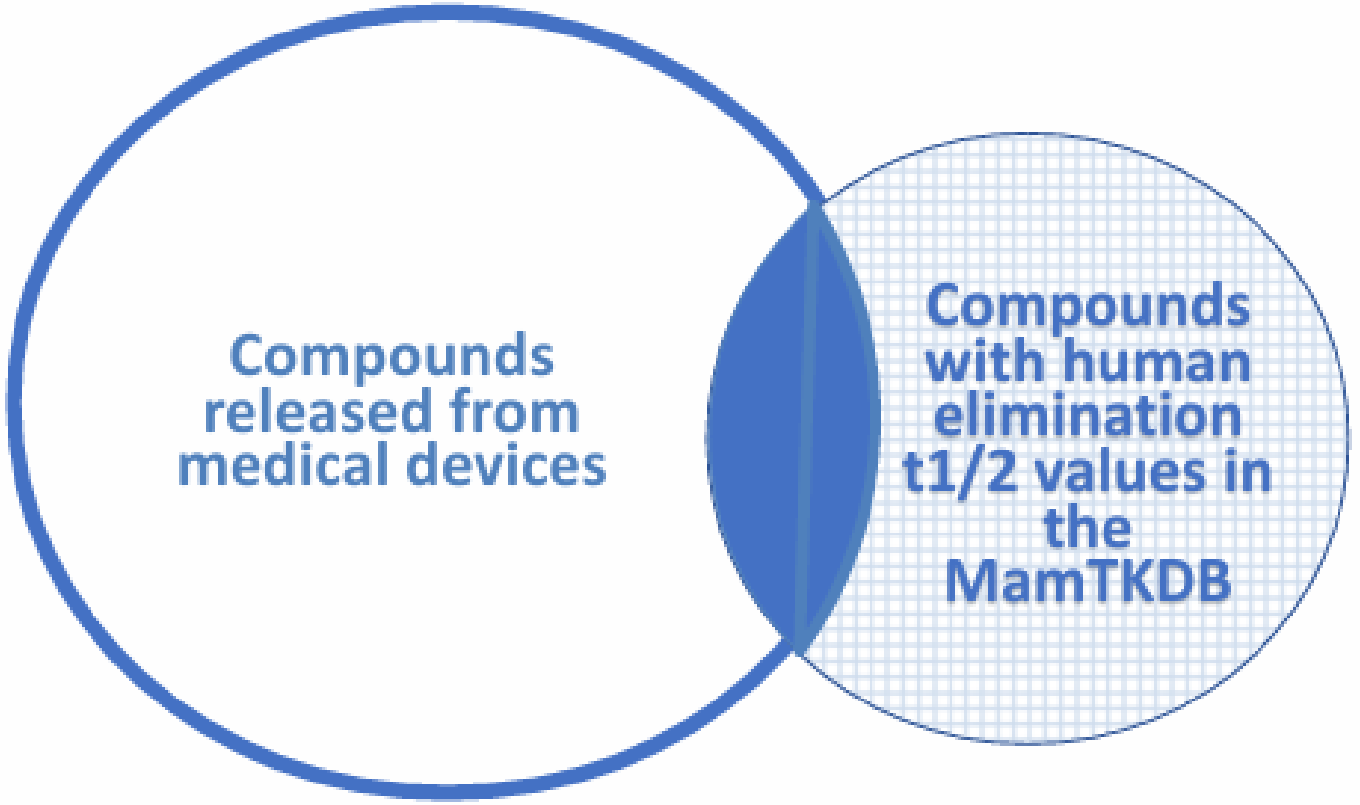
Step 3: Determination of the likelihood that the long half-life compound will bioaccumulate under clinical use conditions of the device, and

Step 4: Determine if the long half-life compound will accumulate in blood and tissues to levels associated with adverse toxicological effects.

Question 1: Are compounds with long elimination half lives actually found in or on medical devices?

- How many of these compounds are there? Thousands? A dozen?
- Perspective of one biocompatibility professional: *In addition, the long-term contact may be considered by the presence of bioaccumulate materials i.e. metal ions, DEHP, BPA, PFAS, silicone droplets, silver complexes.*

Step 1. Identification of extractable and leachable (E&L) compounds with long total body elimination half-lives



We noticed that most of the compounds in the MamTKDB are drugs.

- **Are these compounds representative of the types of compounds released from medical devices?**

We used a computational model in the EAS-E Suite predict elimination t1/2 values for E&L compounds to find additional device-related compounds that are not in the MamTKDB.



https://eas-e-suite.com/

Model Validation

Compared model-derived predictions to experimental values in MamTKDB

Outcome	EAS-E Model
False Negative	53
False Positive	7
True Negative	470
True Positive	15
Total	**545**

Statistic	Value
Sensitivity	22.06%
Specificity	98.53%
Accuracy	88.99%

Model Qualification/Application

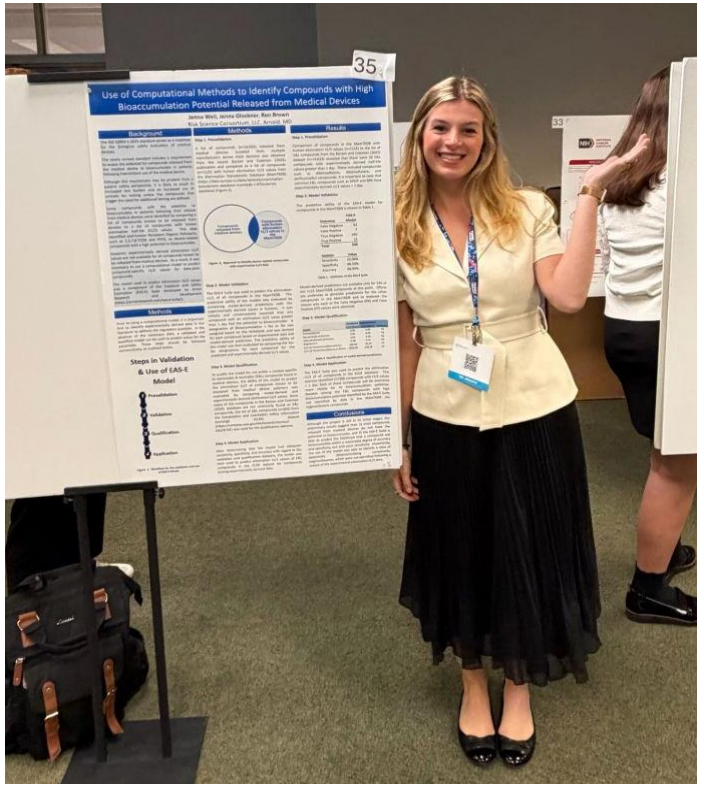
The EAS-E model was not able to return a prediction of human elimination t1/2 for many compounds in the ELSIE E&L database, especially for compounds outside of the applicability domain of the model.

Therefore, as a practical matter, it is not possible to use this model as a tool to identify compounds with long elimination t1/2 values that are released from medical devices.

Poster presented on the performance of the EAS-E model by Jenna Weil

Use of Computational Methods to Identify Compounds with High Bioaccumulation Potential Released from Medical Devices

Presented at the 2026 Summer Immersion on Innovative Approaches in Science hosted by Johns Hopkins CAAT and The Physicians Committee for Responsible Medicine



Jenna Weil, MPH
Risk Science Consortium

Do we really need to account for bioaccumulation when determining an exposure category for devices?

Question 1: Are compounds with long elimination half lives actually found in or on medical devices?

- Yes, but there are exceedingly few compounds with elimination t1/2 values > 2 days that are likely to be found on medical devices.
- We found 23 out of >14,000 in the Coleman and Borton (2026) database with human t1/2 values > 2 days when compared to the MamTKDB.
- These 23 compounds typically fell into three structural classes: perfluoroalkyl compounds, chloro- or bromodiphenyls, and dioxins.

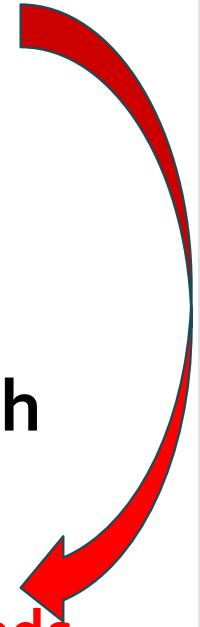
Examples of compounds released from devices with the potential to bioaccumulate

CAS Number	Chemical Name	Elimination t1/2 (days)	Compound Class
335-76-2	Perfluorodecanoic acid (PFDA)	4380.00	Perfluoroalkyl carboxylic acid and derivatives
335-67-1	Perfluorooctanoic acid (PFOA)	1980.00	Perfluoroalkyl carboxylic acid and derivatives
1763-23-1	Perfluorooctane sulfonate (PFOS)	1750.00	Perfluoroalkyl sulfonic acid and derivatives
118-74-1	Hexachlorobenzene	740.00	Chlorobenzenes
189084-64-8	2,2',4,4',6-Pentabromodiphenyl ether	618.00	Bromodiphenyl ethers
375-85-9	Perfluoroheptanoic acid	547.50	Perfluoroalkyl carboxylic acid and derivatives

Do we really need to account for bioaccumulation when determining an exposure category for devices?

We can ask ourselves three questions:

1. **Are compounds with long elimination half lives actually found in or on medical devices?**
2. **If so, do they bioaccumulate device-related exposure scenarios?**
3. **If they do bioaccumulate, do levels of the compound increase to levels associated with toxicity?**



Yes, but there are very few device-related compounds that have an elimination t1/2 > 2 days and those that do are representative of only small group of structural classes.

Do we really need to account for bioaccumulation when determining an exposure category for devices?

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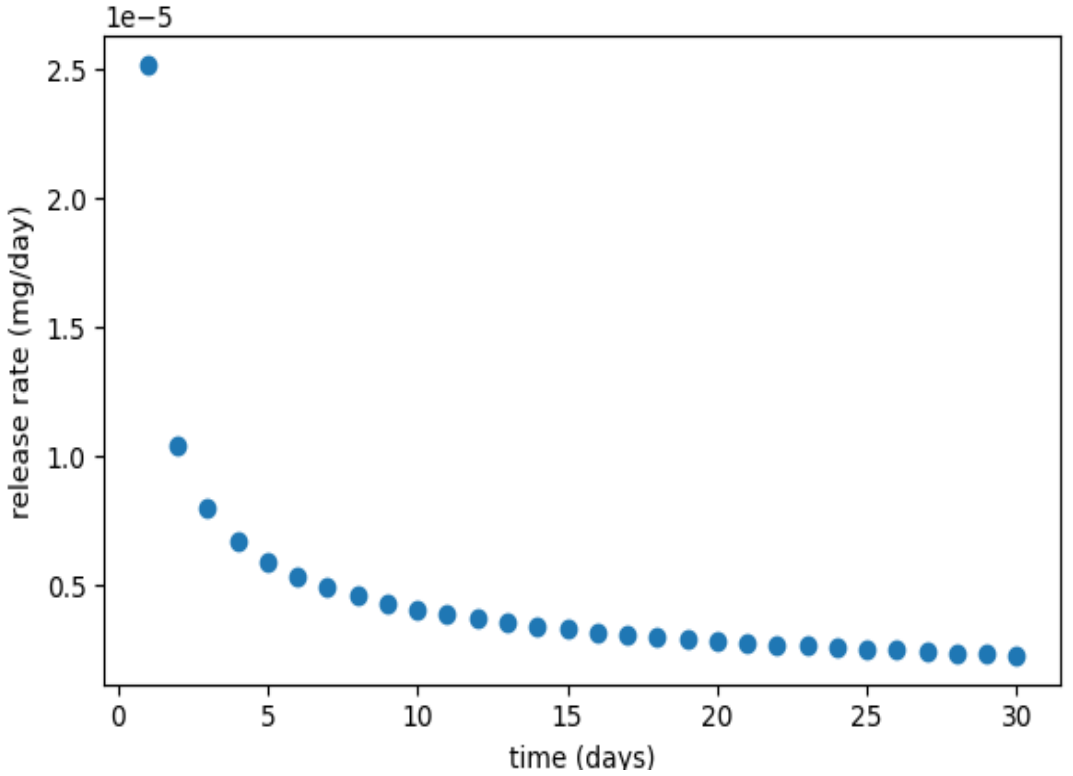
Step 2: Estimation of the amount of the long half-life compound released from medical device under clinically relevant use scenarios,

Step 3: Determination of the likelihood that the long half-life compound will bioaccumulate under clinical use conditions of the device, and

Step 4: Determine if the long half-life compound will accumulate in blood and tissues to levels associated with adverse toxicological effects.

Case Study 1: Evaluation of the bioaccumulation potential of compounds with extremely long t1/2 values (PFOS released from PTFE device)

Henry et al. (2018) noted that the upper limit of low molecular weight residuals in PTFE is < 1 ppm (0.001 mg/g polymer). Conservatively assuming that all of the residuals are PFOS, the CHRIS model predicts that 2.5 x 10^{-5} mg of PFOS would be released from a 10 g PTFE device on Day 1 of exposure.



National Toxicology Program
U.S. Department of Health and Human Services

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NICE v5.0 Release

NICE updates include the following new resources and site improvements:

- Updated chemical quick lists
- PBPK and IVIVE tools updated to align with EPA's httk v2.7.4 including flexibility in dosing scenerios.
- New visualizations for select data sets added to Search Tool

NICE NEWS



NICE version 5.0 Released August 2026

Visit News page for more information.

PAUSE

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Chemical Quest ›

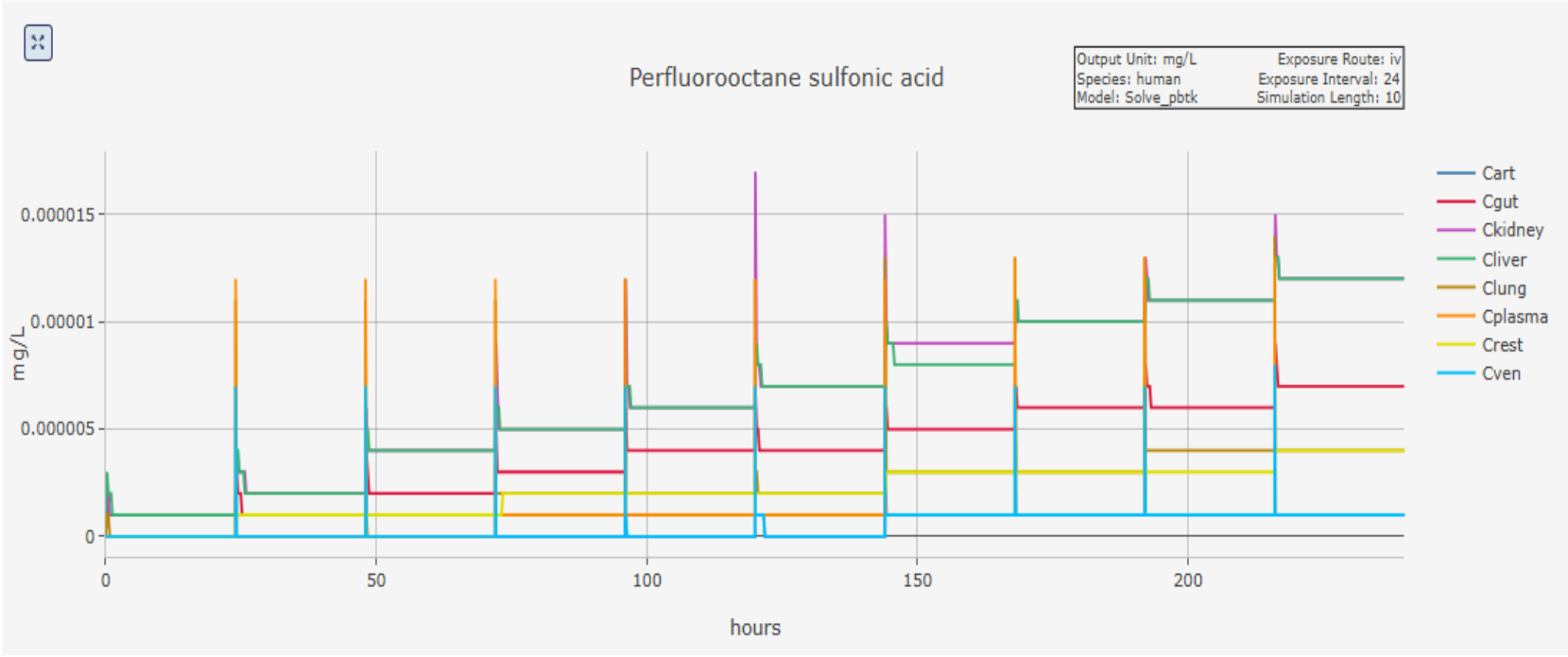
Curve Surfer ›

PBPK ›

Is PFOS predicted to bioaccumulate following repeated exposures?

CASRN: 1763-23-1 **DTXSID:** DTXSID3031864

Chemical Name: Perfluorooctane sulfonic acid



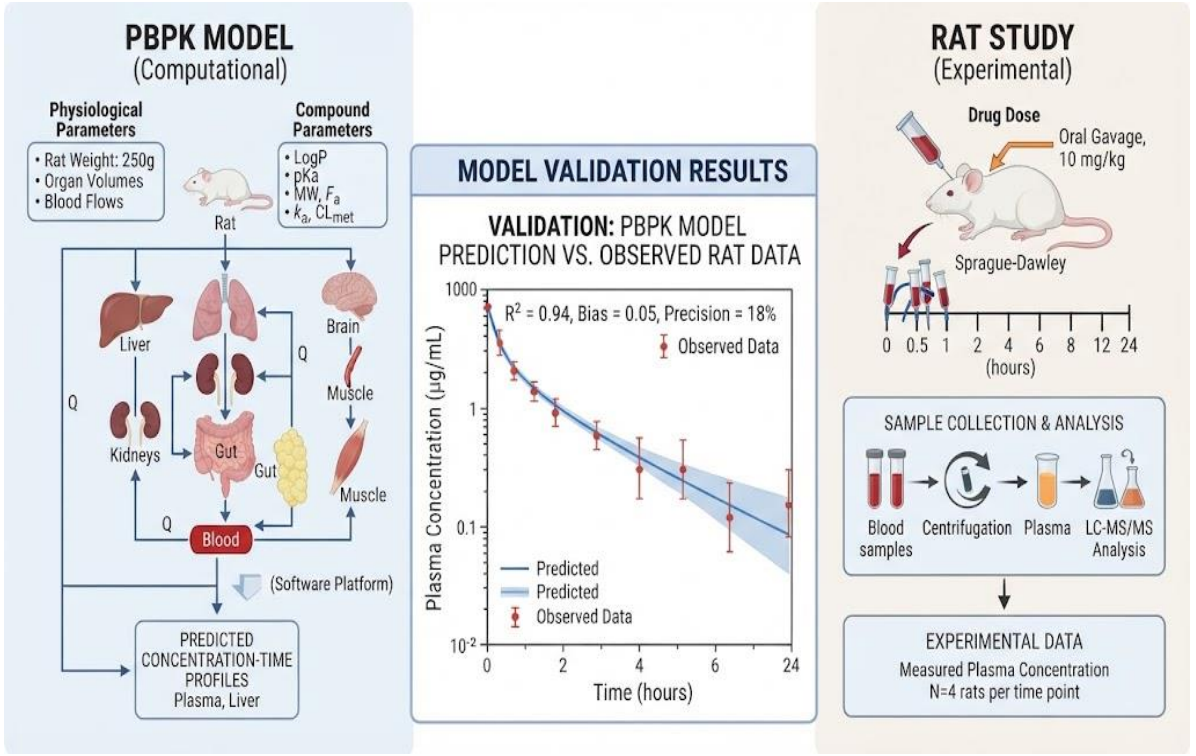
YES!

Case study: PFOS released from cardiac lead

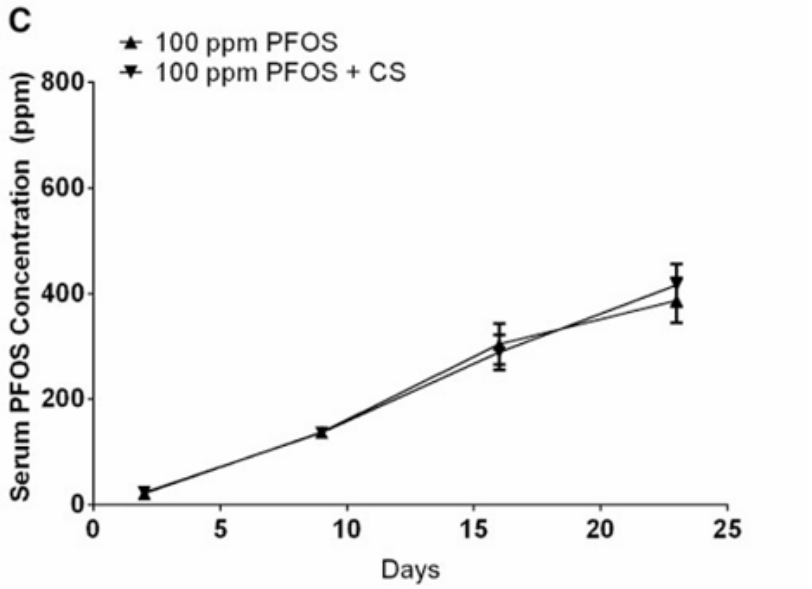
Tissue	Concentration Day 1 (µM)	Concentration Day 10 (µM)	Fold Change	Concentration Day 30 (µM)	Fold Change
Plasma	0.000023	0.000026	1.1		
Liver	0.000008	0.000026	3.25		
Plasma	0.000023			0.000026	1.1
Liver	0.000005			0.000026	5.2

Validation of the NTP ICE PBPK model for PFOS

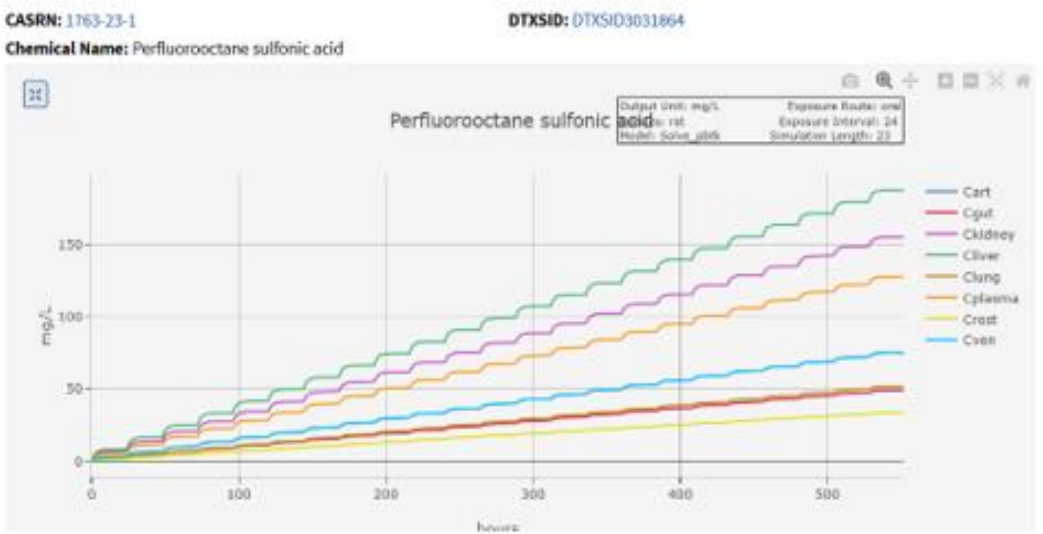
- Model-derived predictions of PFOS in plasma and tissues are only valid if the model is able to accurately predict them.
- Two independent data sets were used to evaluate the NTP ICE PBPK model for PFOS:
  - Bagley et al. (2017)
  - Loccisano et al. (2012)
- Measured PFOS concentrations in plasma and liver were compared with concentrations predicted by the NTP ICE PBPK model.



Validation of the PBPK model using data from Bagley et al. (2017)



Plasma concentration of PFOS in male rats after repeated oral exposure of 6 mg/kg/day for 23 days



Predicted plasma concentration of PFOS in rats after repeated oral exposure of 6 mg/kg/day for 23 days using the NTP ICE PBPK model.

	Serum/Plasma µg/ml	Liver µg/ml
Experimental (Bagley et al. 2017)	400	400
Predicted (NTP ICE)	127	187

An UF of 3 was applied to ensure that the model-derived PFOS concentrations did not underpredict experimentally derived values.

Do we really need to account for bioaccumulation when determining an exposure category for devices?

We can ask ourselves three questions:

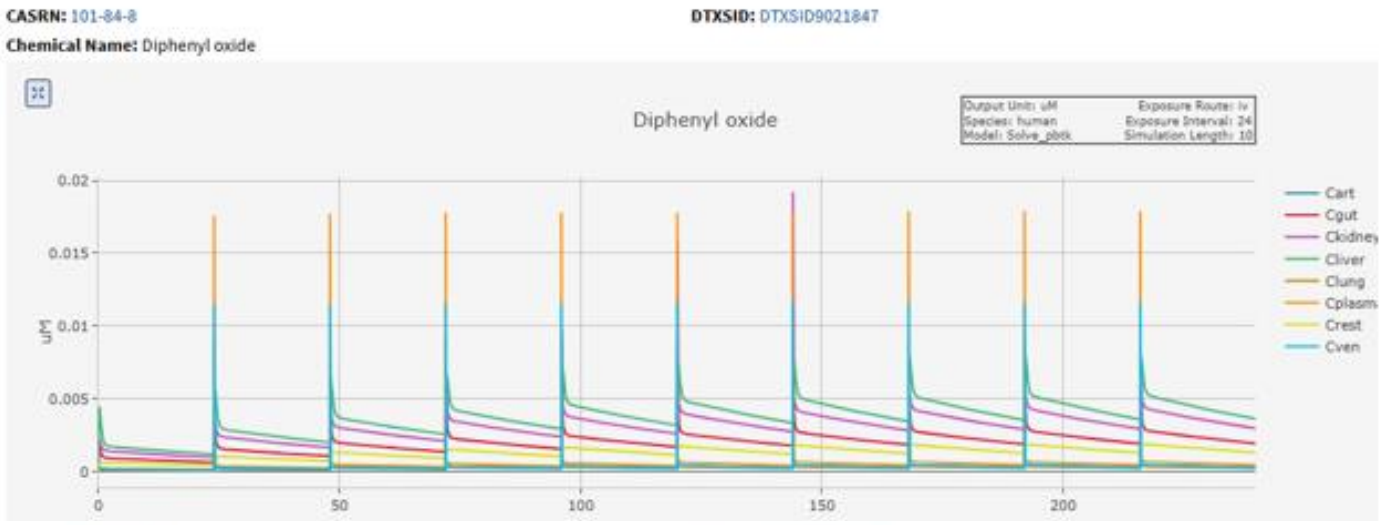
1. **Are compounds with long elimination half lives actually found in or on medical devices?**
2. **If so, do they bioaccumulate device-related exposure scenarios?**
3. **If they do bioaccumulate, do levels of the compound increase to levels associated with toxicity?**

Does PFOS bioaccumulate to toxic levels following its release from a medical device?

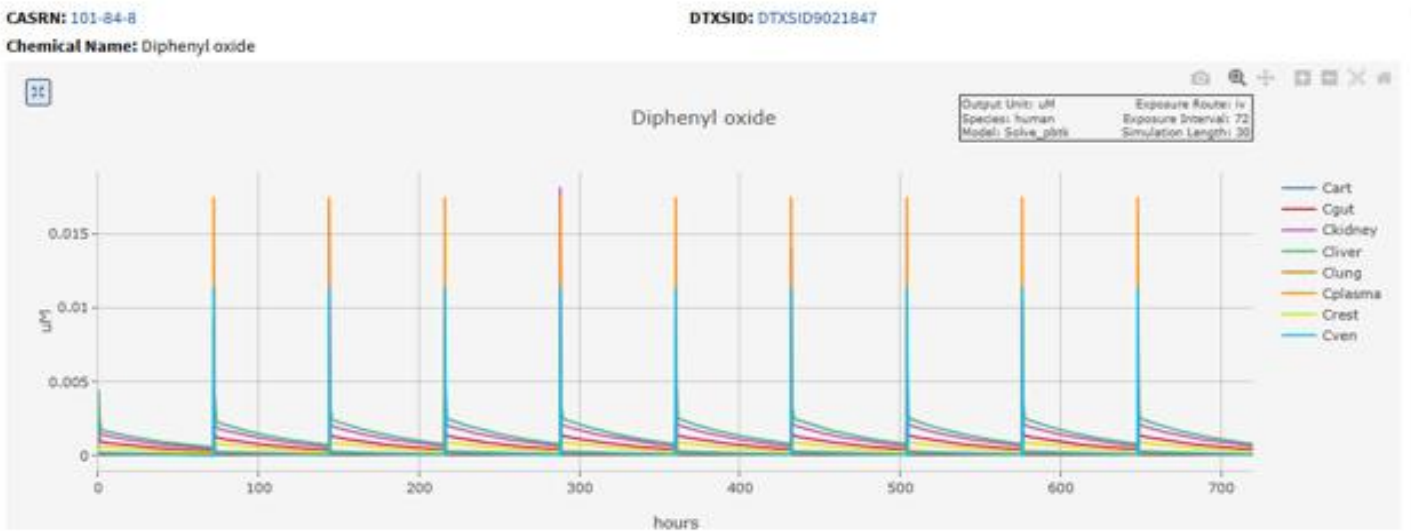
	Concentration (µM)
Concentration in plasma predicted by PBPK model following repeated device use (Table 2)	0.000026
Concentration in plasma predicted by PBPK model following repeated device use modified using 3x UF	0.000078
Background level in population (95th percentile NHANES 2013-2014)	0.000549
Lowest benchmark concentration associated with any bioactivity endpoint in vitro (NTP ICE Curve Surfer)	0.023 (CYP450 activity)
Lowest benchmark concentration associated with reduced cell viability in vitro (NTP ICE Curve Surfer)	0.649

NO!

Case study 2: Diphenyl oxide
Elimination t1/2 = 3.5 days



Every day for
10 days



Every third day for
30 days

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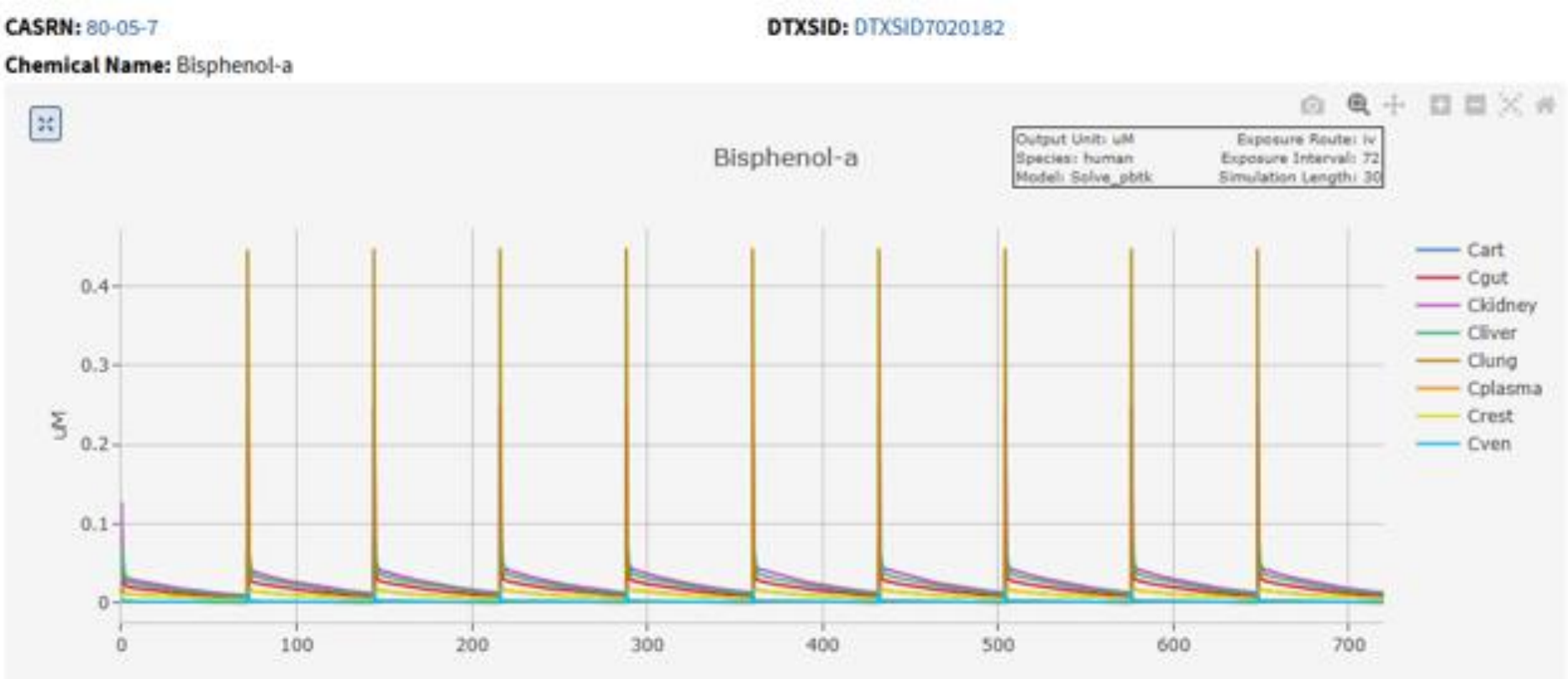
Does diphenyl oxide bioaccumulate to toxic levels following release from a medical device?

	Concentration (µM)
Concentration in plasma predicted by PBPK model following repeated device use (Table 4)	0.018
Background level in population	Not available
Lowest benchmark concentration associated with any bioactivity endpoint in vitro	22.6
Lowest benchmark concentration associated with reduced cell viability in vitro	22.6

NO!

Case study 3: BPA Elimination t1/2 = 4-6 hours

Exposure scenario: BPA released from a hemodialyzer (Haq et al., 2023)



Do we really need to account for bioaccumulation when determining an exposure category for devices?

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2. **If so, do they bioaccumulate device-related exposure scenarios?**
3. **If they do bioaccumulate, do levels of the compound increase to levels associated with toxicity?**

Is BPA expected to bioaccumulate following its release from a medical device?

- No, based on model-derived predictions from the NTP ICE PBPK model.
- Model was validated using two data sets
- No need to consider further since bioaccumulation is not expected to occur.

Summary of findings from PBPK model predictions

Compound	Elimination t1/2 (days)	Potential to bioaccumulate based on t1/2	Predicted bioaccumulation following intermittent device use?	Bioaccumulates to toxic concentrations under clinical use conditions?
PFOS	1750.00	Yes	Yes	No
Diphenyl oxide	3.5	Yes	Depends on exposure interval	No
BPA	0.2-0.4	No	No	No

What if the model is wrong?

The conclusions of the workflow depend on the accuracy of the NTP ICE PBPK model.

Why do we think the model is accurate?

- It predicts the concentration-time curves that we expect for each compound based on elimination t1/2.
- It was validated by independent data sets.

Therefore, we believe the model can be relied upon to give accurate predictions of plasma and tissue concentrations. If the model provides accurate predictions, the conclusions drawn from those predictions are well supported.

Additional considerations and conclusion

- A central concept in the ISO 10993-1:2025 standard is the use of a risk management approach. However, the approach recommended in the standard that describes how to take bioaccumulation into account is hazard-based, not risk-based.
- The approach in the standard is not consistent with a least burdensome approach advocated by the FDA.
- The approach in the standard is not consistent with evidence-based toxicology. Similar to the MMP issue.
- Based on our preliminary findings, we believe that the section on bioaccumulation should be deleted from the standard and, therefore, there is no need for a Technical Specification to provide guidance on how to implement this section of the standard.

Next steps

- We welcome your feedback on the draft manuscript, which is now available for review on the Risk Science Consortium website: www.riskscienceconsortium.com
- We are seeking additional data on the amount of PFOS and other perfluoroalkyl compounds released from medical devices to expand Case Study 1.
- I appreciate the opportunity to share these ideas with you. I'd be happy to answer your questions and hear your thoughts.