Exposure considerations when assuring human safety of cosmetic ingredients without animal testing

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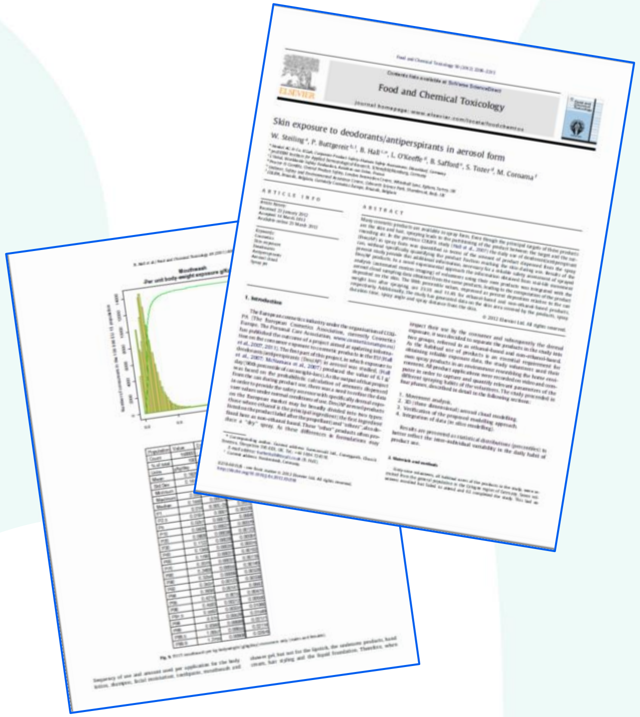
Data on how humans are exposed to cosmetic ingredients

Consumers

Table 3A: Daily exposure levels for different cosmetic product categories in Europe, calculated by multiplying daily amounts (Hall *et al.*, 2007, 2011) and f_{ret}.

Product type	*Estimated daily amount applied* q_x (g/d)	*Relative daily amount applied*[1] q_x /bw (mg/kg bw/d)	*Retention factor*[2] f_{ret}	*Calculated daily exposure* $E_{product}$ (g/d)	*Calculated relative daily exposure*[1] $E_{product}$ /bw (mg/kg bw/d)
Bathing, showering					
Shower gel	18.67	279.20	0.01	**0.19**	**2.79**
Hair care					
Shampoo	10.46	150.49	0.01	**0.11**	**1.51**
Hair styling products	4.00	57.40	0.10	**0.40**	**5.74**
Skin care					
Body lotion	7.82	123.20	1.00	**7.82**	**123.20**
Face cream	1.54	24.14	1.00	**1.54**	**24.14**
Hand cream	2.16	32.70	1.00	**2.16**	**32.70**
Make-up					
Liquid foundation	0.51	7.90	1.00	**0.51**	**7.90**
Lipstick, lip salve	0.057	0.90	1.00	**0.057**	**0.90**
Deodorant					
Deodorant non-spray	1.50	22.08	1.00	**1.50**	**22.08**
Deodorant spray	0.69	10.00	1.00	**0.69**	**10.00**
Oral hygiene					
Toothpaste (adult)	2.75	43.29	0.05	**0.138**	**2.16**
Mouthwash	21.62	325.40	0.10	**2.16**	**32.54**



https://ec.europa.eu/health/system/files/2021-04/sccs_o_250_0.pdf

Creme GLOBAL

Workers

https://chesar.echa.europa.eu/documents/736332/8711025/Chesar_3-6_user_man_en.pdf/65edfa9e-57b8-f334-07f7-afb9841e8099

Using probabilistic modelling and aggregate exposure considerations

Generating specific information on human exposure

e.g. Skin Penetration

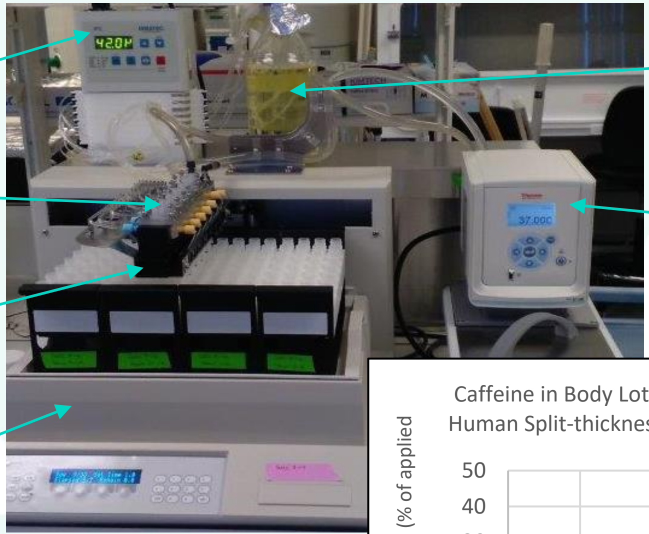
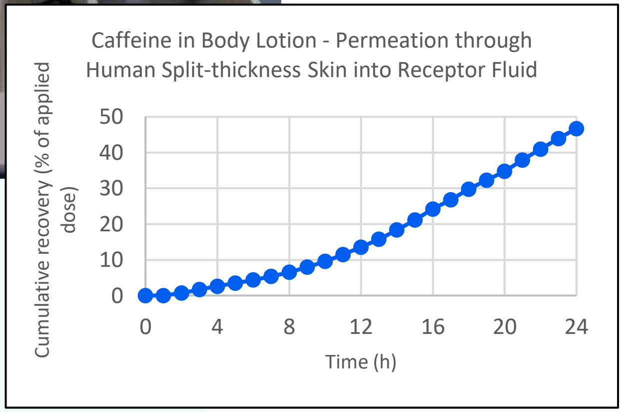


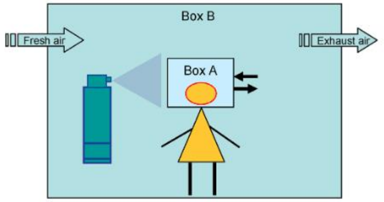
Photo: Ruth Pendlington



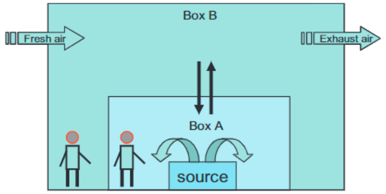
e.g. Inhalation Exposure

Exposure Modelling

Near-field
Products sprayed directly at the body



Far-field
Spray directed away from the body



Simulated consumer exposure methods

Steiling et al (2014) *Toxicology Letters*, **227**, 41-49

Exposure in Next Generation Risk Assessment (NGRA)

4 Main overriding principles:

International Cooperation on Cosmetics Regulation (ICCR)

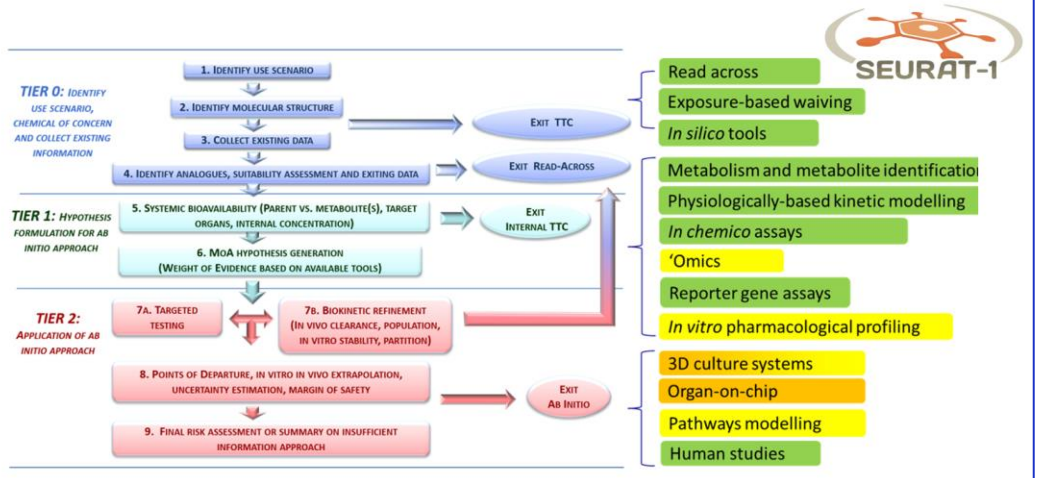
- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:

- Following an appropriate appraisal of existing information
- Using a tiered and iterative approach
- Using robust and relevant methods and strategies

2 Principles for documenting NGRA:

- Sources of uncertainty should be characterized and documented
- The logic of the approach should be transparently and documented



Dent *et al* (2018), Computational Toxicology, **7**, 20-26

Berggren *et al* (2017) Computational Toxicology **4**, 31-44

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Physiologically-based Kinetic (PBK) Modelling

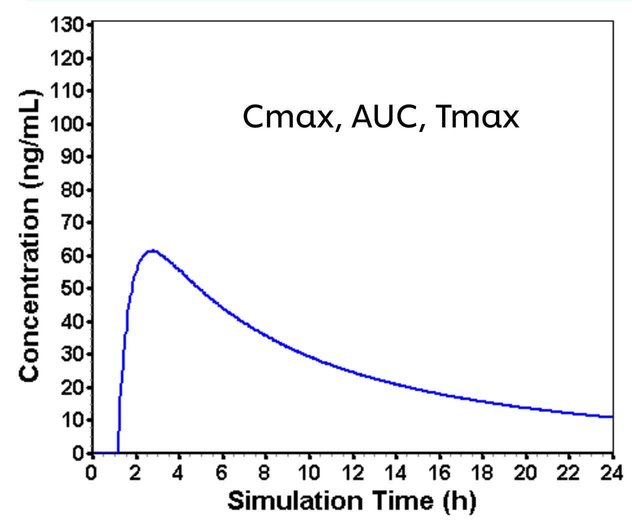
Input

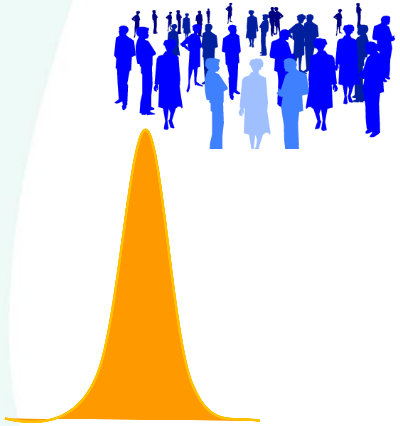
ADME properties

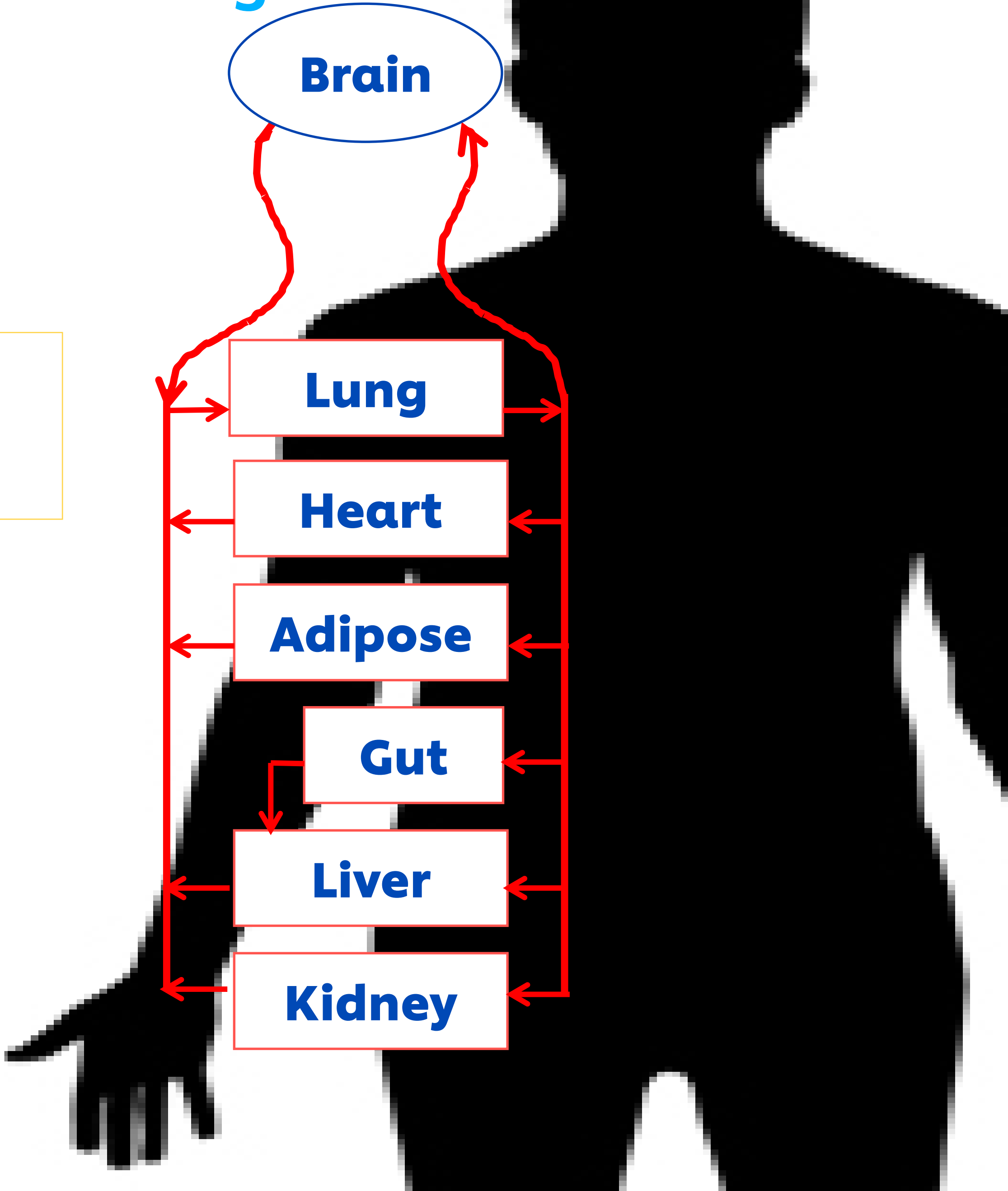
Absorption, Distribution, Metabolism, Excretion

- Physiological parameters (e.g. body weight, blood flow rates, tissue volume)
- Physico-chemical parameters (e.g. LogP, Fup, tissue/plasma partition coefficients)
- Kinetic parameters (e.g. dermal absorption, hepatic metabolism, renal excretion)
- Product use information (e.g. dose, frequency, site area, formulation)

Output







Li *et al* (2022) *Toxicology and Applied Pharmacology*, **442**, 115992

Exposure estimation: From applied dose to internal exposure based on NAM*s

Level 0:

- Characterise exposure scenario (who, where, how often, and how much)
- Product & chemical information

Level 1:

- Predictions from *in silico* only
- parameterisation & sensitivity

Level 2:

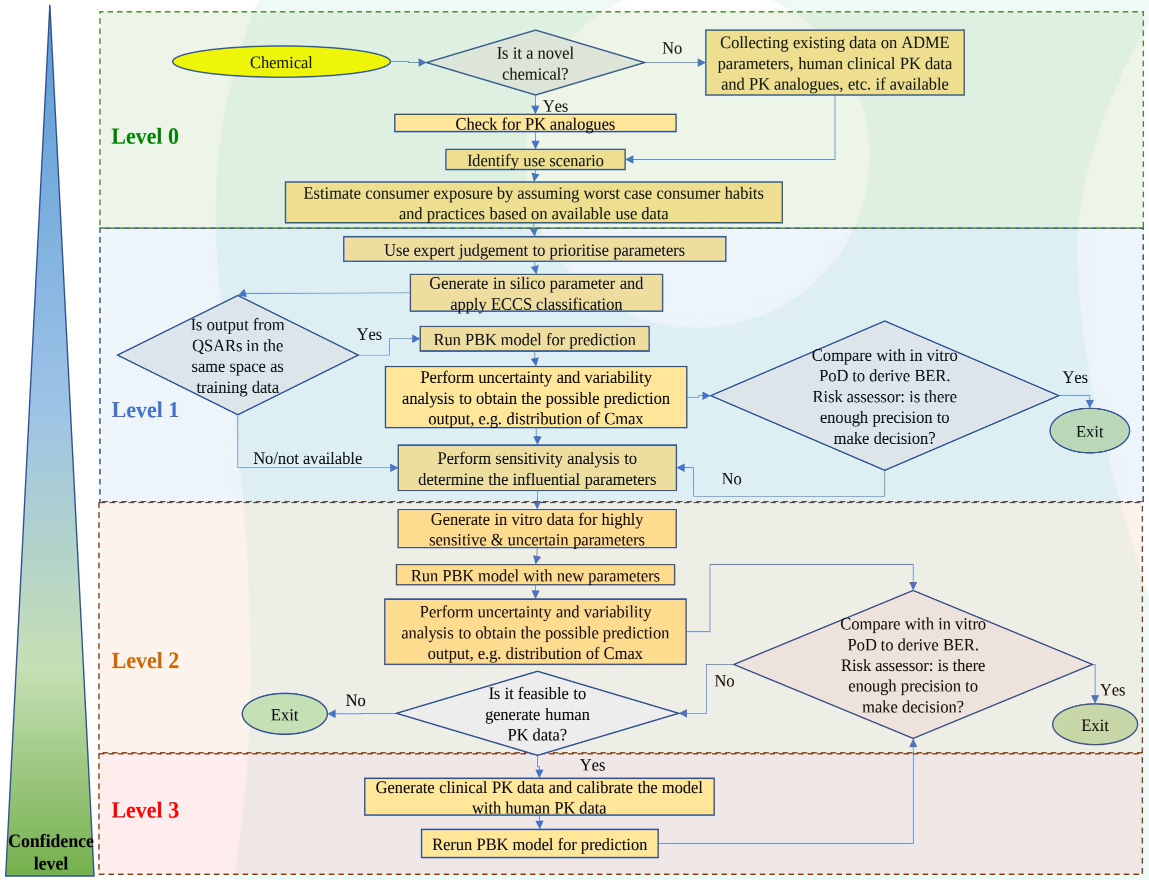
- PBK modelling based on *in vitro* parameterisation

Level 3:

- Generating human PK data for validation or/and calibration

- The progression between levels is closely related to the risk assessment process
- Use tools that are as complex as necessary to make the decision
- move to more complex tools if more data is needed

PBK Modelling Framework



Li *et al* (2022) *Toxicology and Applied Pharmacology*, **442**, 115992

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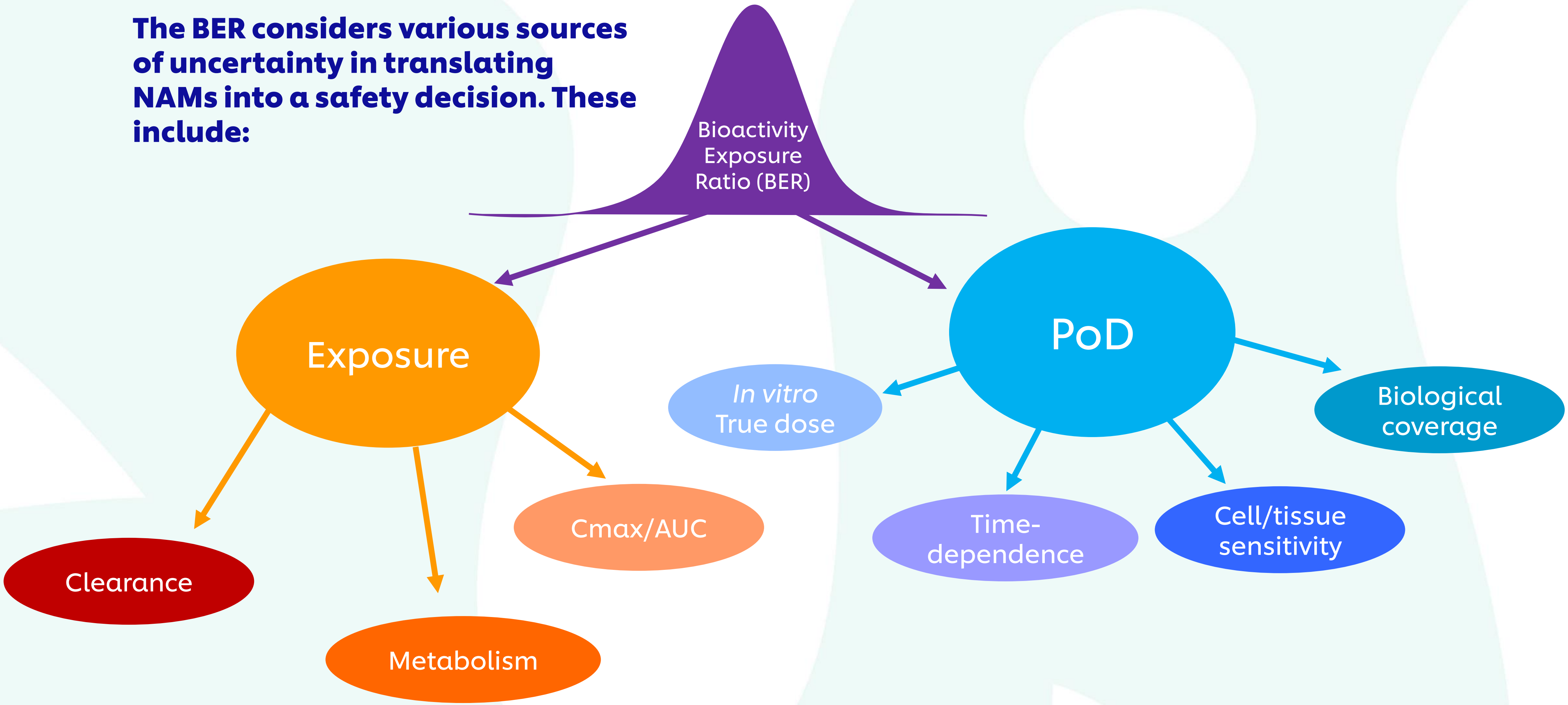
* = New Approach Methodology

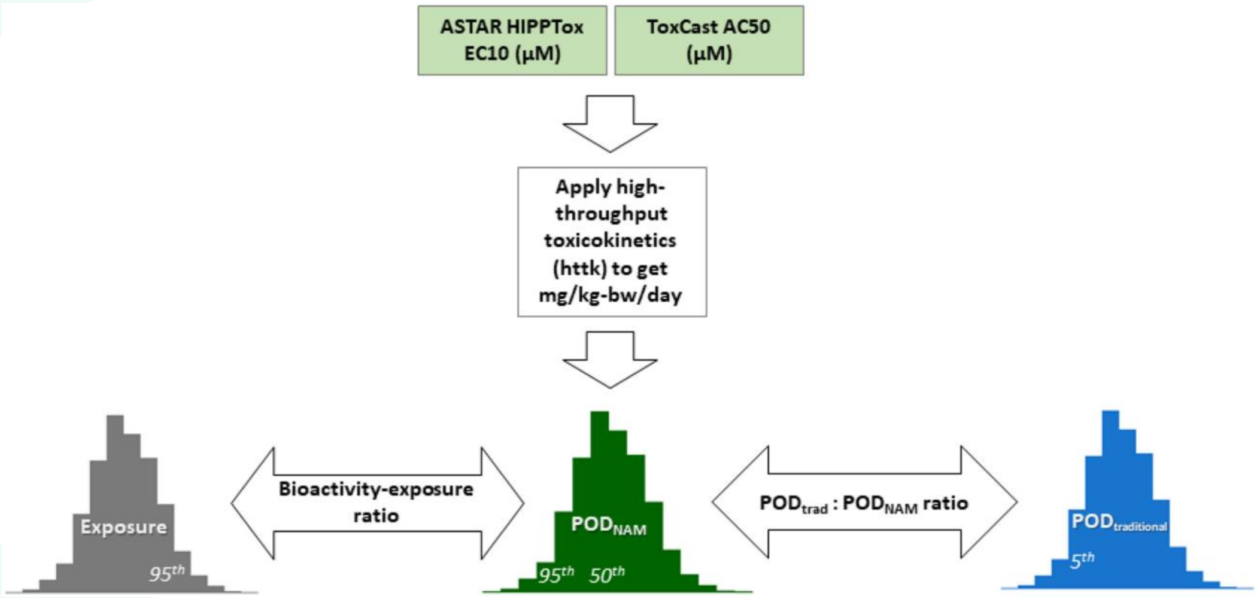
Integrating Exposure and Bioactivity Data from NAMs to Make Safety Decisions

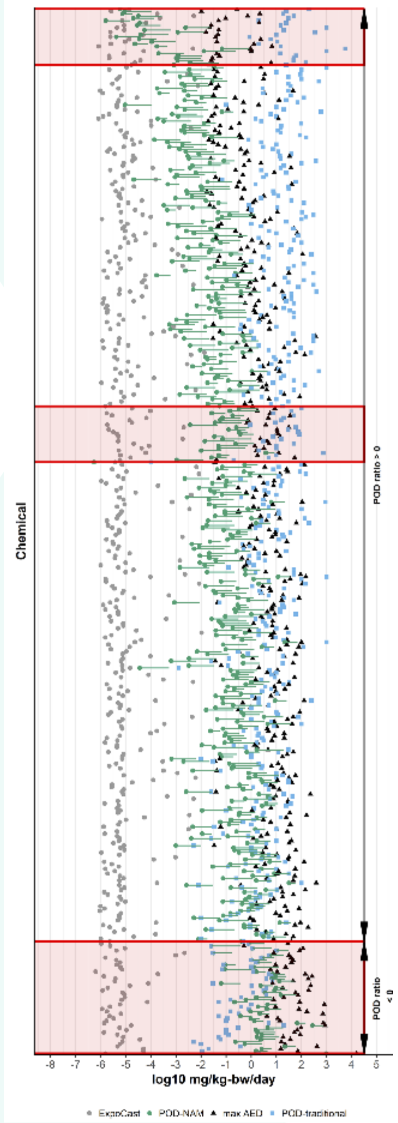
The BER considers various sources of uncertainty in translating NAMs into a safety decision. These include:



Baltazar *et al*., (2020) *Toxicol Sci* **176**, 236–252

APCRA* approach to evaluate the integration of exposure and bioactivity





- Evaluation of *in vitro* NAMs, exposure modelling and dose-response models.
- For 89% of the chemicals NAM PoD was more conservative than the traditional POD.
- Bioactivity : exposure ratios (BERs) approach useful for accelerate screening and assessment using NAMs for hazard and exposure.

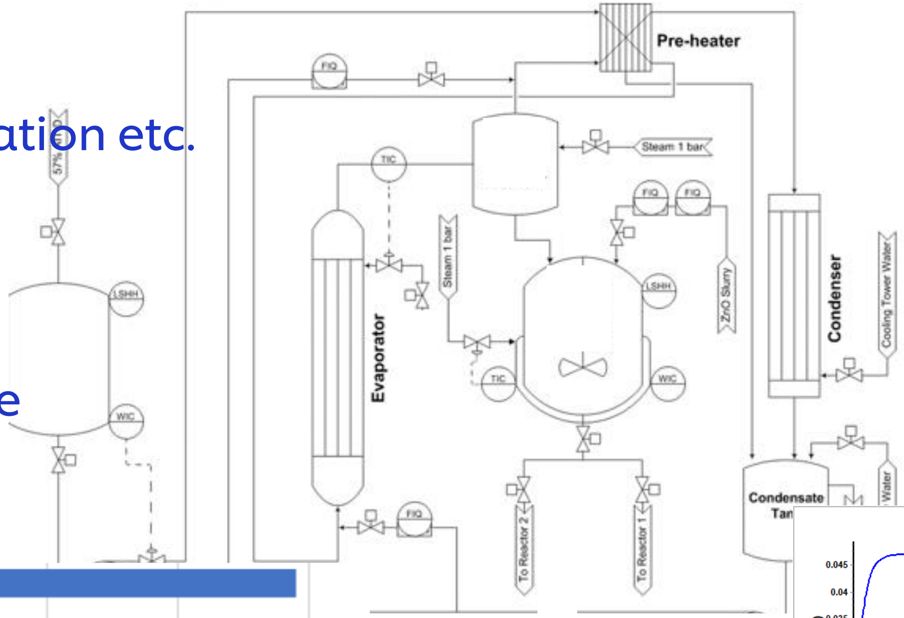
Paul Friedman *et al* (2020), Toxicol Sciences, 173, 202-225

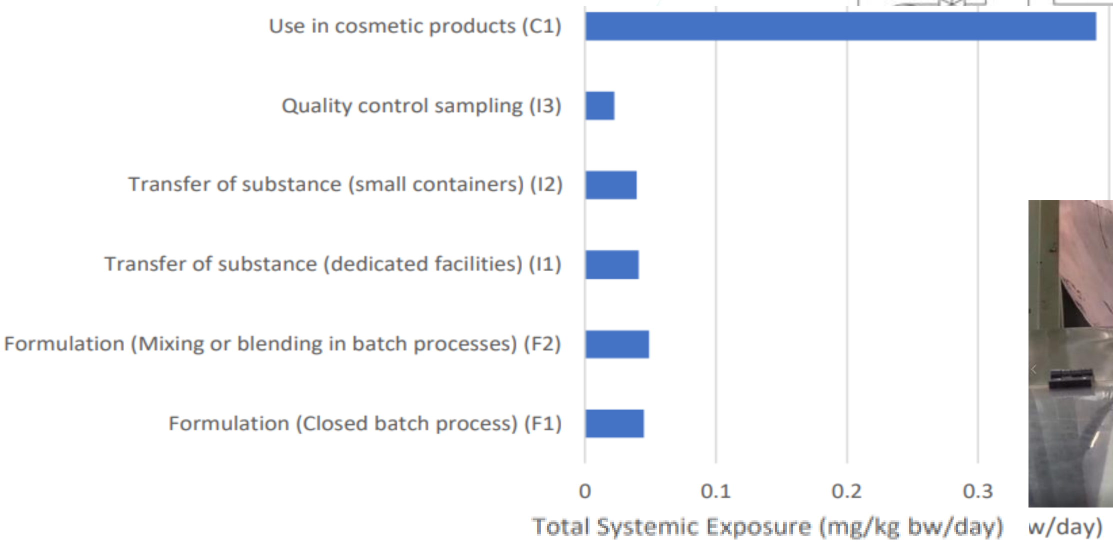
* Accelerating the Pace of Chemical Risk Assessment

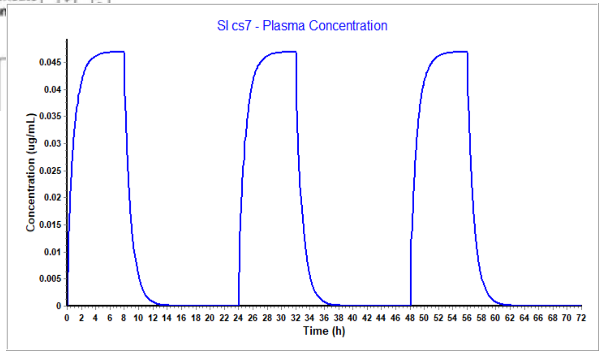
NGRA and Worker Safety

- Understanding worker exposure
  - Routes
  - Levels of exposure
  - PPE*, engineering controls, ventilation etc.
  - PBK for worker exposure

- NGRA
  - BER approach for worker exposure



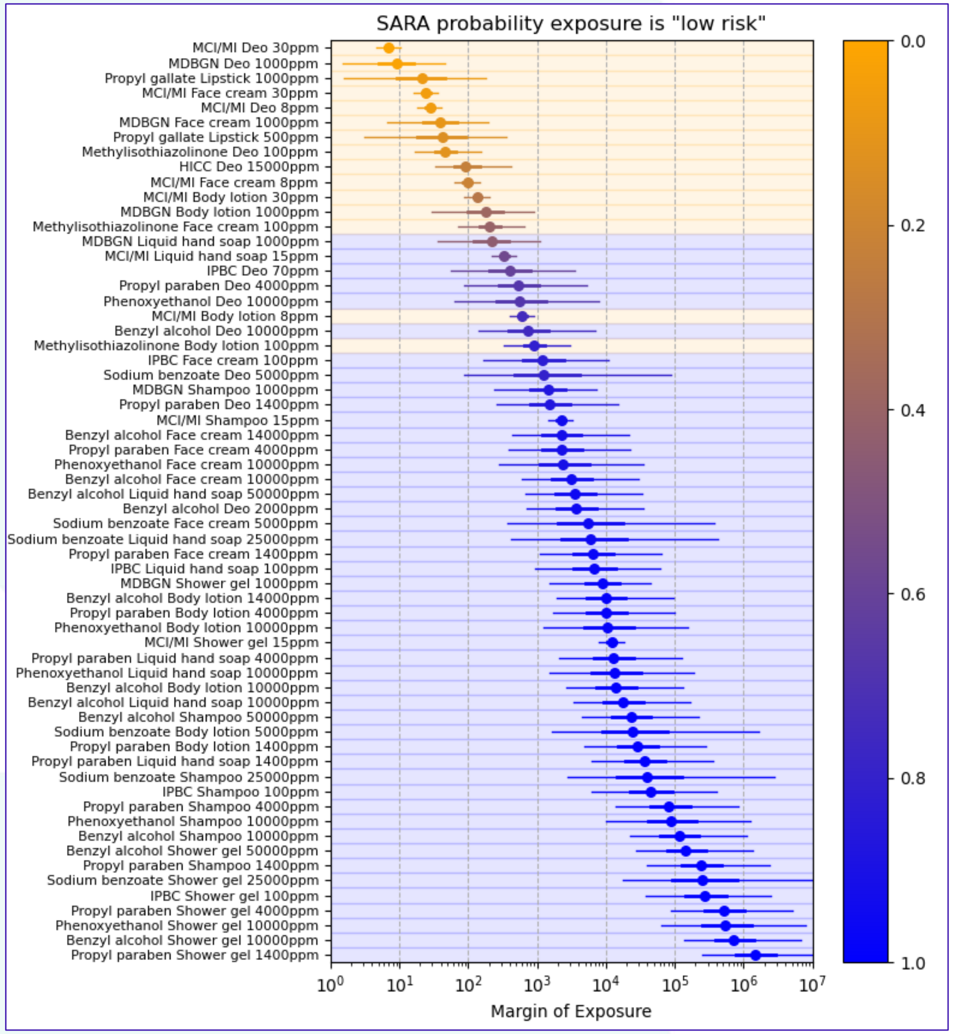


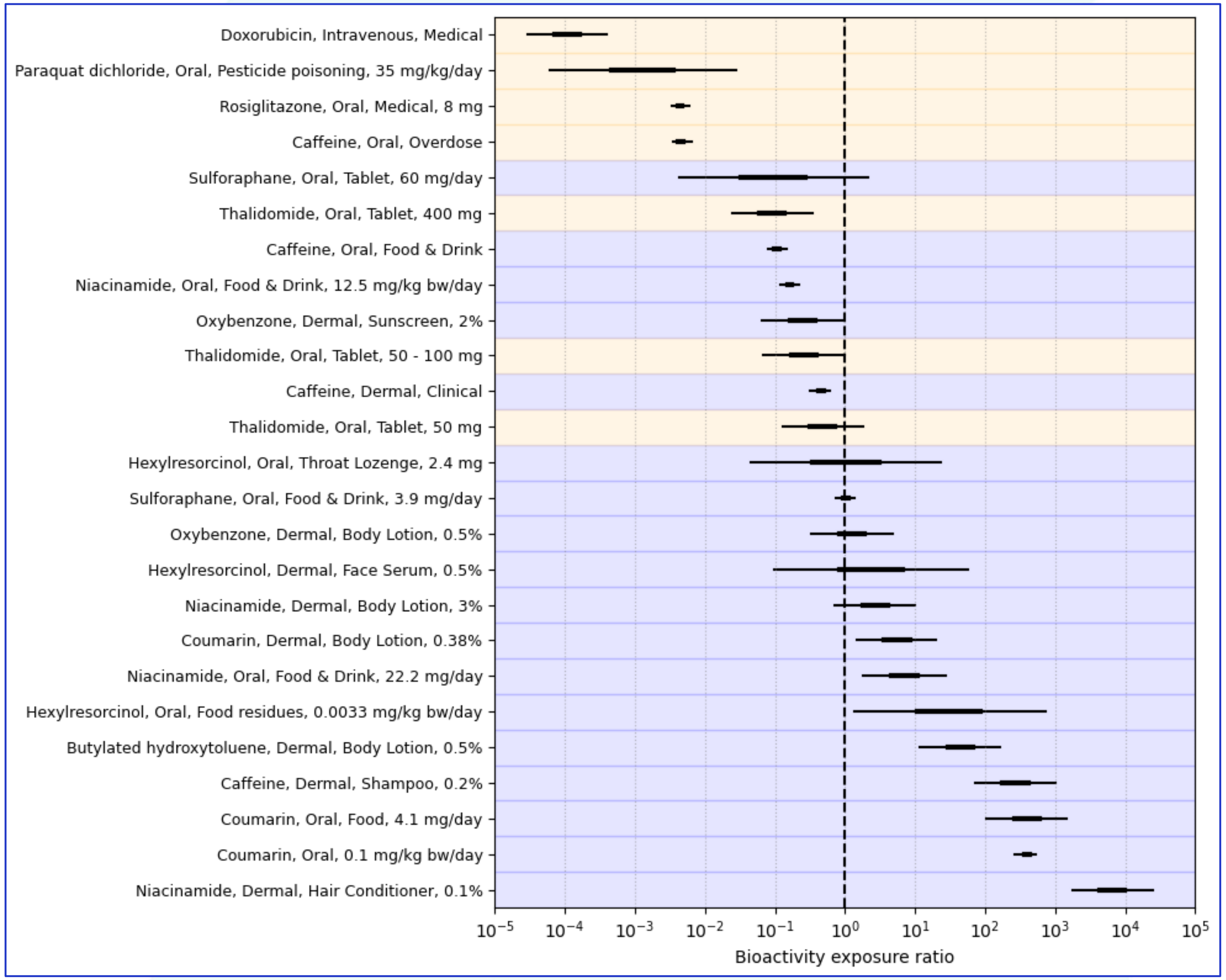


Dosage Form	Dose [mg]	TD Dose Vol [ml]	Start [h]	End [h]	Physiology or .cat file	PBPK Physiology or .pbk file
IV: Infusion	8.68	0	0	8	Human - Physiological - Fed	HumAmeFemPreg1GA30YO_75.58kg_28.7
IV: Infusion	8.68	0	24	32	Human - Physiological - Fed	HumAmeFemPreg1GA30YO_75.58kg_28.7
IV: Infusion	8.68	0	48	56	Human - Physiological - Fed	HumAmeFemPreg1GA30YO_75.58kg_28.7
IV: Infusion	8.68	0	72	80	Human - Physiological - Fed	HumAmeFemPreg1GA30YO_75.58kg_28.7
IV: Infusion	8.68	0	120	128	Human - Physiological - Fed	HumAmeFemPreg1GA30YO_75.58kg_28.7

* PPE = Personal protective equipment

Exposure and Hazard must BOTH be considered when evaluating NAMs for safety assessment





Skin allergy risk assessment:
Reynolds, et al (2021) Reg Tox & Pharmacol, **127**, 105075

Systemic safety risk assessment:
Middleton *et al* (2022) Toxicol Sciences (submitted)

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Summary Slide

Safety assessments for cosmetics are always exposure-led

Exposure assessment is equally important for NAM-based consumer safety assessment as it has always been for safety assessments that utilise toxicology data from animals

NAM-based human safety assessments rely on estimates of systemic exposure (PBK), not just habits and practices information

Worker and consumer exposures can be different, both must be defined for NAM-based safety assessment

To fully understand the use and validity of NAMs for safety decision-making, exposure AND hazard information must be used

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