Physics-based models to predict patient exposure to medical device leachables

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Overview

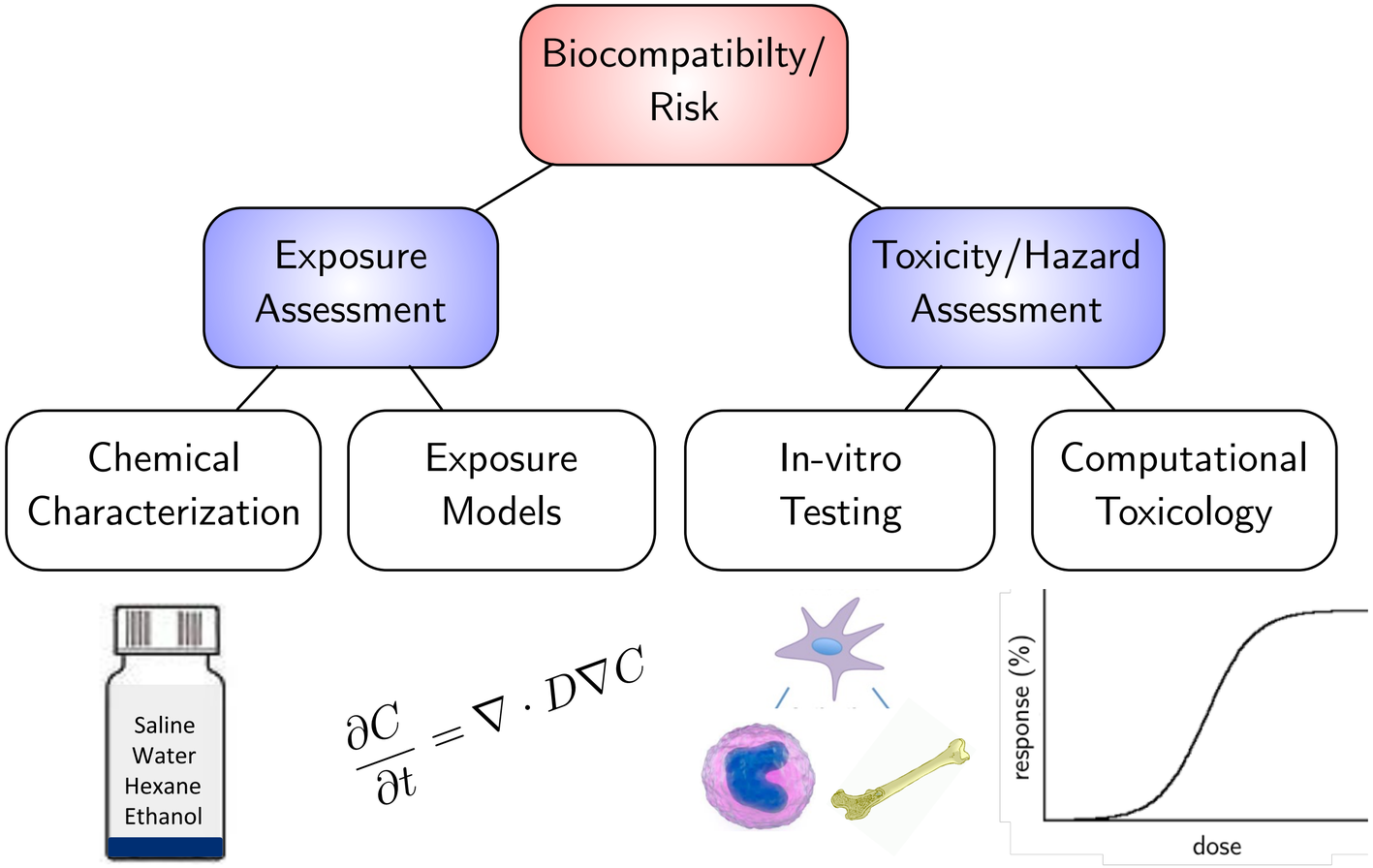
Key message: Physics-based models based on conservative assumptions can provide more clinically relevant maximum exposure estimates, in lieu of or supplementary to extraction testing

Outline:

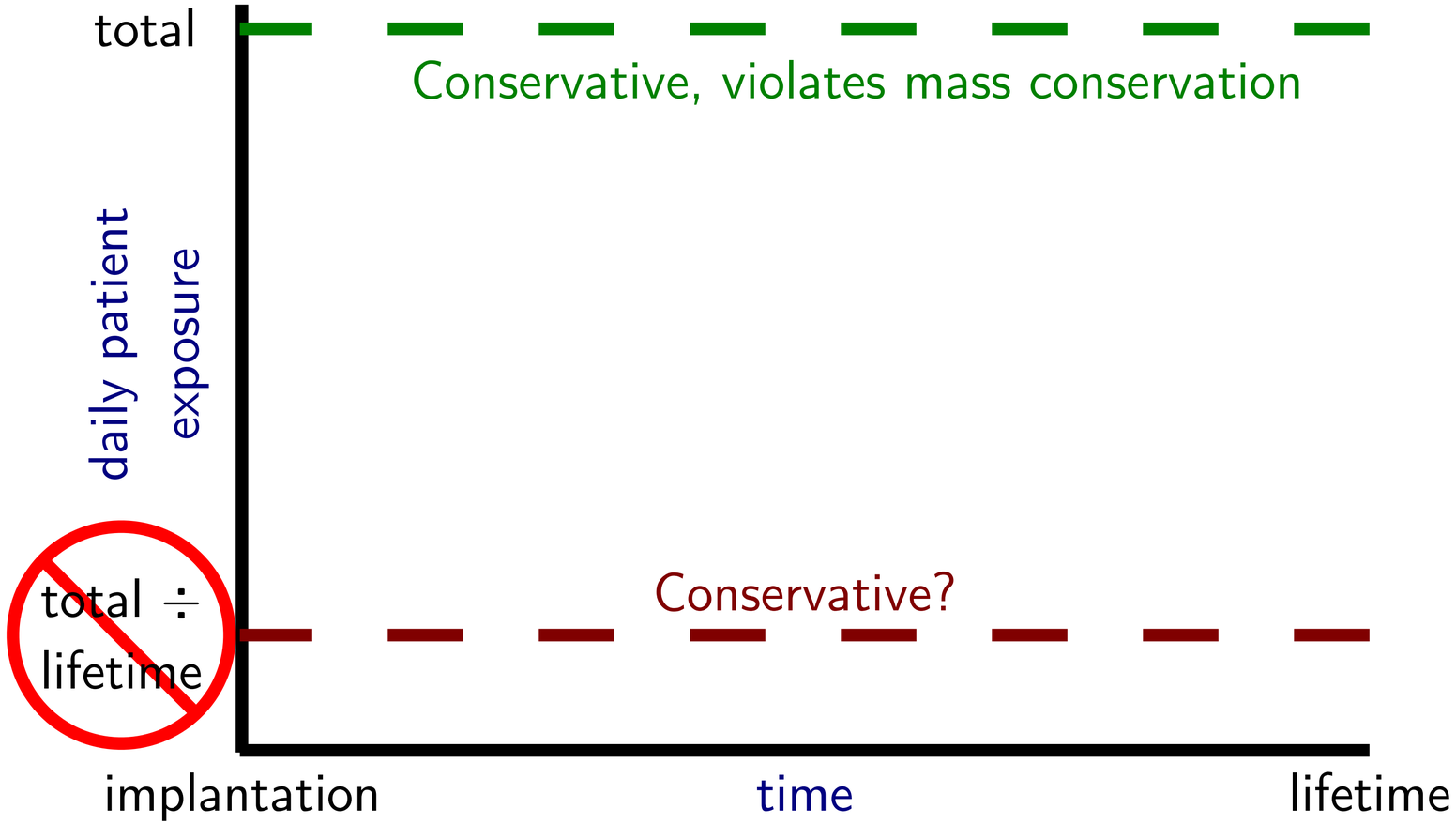
- Potential benefits and challenges of using physics-based exposure models (PBEM) to aid toxicological risk assessment of medical devices
- Strategy to address challenges in device polymers and application to color additives and other additives of known quantity
- Efforts to extend applicability of PBEM to non-targeted additives/impurities by leveraging extraction test results
- Current and future efforts for improving PBEM

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"



No physical/physiological basis - significant room for improvement!

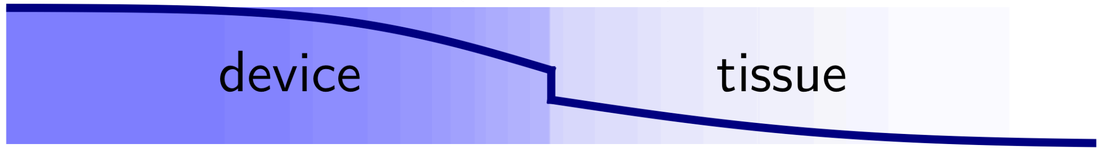
Mass transport models

$C^i(x, t = 0)$

physics-based model

$$\frac{\partial C^i}{\partial t} = \begin{cases} \nabla \cdot D^{ij}_{\alpha\beta} \nabla C^j & \text{diffusion} \\ [U_\alpha(\mu_{\alpha\beta}, p_{\alpha\beta}) \cdot \nabla] C^i & \text{advection} \\ v^{ij} R^j & \text{reaction} \end{cases}$$

$C^i(x, t = t^*)$



Minimal Model

physics-based model

$$\frac{\partial C^i}{\partial t} = \begin{array}{ll} \nabla \cdot D^{ij}_{\alpha\beta} \nabla C^j & \text{diffusion} \\ [U_\alpha(\mu_{\alpha\beta}, p_{\alpha\beta}) \cdot \nabla] C^i & \text{advection} \\ v^{ij} R^j & \text{reaction} \end{array}$$

Additional assumptions

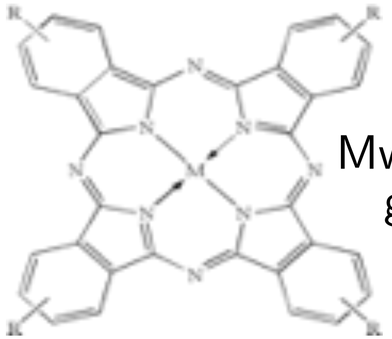
- "durable" matrix
- dilute, bulk additive/impurity
- homogeneity (macroscopic)
- worst-case implant environment
- worst-case geometry

$$M(t) \leq 2AC_0\sqrt{\frac{Dt}{\pi}}$$

One material parameter, D, the diffusion coefficient of the leachable in the polymer matrix

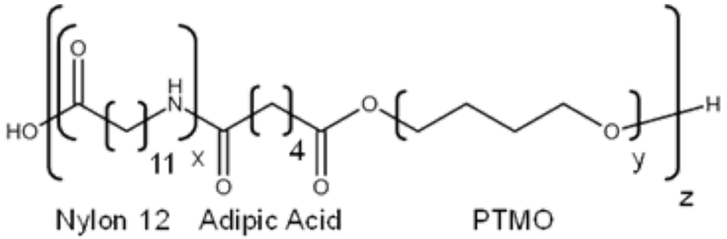
Sorption experiments

Even for simple cases, experimental challenges result in limited data that can be used to specify these quantities.



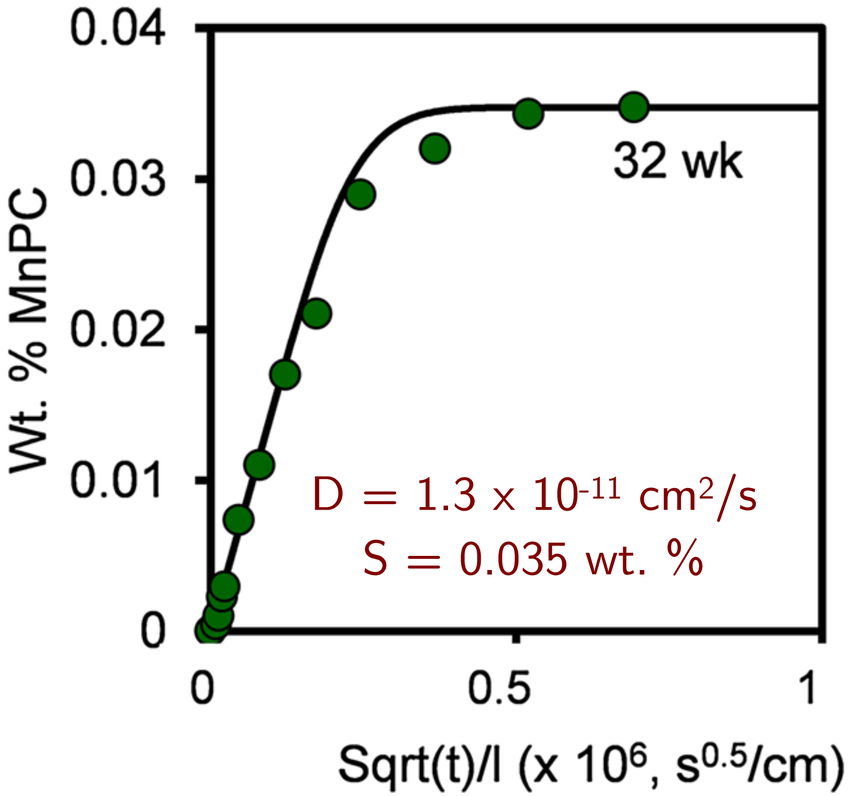
Mw = 567 g/mol

Mn phythalocyanine



PEBAX block co-polymer

V. Chandrasekar, et al, Annals of Biomedical Engineering. 46 (2018) 14–24.



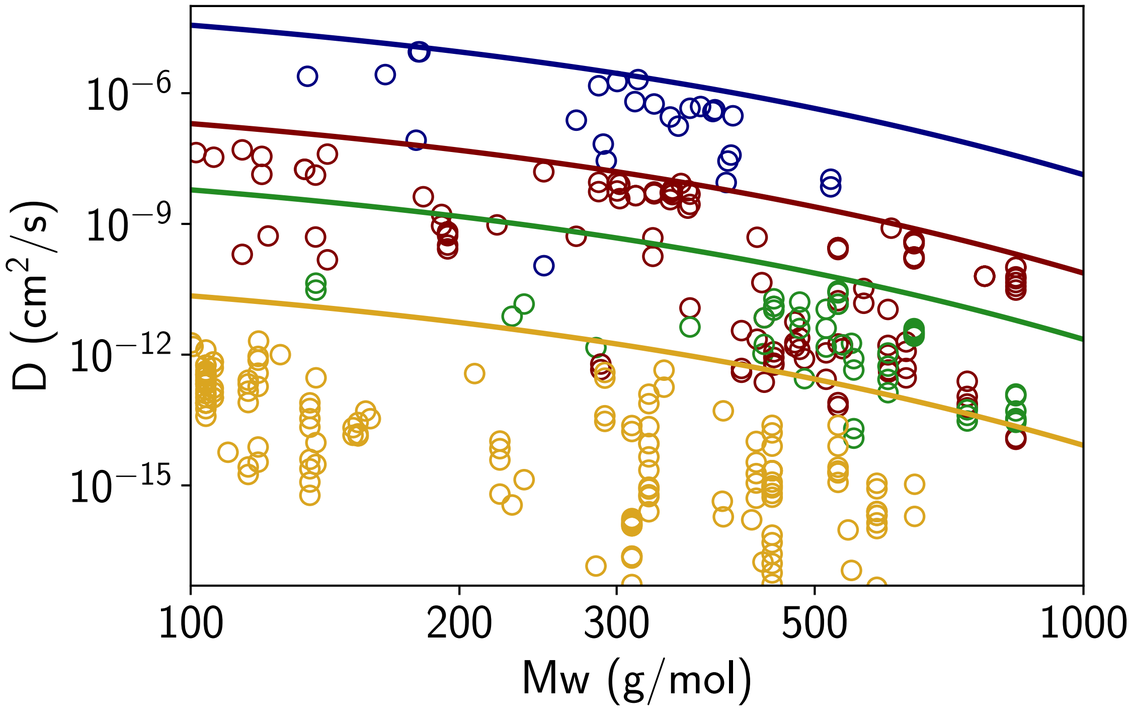
D characterization took ≈ 8 months for a single additive-polymer system

Upper bounds for D in device polymers

Following EPA[1], categorize relevant polymers based on literature D and used the "Piringer model" to parameterize upper bounds[2]:

rubbers		plastics 1	
Silicone	PVC(P)	LDPE	PP
Nitrile	Natural	PU	MBS
Neoprene		PEBAX	EVA

plastics 2		glasses	
HDPE	PVA	PET	PS
POM	PBT	PC	PAN
ABS	PEEK	PMMA	PEN
PTFE	FEP	PA	PVC



Upper bounds consistent with aggregated data from commodity materials[1], food packaging[2], and drug delivery systems[3].

[1] AD Schwope, R Goydan, and RC Reid, Methods for assessing exposure to chemical substances. Volume 11., 1992.

[2] T Begley, et al., Food Additives and Contaminants. 22 (2005) 73–90.

[3] AF Kydonieus, Treatise on Controlled Drug Delivery: Fundamentals-optimization-applications. Taylor & Francis, 1991.

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 ($C_0 < 2$ %)

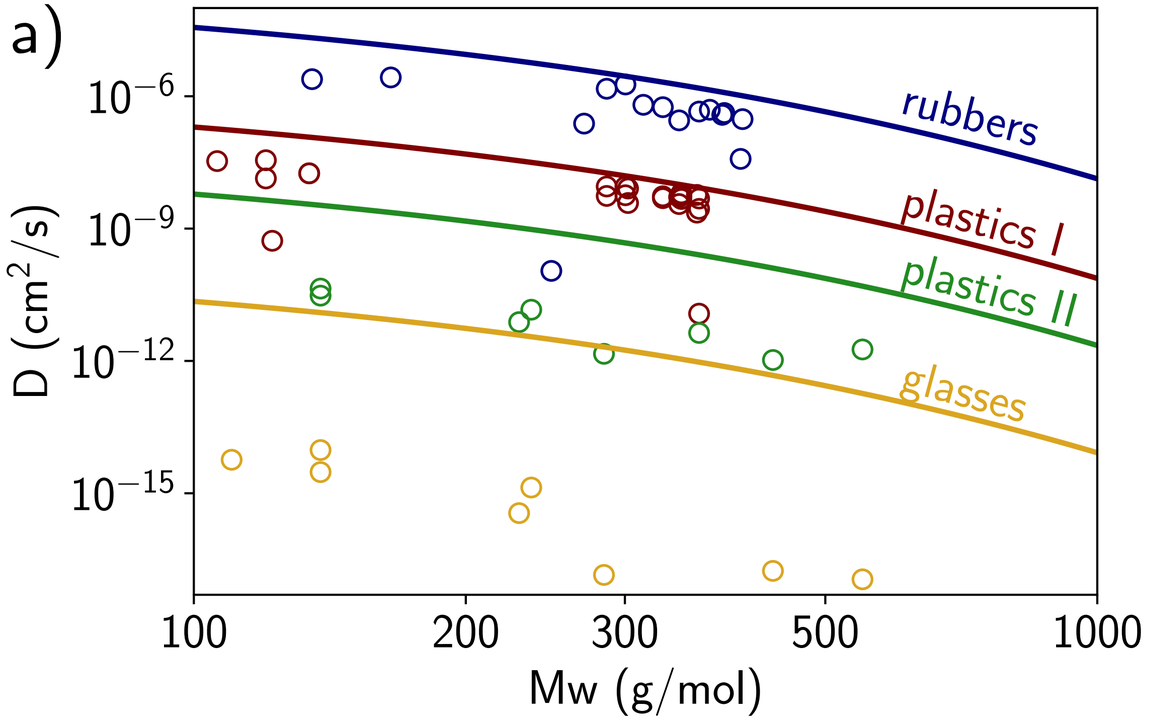
Additional conservative assumptions yield:

$$M(t) \leq 2AC_0\sqrt{\frac{D^M t}{\pi}}$$

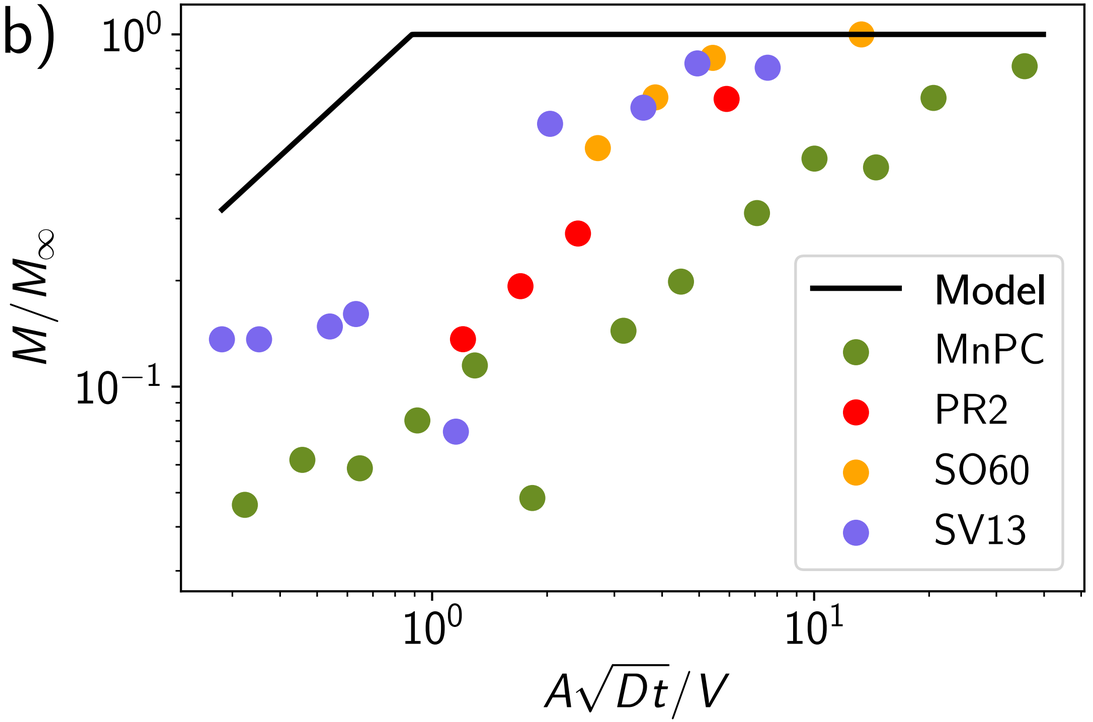
Validation

Validation of the constitutive (Piringer) model for D and exposure model for release. In cases, the model(s) remain protective:

Constitutive model



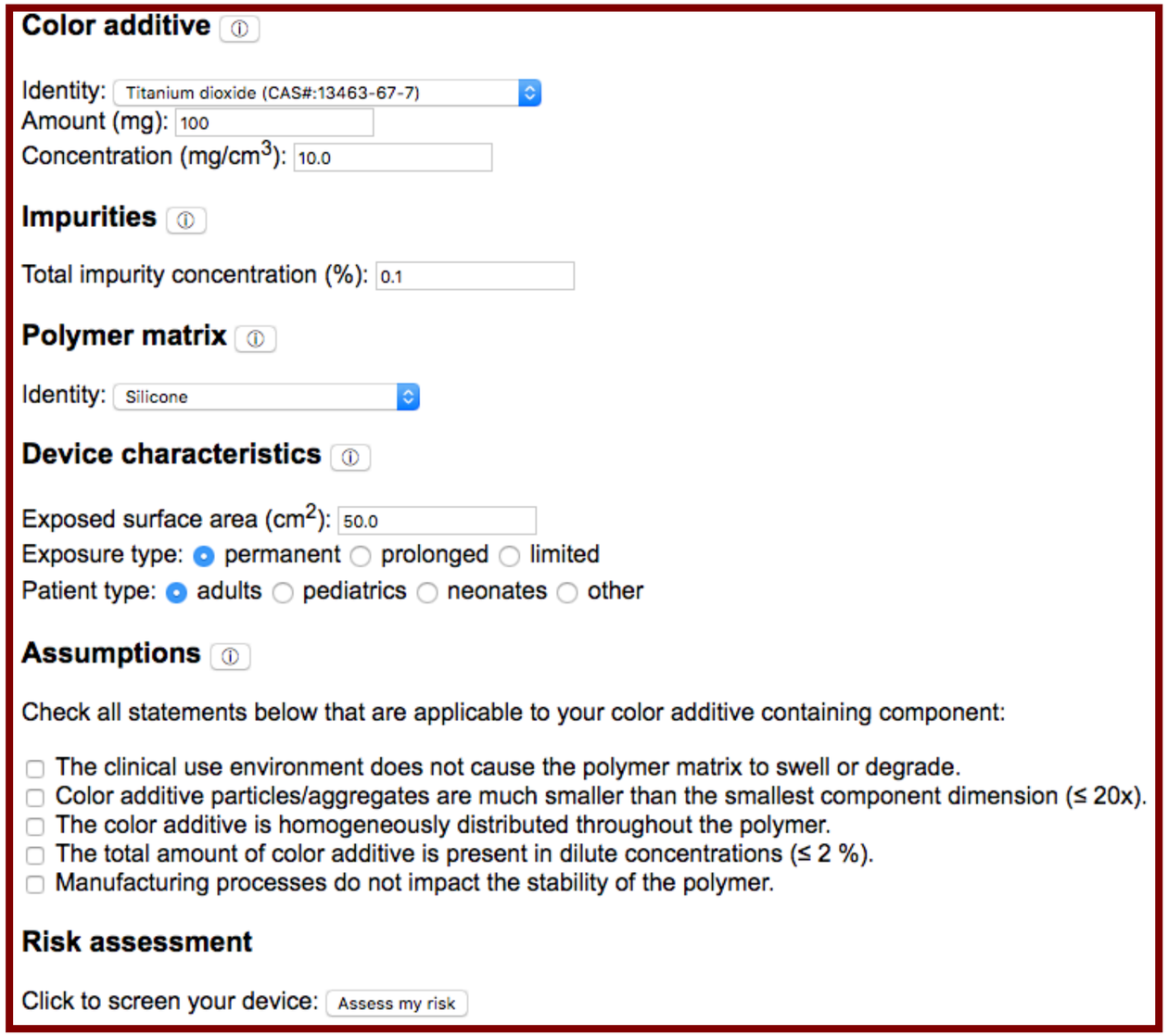
Exposure model



Tolerable intake (TI) values for CAs

color additive	Ref.	POD (mg/kg/day)	UF_1	UF_2	UF_3	TI (mg/kg/day)
titanium dioxide	a	1 000	10	10	10	1
carbon black	b	20 000	10	10	100	2
pigment brown 24	c	500	10	10	10	0.5
solvent violet 13	d	NA	NA	NA	NA	0.0013
Mn phthalocyanine	e	40	3	3	30	0.15
pigment blue 15	e	40	3	3	30	0.15
phthalocyanine green	e	40	3	3	30	0.15
ultramarine blue	f	300	3	1	30	3.3

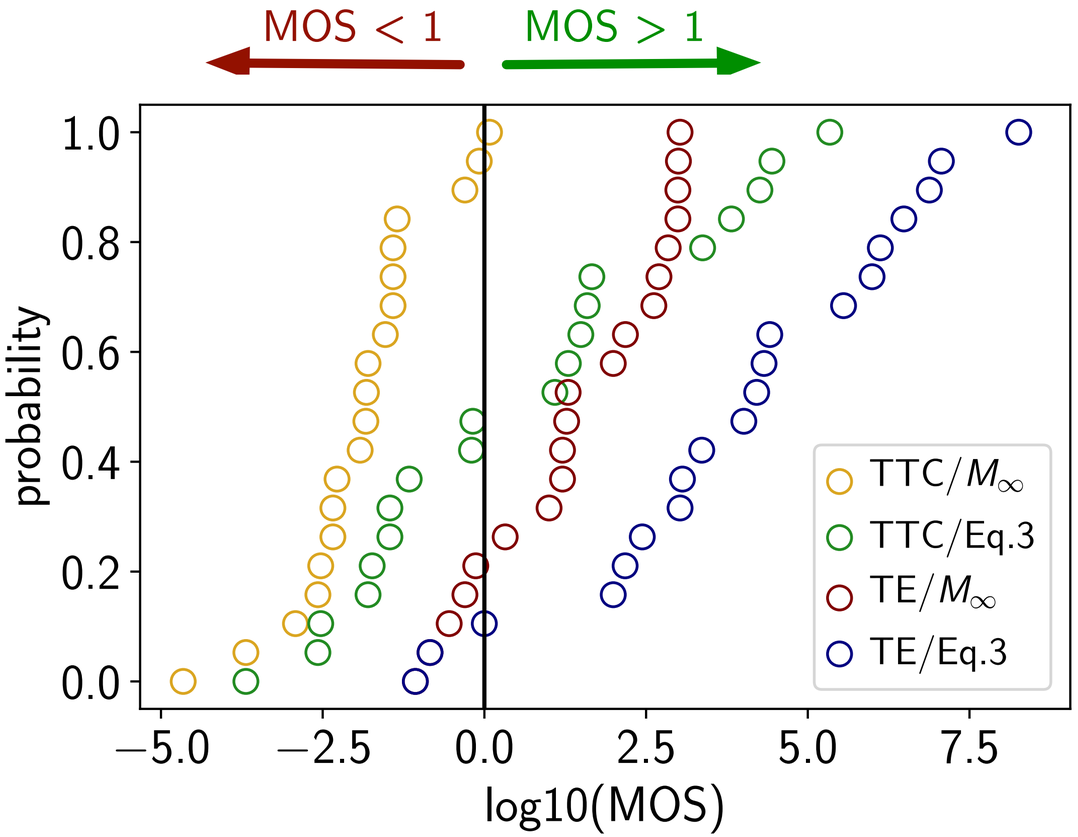
Color Hazard and RISk calculator (CHRIS)



- 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 with industry (20 CA-polymer combinations):

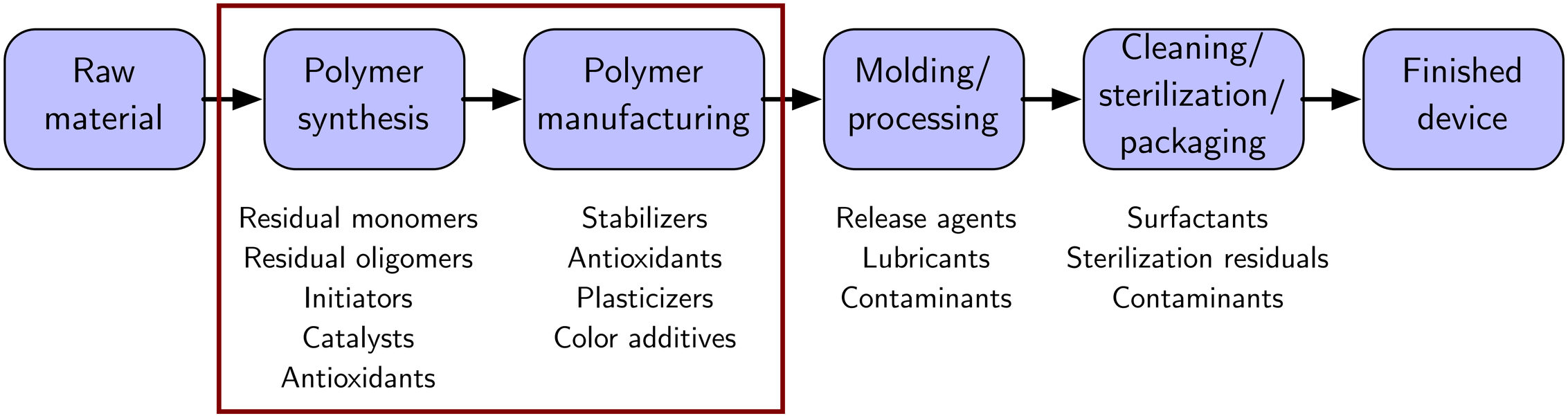


Margin of safety (MOS) =
TI ÷ exposure

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

Potential sources of leachables

Straightforward to extend CHRIS concepts to other bulk (i.e. homogeneously distributed) leachables:



However, the identity and total amount must be established a priori.

Graphic courtesy of Sharlene Dai (Medtronic)

CHemical RISk calculator (CHRIS v2)

Leachable ⓘ

Molecular weight (g/mol): 500
Amount (mg): 1
Is the leachable a color additive?: ◉ no ○ yes

Polymer matrix ⓘ

Matrix: Silicone
Mass (g): 1.0
Density (g/cm^3): 1.0

Device characteristics ⓘ

Exposed surface area (cm^2): 5.0
Exposure type: ◉ long-term ○ prolonged ○ limited

Assumptions ⓘ

Check all statements below that are applicable to your leachable containing component:

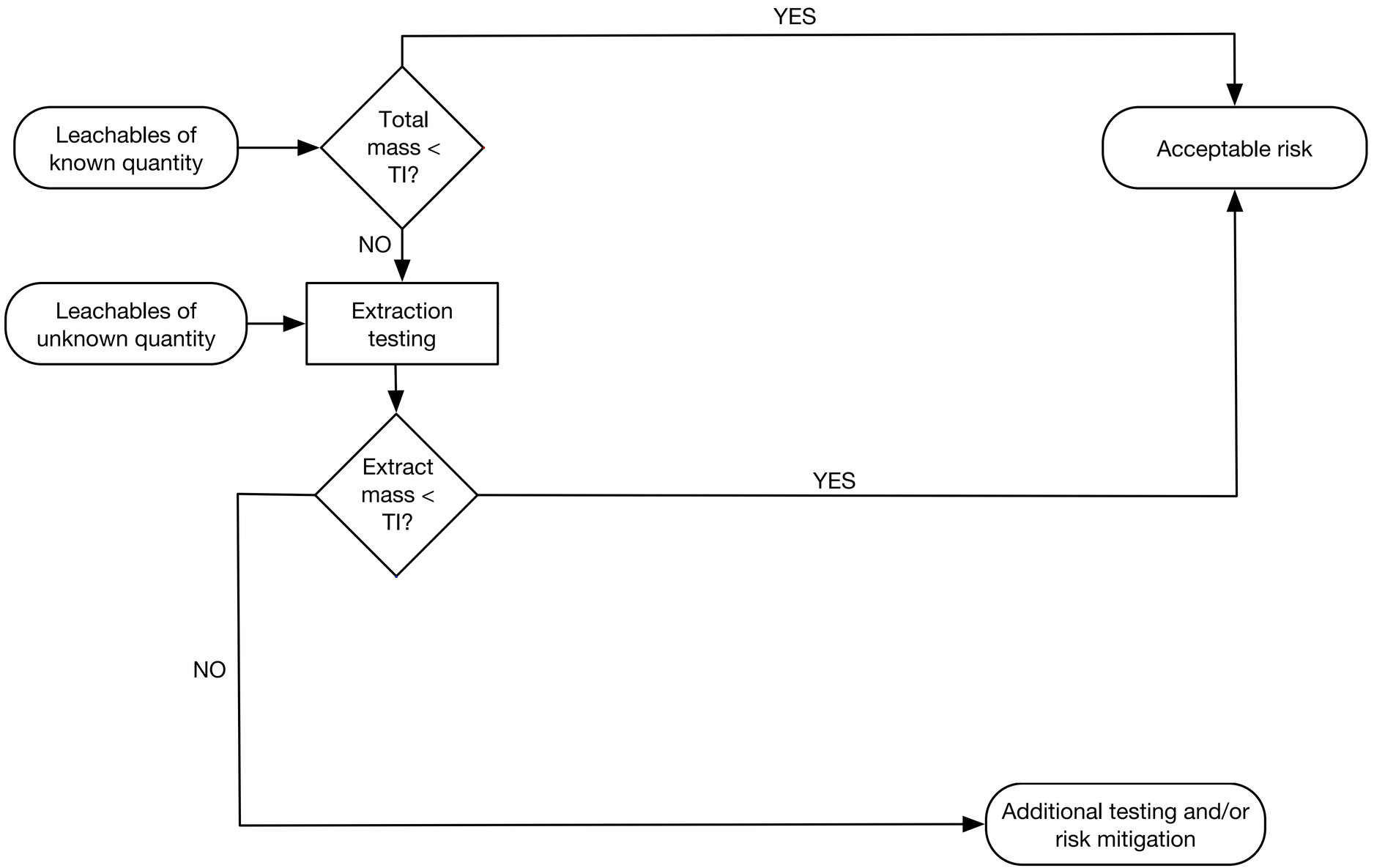
- ☐ The clinical use environment does not cause the polymer matrix to swell or degrade.
- ☐ Leachable particles/aggregates are much smaller than the smallest component dimension (≤ 50x).
- ☐ The leachable is homogeneously distributed throughout the polymer.
- ☐ The total amount of leachable is present in dilute concentrations (≤ 2 m/v %).
- ☐ Manufacturing processes do not impact the stability of the polymer.

Exposure assessment

Click to screen your device: Estimate exposure

- Extends CHRIS v1 to any bulk leachable
- Defaults to mutagenic TTC, except for CAs
- Beta version: http://dsaylor.pythonanywhere.com
- Feedback appreciated

Chem char/TRA workflow



Leachables with unknown M_0

Proposed Approach: leverage results of extraction testing

For bulk extractables when matrix swelling is rapid relative to extractable migration:

$$M_0 = M_0\left(t^*, M_{t^*}, V_p, V_m, A_p, D_E, K_E\right)$$

t^* = extraction time

M_{t^*} = mass extracted at t^*

V_p = polymer volume

V_m = media volume

A_p = polymer surface area

D_E = diffusion coefficient of the extractable in the (potentially swollen) polymer

K_E = polymer/media partition coefficient

In theory, M_0 can be determined from a single extraction test; however, need relevant material parameters

Deriving D_E and K_E from extraction data

OXFORD

SOT | Society of Toxicology

academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 178(1), 2020, 201–211

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Research Article

Leveraging Extraction Testing to Predict Patient Exposure to Polymeric Medical Device Leachables Using Physics-based Models

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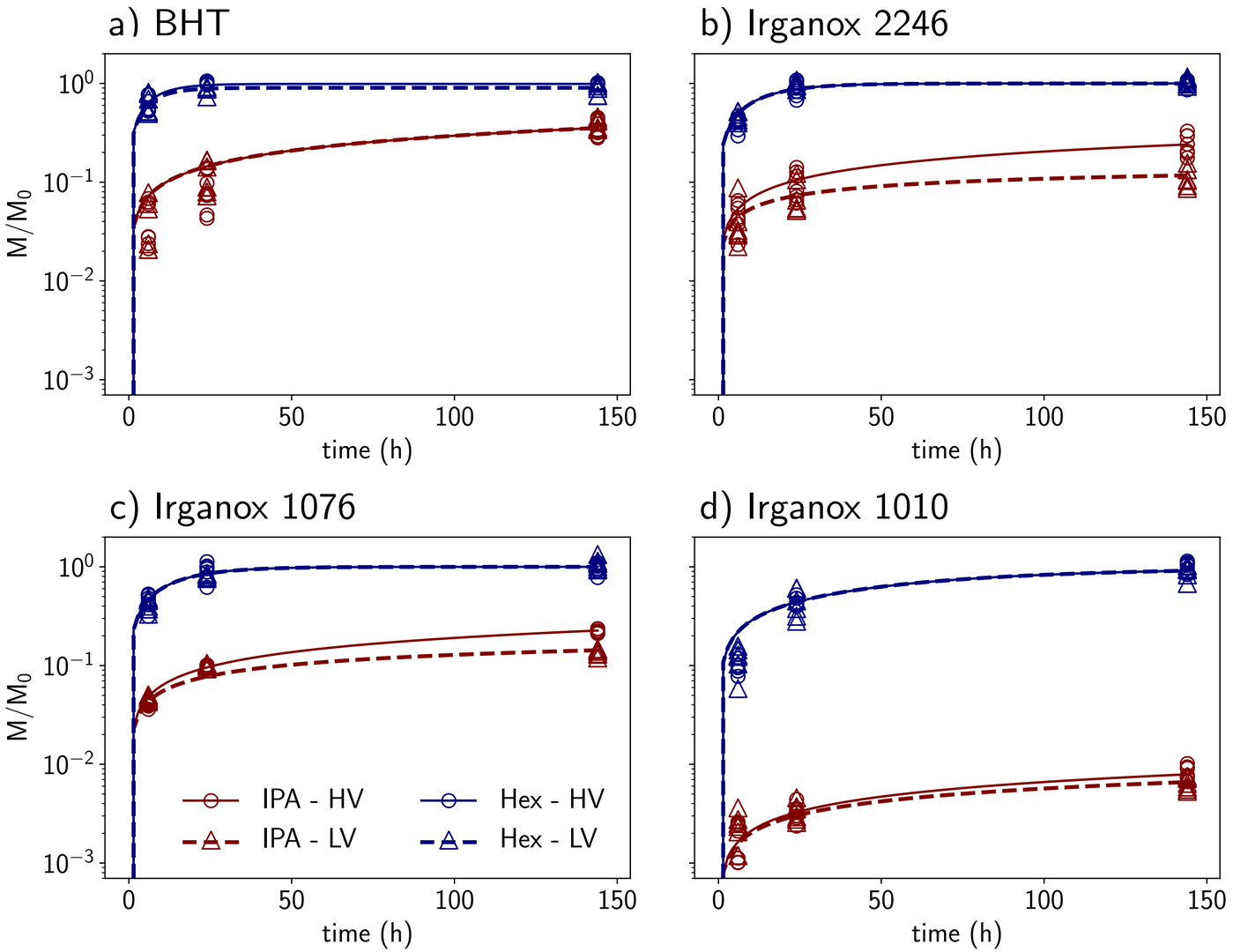
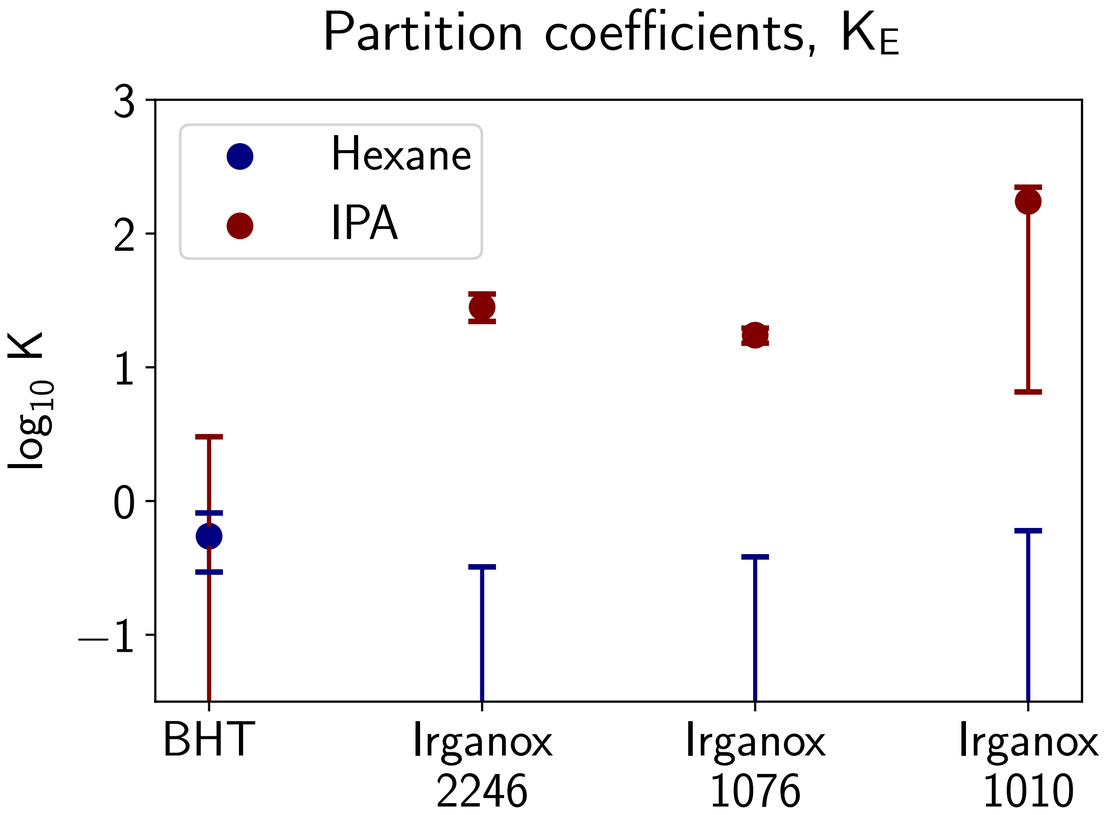
Proof on concept that the relevant material properties (D_E and K_E) can be quantified from extraction data and used to estimate the total pool of a given leachable.

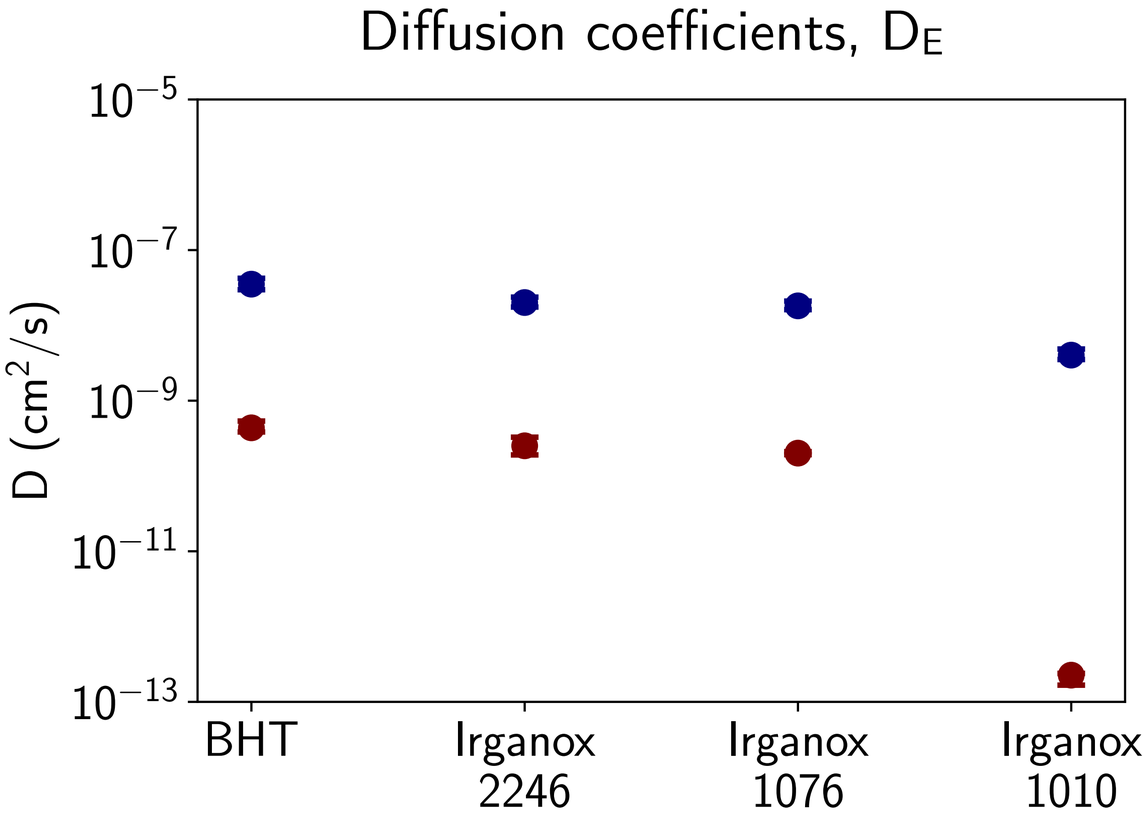
Antioxidants in HDPE



- increased release rate in hexane due to polymer swelling
- decrease release rate within increasing leachable Mw
- media volume effects suggest solubility limitations
- release data are well fit by the model equation; fit parameters are D_E and K_E

Fit material parameters





Demonstrated that the total pool can be reasonably estimated based on limited extraction testing and knowledge of material properties

Current status

For ≈20 common polymer matrices, improved exposure predictions can be made for (bulk) leachables with M_w in the range of 100-1000 Da, if the total amount, M_0:

- is known *a priori*
- can be determined directly from extraction, e.g. repeat extraction demonstrates complete exhaustion of the specific leachable
- can be inferred for a well-characterized system (D_E and K_E for extraction system established)

Current and future efforts:

- Expand applicability of CHRIS to more systems: determine conservative bounds on D_E and K_E for common extraction media to facilitate determining M_0 from limited extraction testing
- Improve the screening success rate: improve clinical relevance of the model by addressing uncertainty of the inputs

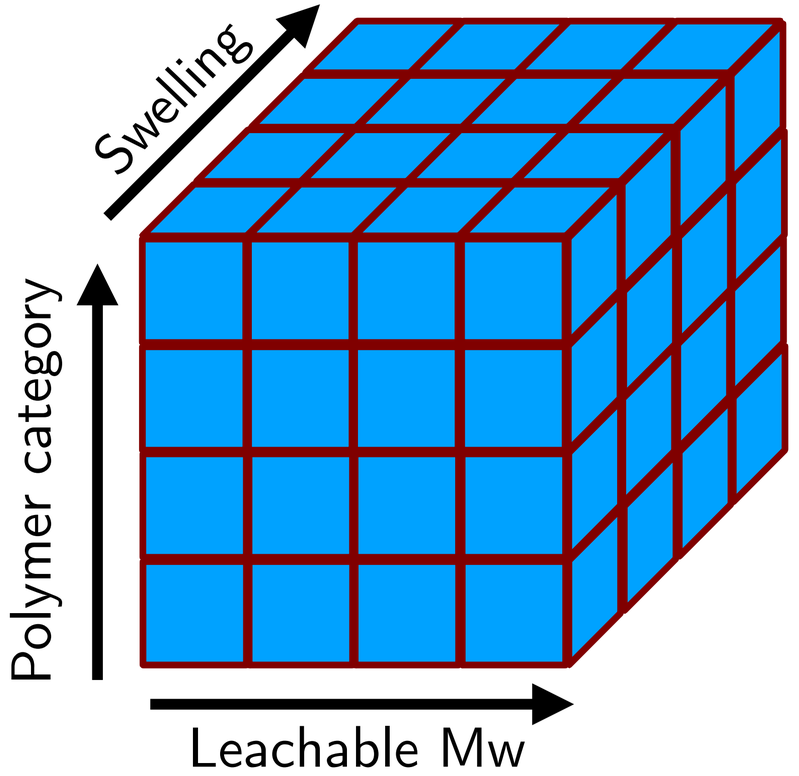
Conservative property bounds for estimating M_0

For "good" solvents ($K_E \leq 1$), we can focus on establishing a lower bound on D_E.

Lowest order effects:

- Polymer glassiness/crystallinity
- Leachable Mw
- Media/polymer affinity, i.e. swelling

While models can be helpful in interpolation, reasonable segmentation suggests $\geq$ 4 x 4 x 4 categories x 10 observations = 640 data points needed



Aggregation of extraction data?

If enough information is available, aggregation of routine extraction results may enable conservative property bounds for common extraction media to be established.

Three potential "buckets":

1) Chemical specific characterization at multiple time points and potentially different media volumes (most useful, but uncommon)

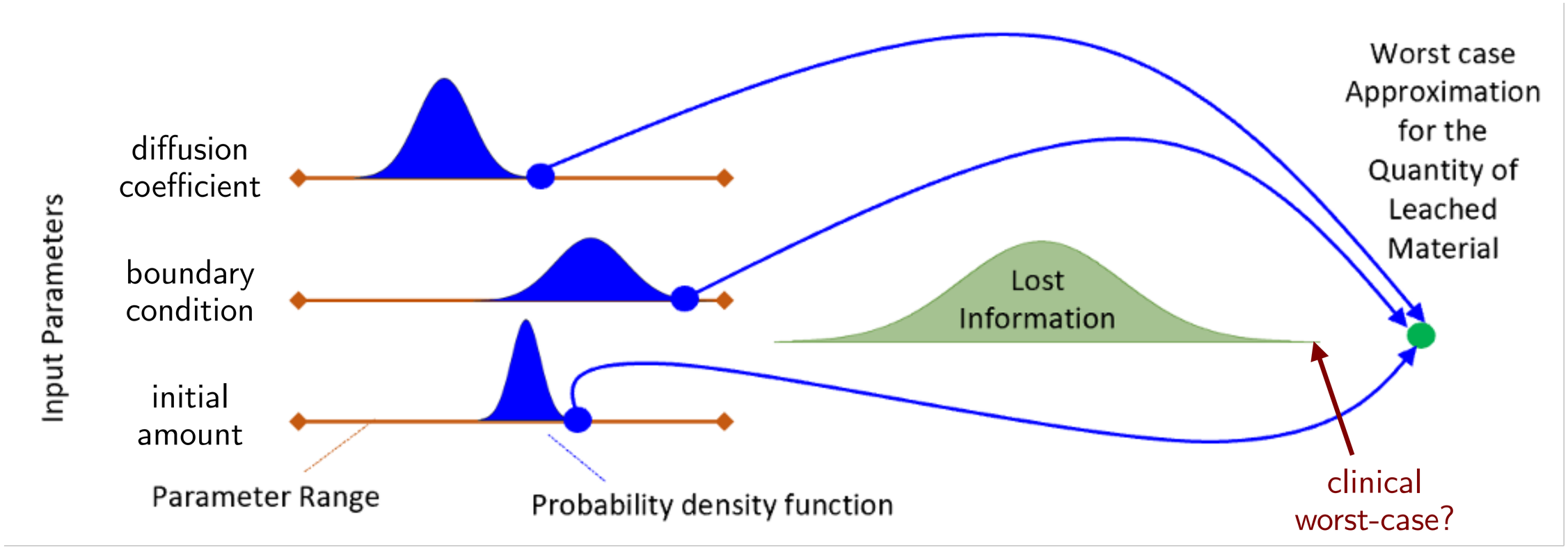
2) Known initial quantity and characterization at single time point (more common, requires a single (worst-case) assumption to apply the analysis)

3) Unknown initial quantity and characterization at single time point (most common, requires multiple assumptions to apply the analysis, less useful than the other two buckets)

Please contact me if you have relevant extraction data that you are willing to share

Uncertainty/variability assessment

"Stacked" worst-case assumptions can lead to excessively conservative exposure estimates:



What is "worst-case" (e.g. 3σ, 6σ, 12σ, etc.)?

Graphic courtesy of Martin Tanaka (WCU)

Boundary condition refinement

If advection is negligible:

$$M(t) = \frac{2AM_0}{V_p}\sqrt{\frac{\xi t}{\pi}}$$

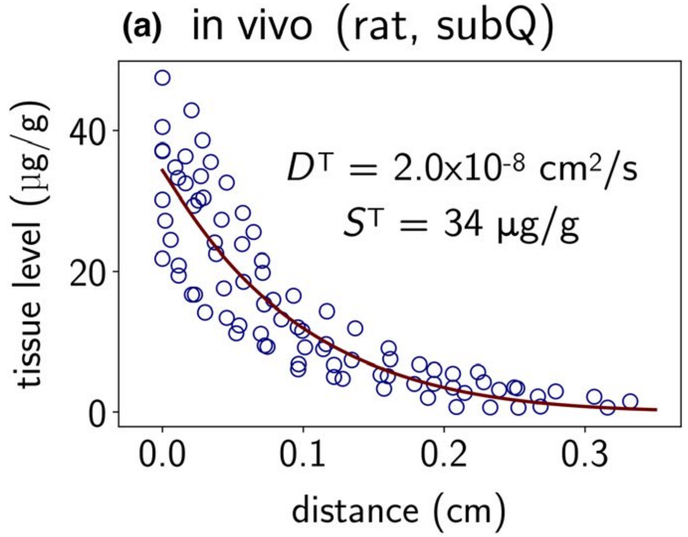
where

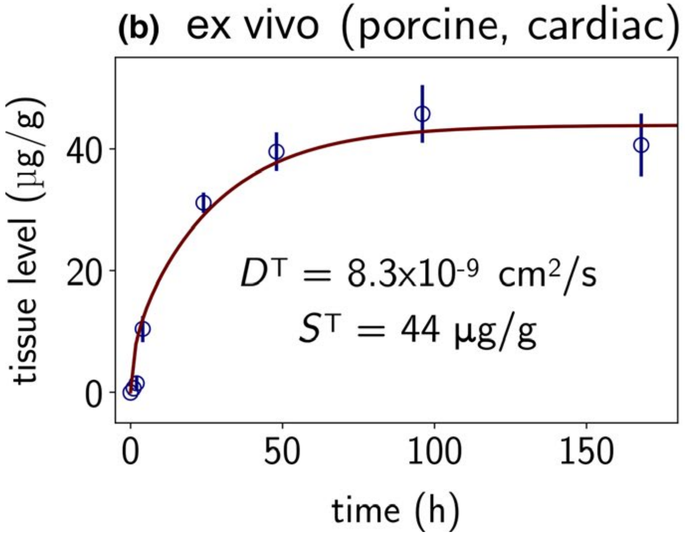
$$\xi = \left(\frac{S_T\sqrt{D_T}}{S_T\sqrt{D_T} + S\sqrt{D}}\right)^2 D$$

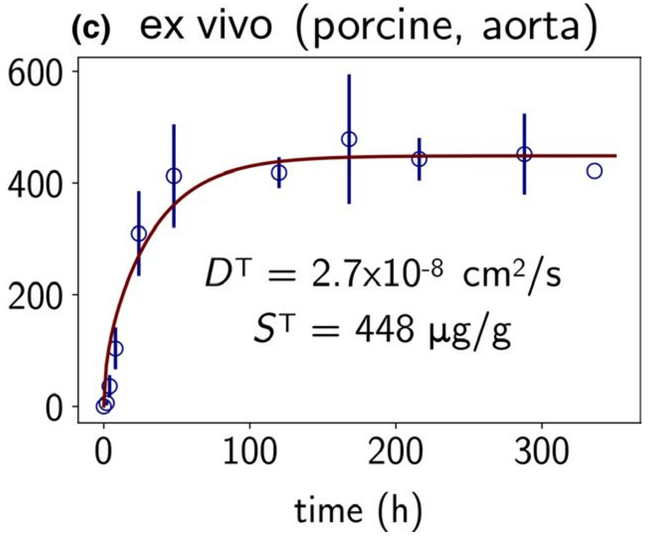
subscript T indicates tissue property

Ni tissue properties

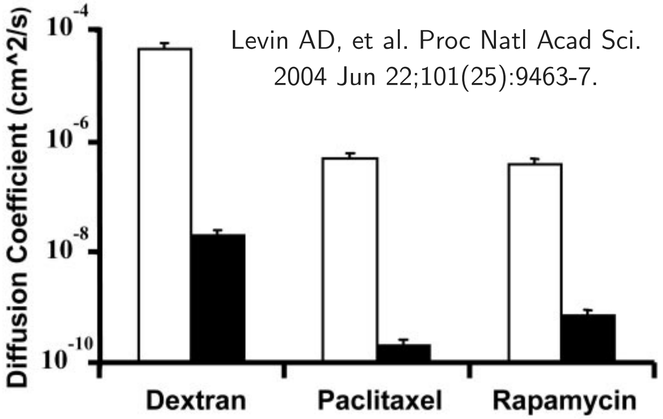
DM Saylor et al.,
Medical Devices & Sensors 3 (1), e10063





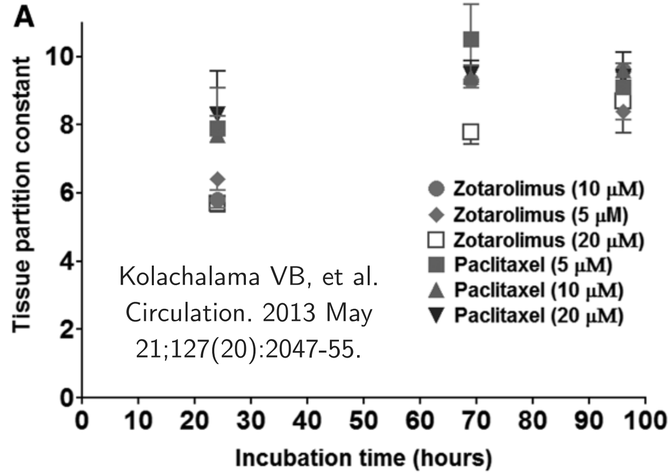


Drug PK literature



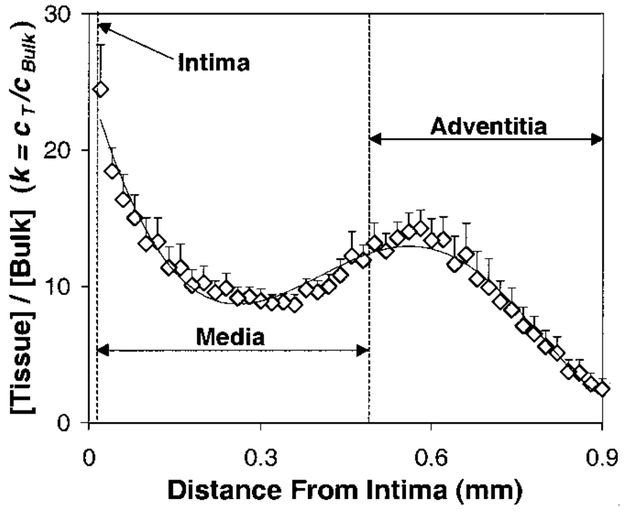
Levin AD, et al. Proc Natl Acad Sci. 2004 Jun 22;101(25):9463-7.

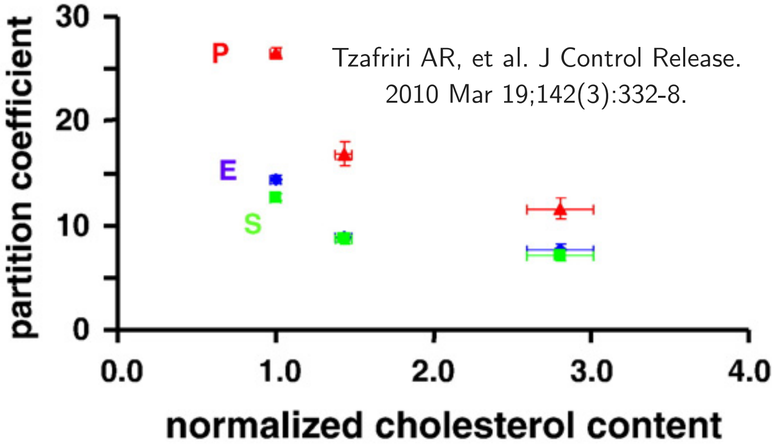
- D_T between 1e-4 to 1e-10 cm^2/s
- S_T/S_w between 0.01 to 100



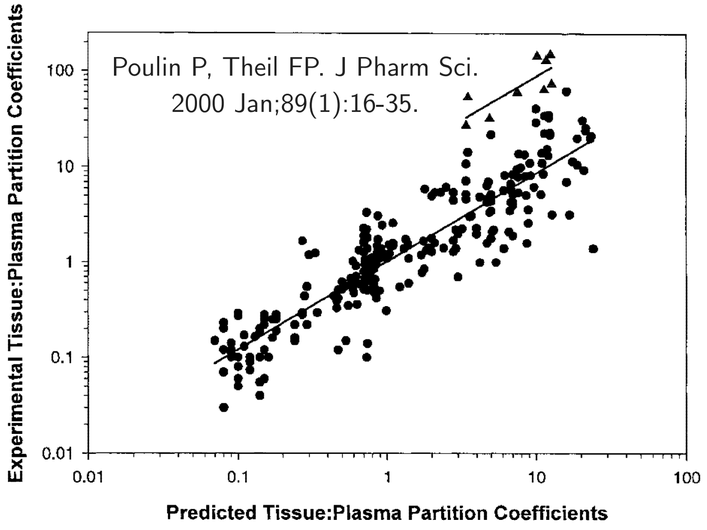
Kolachalama VB, et al. Circulation. 2013 May 21;127(20):2047-55.

Creel CJ, et al. Circ Res. 2000 Apr 28;86(8):879-84.





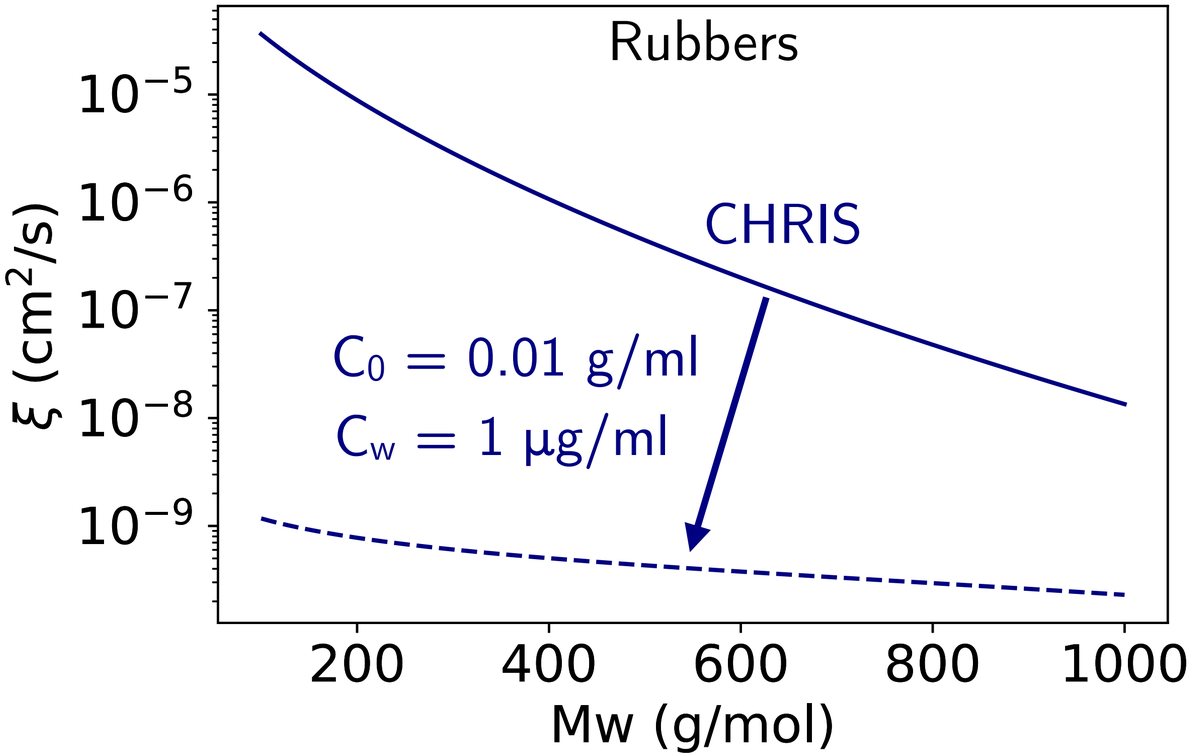
Tzafriri AR, et al. J Control Release. 2010 Mar 19;142(3):332-8.



Poulin P, Theil FP. J Pharm Sci. 2000 Jan;89(1):16-35.

"Worst-case" approach

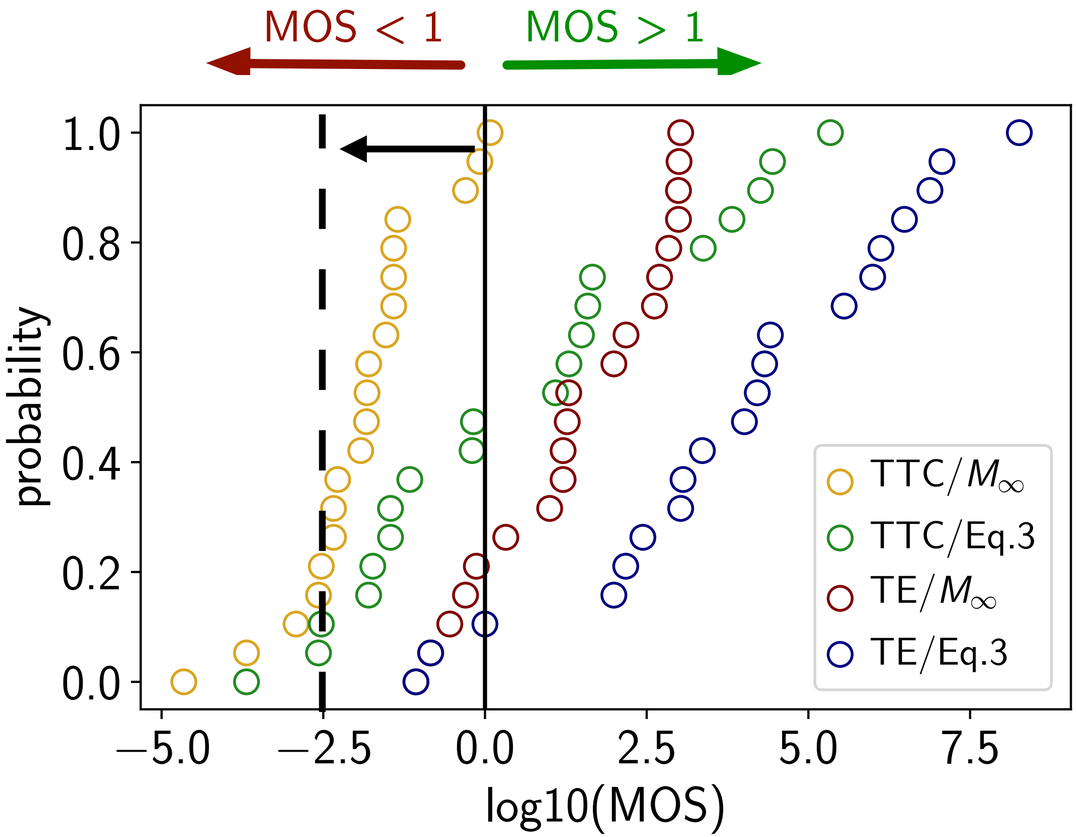
- S lower bound given by total leachable concentration, C_0
- D_T upper bound given by linear alkanes in water (Wilke-Chang)
- S_T upper bound given by 100x water solubility, S_w



$$\xi = \left(\frac{S_T \sqrt{D_T}}{S_T \sqrt{D_T} + S\sqrt{D}} \right)^2 D$$

Suggests 10-300x reduction in maximum release rate in the absence of flow for rubbery materials

Potential impact



Margin of safety (MOS) =
TI ÷ exposure

Suggests significant improvements can be made, at least for certain subsets of devices

Summary

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

- Physics-based (mass transport) models can be useful tools in toxicological risk assessment; however, data needed to parameterize and validate is limited.

- We have developed a protective model based on conservative assumptions that can be helpful as a screening tool, but it is limited to bulk leachables with known initial quantity.

- For bulk leachables with unknown initial quantity, we have demonstrated that extraction test results can be leveraged to estimate the total pool. However, more data are needed to generalize this approach and we are seeking collaborations to aggregate the necessary data.

- We are initiating efforts to assess the variability and uncertainty associated with the model inputs, which should enable more clinically relevant exposure estimates.

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Berk Oktem
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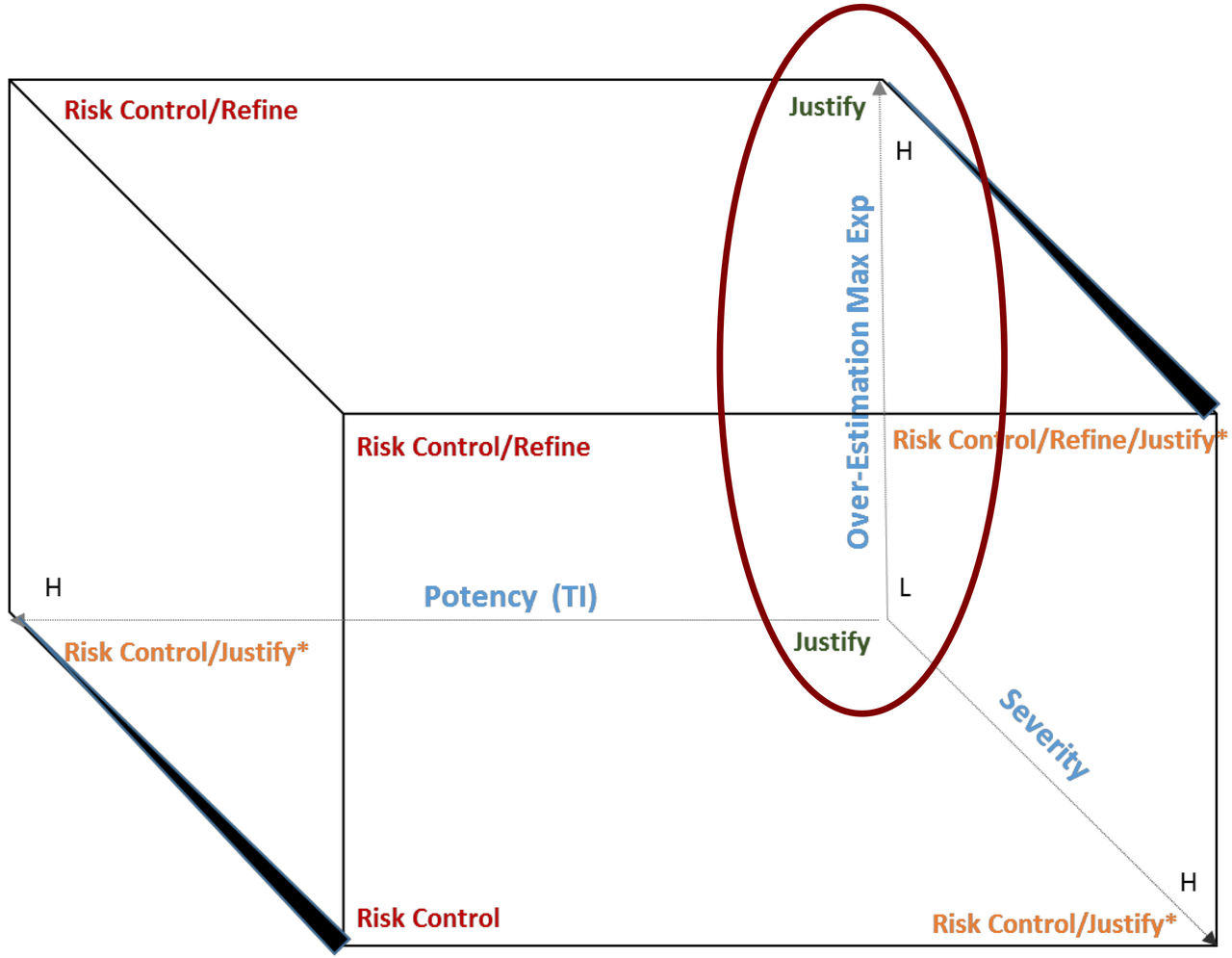
CDRH Critical Path

Final thought

Categorization relies on subjective qualitative assessment of:

- Uncertainty in identity/quantity
- E&L vs. clinical conditions
- Clinical factors that reduce/limit exposure

PBEMs can provide an formal, objective framework for quantitation of exposure estimate uncertainty and extent of overestimation



Risk estimation and evaluation paradigm (TC194 WG11)