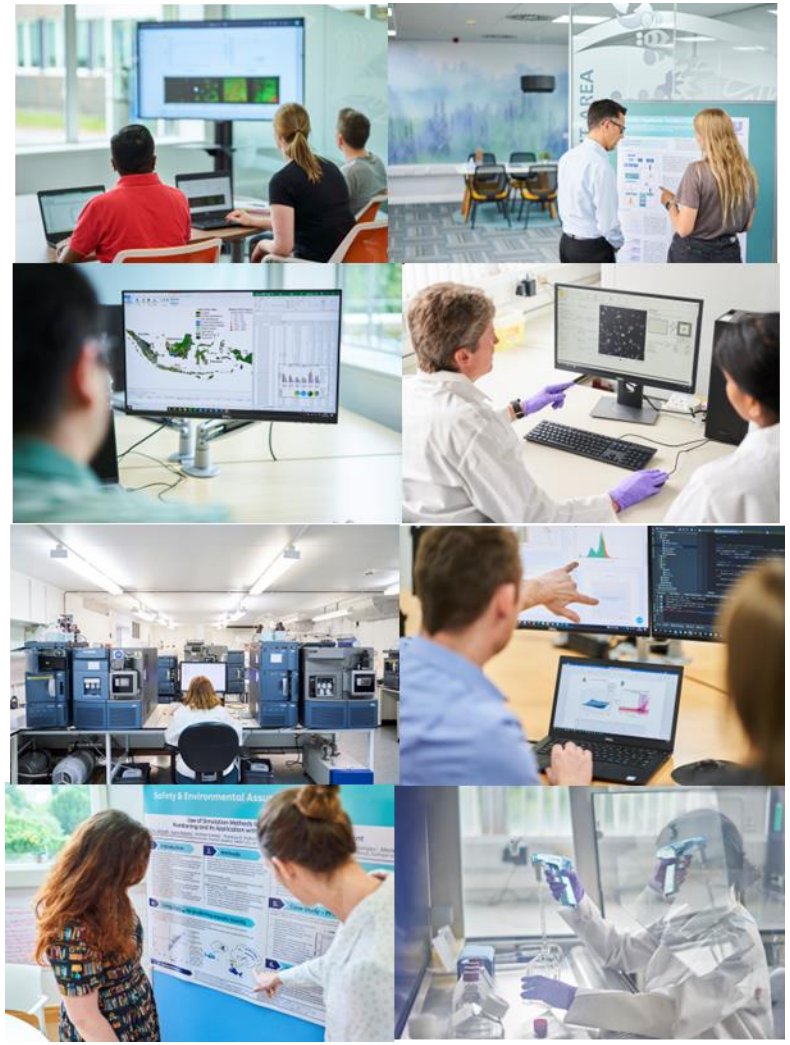
Next Generation Risk Assessment for Occupational Chemical Safety – a Real World Example with Sodium-2-hydroxyethane sulfonate

Adam Wood (adam.wood@unilever.com):

Safety & Environmental Assurance Centre, Unilever, UK

BTS annual congress 2024 – April 2024



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Scientific Excellence And Collaboration

Overview

1.) How are worker/occupational safety assessments performed currently.

2.) Overview of NGRA for systemic toxicity assessment.

3.) Opportunities and a strategy for integrating NGRA into worker safety assessment.

4.) Case study chemical: Sodium-2-hydroxyethane sulfonate (SI)

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Current worker safety assessment approach

- Workers can be exposed to substances that could be detrimental to health if not assessed and managed adequately.

- Typically, assessment of risks from occupational exposures come from comparisons of exposures with occupational limit values, e.g., occupational exposure limits (OELs) or Derived No-effect levels (DNELs).

- A large proportion of OELs/DNELs are based on outputs of toxicological studies performed using experimental animals.

29.6.2004 EN Official Journal of the European Union L 229/23

Corrigendum to Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC) (codified version)

(Official Journal of the European Union L 158 of 30 April 2004)

Directive 2004/37/EC should read as follows:

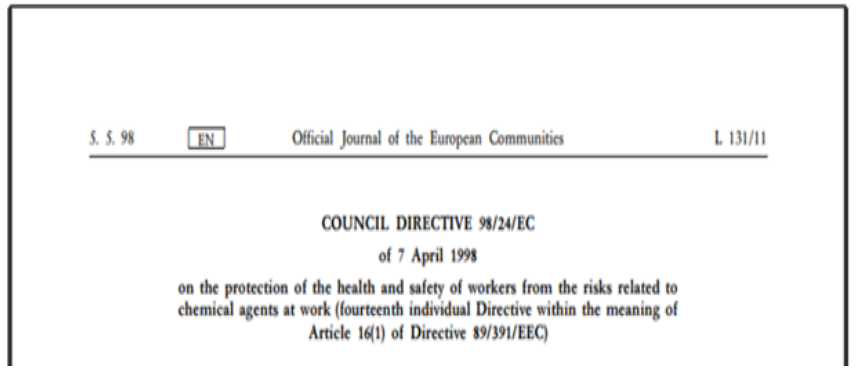
DIRECTIVE 2004/37/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 29 April 2004

on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC)

(codified version)

(Text with EEA relevance)

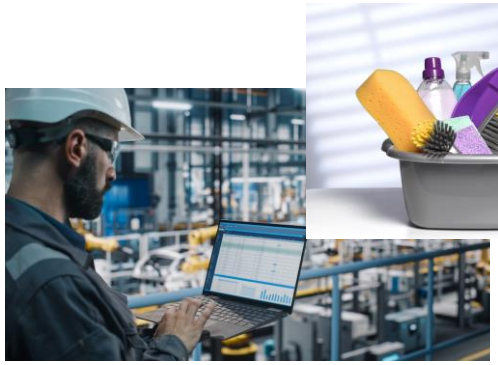


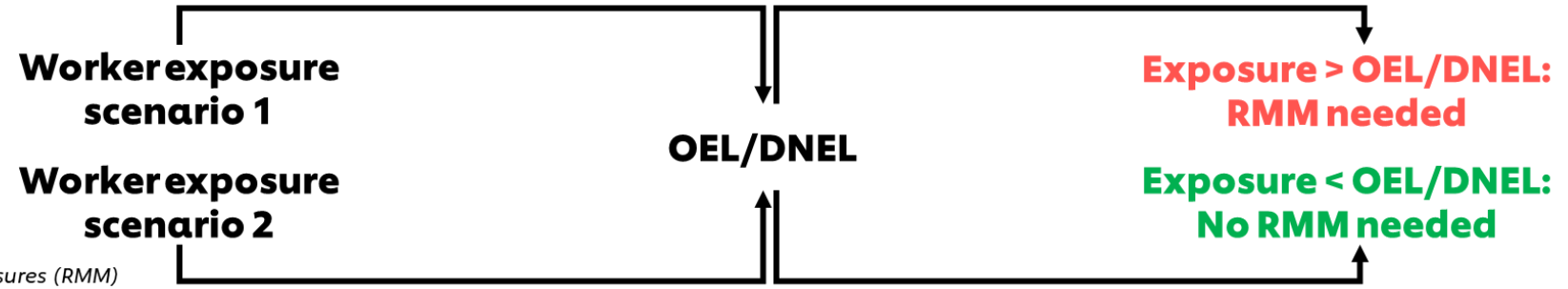
5. 5. 98 EN Official Journal of the European Communities L 131/11

COUNCIL DIRECTIVE 98/24/EC

of 7 April 1998

on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC)



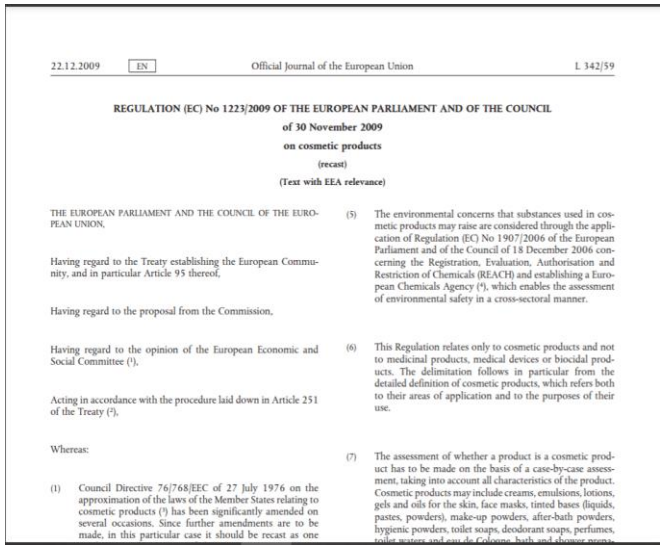


Risk management measures (RMM)

The need for non-animal safety assessments

Human Relevance

Societal Attitudes/Consumer Preference



22.12.2009 EN Official Journal of the European Union L 342/59

REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 30 November 2009
on cosmetic products
(recast)
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Economic and Social Committee (1),

Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

Whereas:

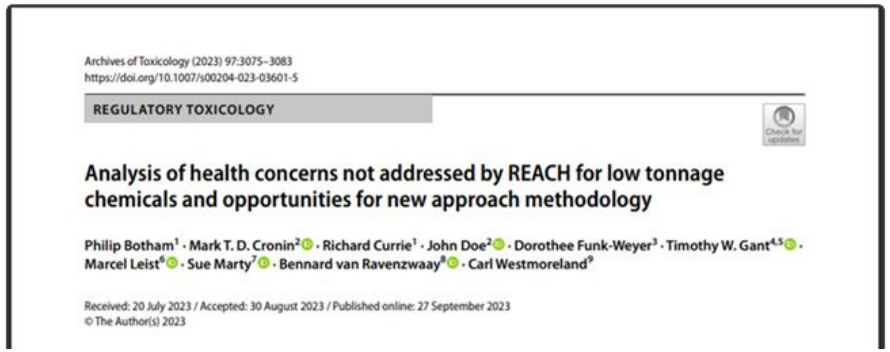
(1) Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (3) has been significantly amended on several occasions. Since further amendments are to be made, in this particular case it should be recast as one

(5) The environmental concerns that substances used in cosmetic products may raise are considered through the application of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and establishing a European Chemicals Agency (4), which enables the assessment of environmental safety in a cross-sectoral manner.

(6) This Regulation relates only to cosmetic products and not to medicinal products, medical devices or biocidal products. The delimitation follows in particular from the detailed definition of cosmetic products, which refers both to their areas of application and to the purposes of their use.

(7) The assessment of whether a product is a cosmetic product has to be made on the basis of a case-by-case assessment, taking into account all characteristics of the product. Cosmetic products may include creams, emulsions, lotions, gels and oils for the skin, face masks, tinted bases (liquids, pastes, powders), make-up powders, after-bath powders, hygienic powders, toilet soaps, deodorant soaps, perfumes,

Regulatory Change (e.g. EU Cosmetic regulation)



Archives of Toxicology (2023) 97:3075–3083
https://doi.org/10.1007/s00204-023-03601-5

REGULATORY TOXICOLOGY

Analysis of health concerns not addressed by REACH for low tonnage chemicals and opportunities for new approach methodology

Philip Botham[1] · Mark T. D. Cronin[2] · Richard Currie[1] · John Doe[2] · Dorothee Funk-Weyer[3] · Timothy W. Gant[4,5] · Marcel Leist[6] · Sue Marty[7] · Bennard van Ravenzwaay[8] · Carl Westmoreland[9]

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Resource/time constraints

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

ELSEVIER

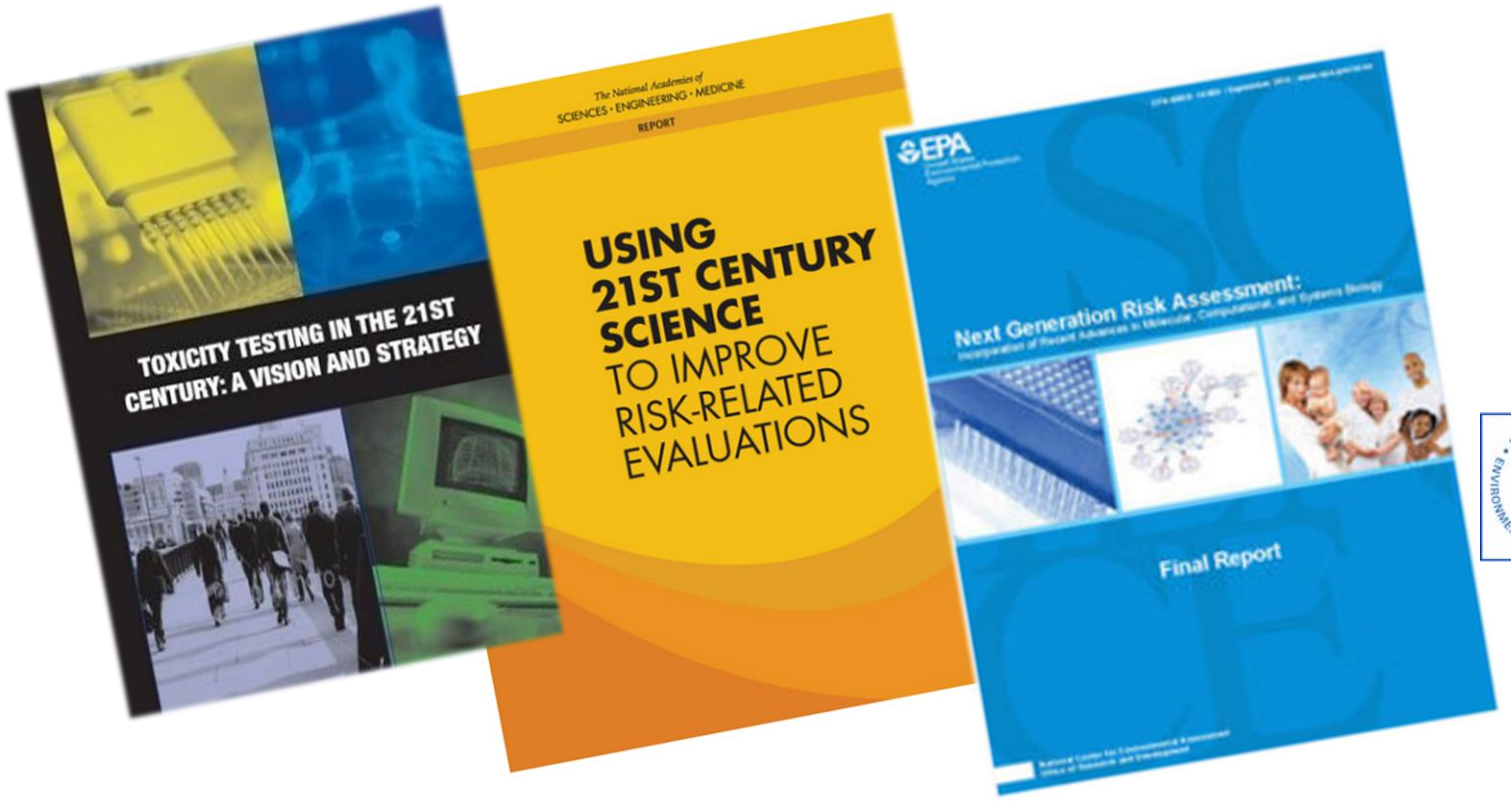
Does REACH provide sufficient information to regulate substances toxic to reproduction?

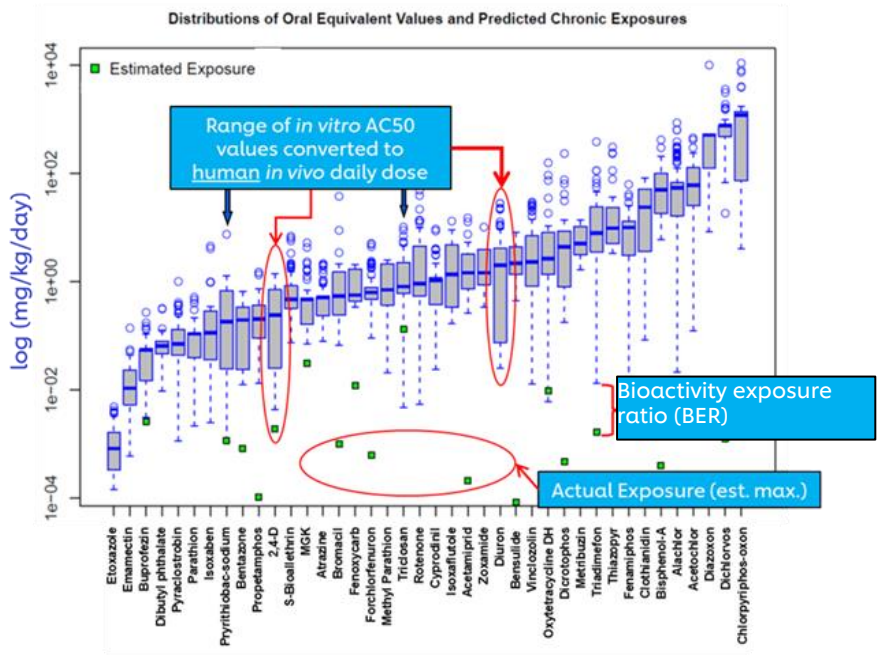
Gaby A.M. Eliesen *, M. Woutersen, J. van Engelen, A. Muller

National Institute for Public Health and the Environment (RIVM), Centre for Safety of Substances and Products (VSP), Bilthoven, the Netherlands

Unilever

What is next generation risk assessment (NGRA)?





Graph from Rusty Thomas EPA, with thanks. Rotroff *et al* (2010) Toxicological Sciences , **117**, 348-358

$$BER = \frac{Lowest\ bioactivity\ POD}{Internal\ in\ vivo\ exposure\ (Cmax)}(uM)$$

"An exposure-led, hypothesis driven risk assessment approach that incorporates one or more NAMs to ensure that chemical exposures do not cause harm to consumers"

Dent *et al.*, (2018) *Comp Tox*7:20-26

Introduction to NGRA

ICCR
9 principles of NGRA

Main overriding principles:

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

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

Principles for documenting NGRA:

Sources of uncertainty should be characterized and documented
The logic of the approach should be transparent and well documented

Dent et al 2018. Computational Toxicology Volume 7, August 2018, Pages 20-26

Computational Toxicology 7 (2018) 20–26

Contents lists available at ScienceDirect

Computational Toxicology

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

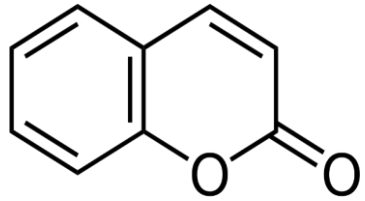
ELSEVIER

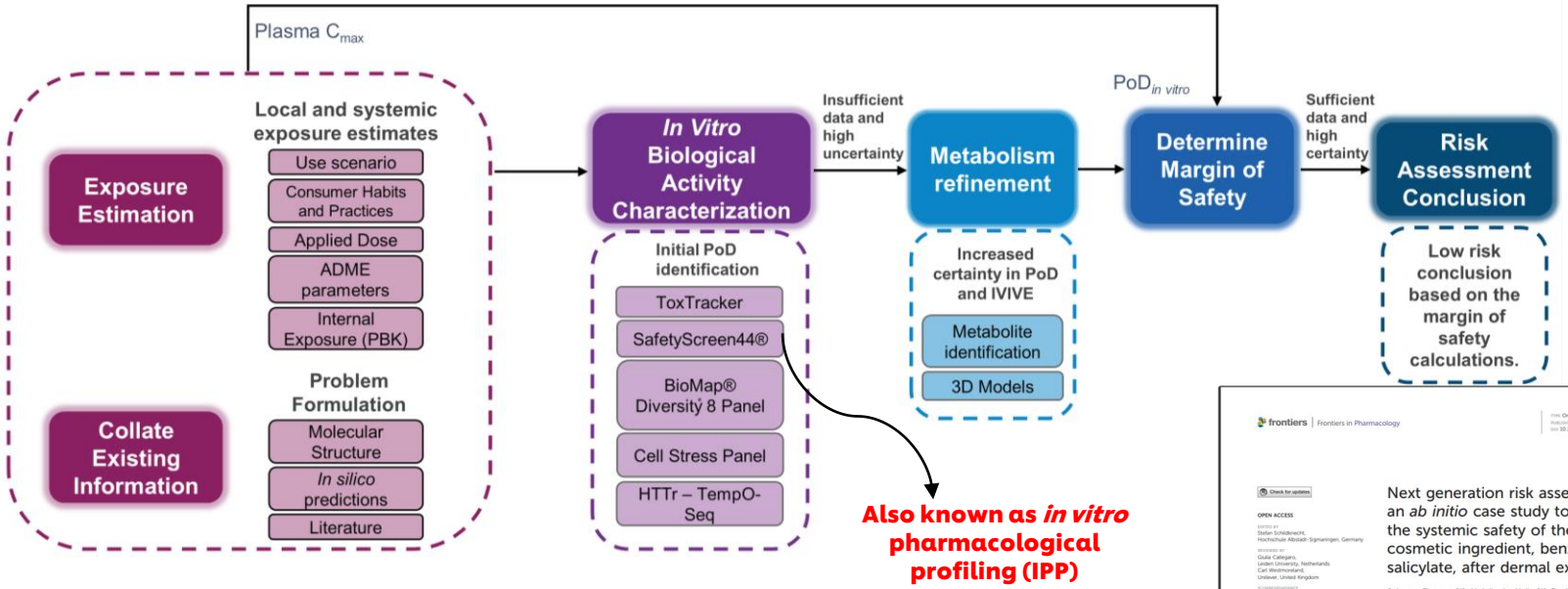
Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

Matthew Dent[a,*], Renata Teixeira Amaral[b], Pedro Amores Da Silva[b], Jay Ansell[c], Fanny Boisleve[d], Masato Hatao[e], Akihiko Hirose[f], Yutaka Kasai[g], Petra Kern[h], Reinhard Kreiling[i], Stanley Milstein[j], Beta Montemayor[k], Julcemara Oliveira[l], Andrea Richarz[m], Rob Taalman[n], Eric Vaillancourt[o], Rajeshwar Verma[j], Nashira Vieira O'Reilly Cabral Posada[l], Craig Weiss[p], Hajime Kojima[f]

Testing the principles with case studies

0.1% COUMARIN IN FACE CREAM AND BODY LOTION (NEW FRAGRANCE)






frontiers | Frontiers in Pharmacology

Next generation risk assessment: an *ab initio* case study to assess the systemic safety of the cosmetic ingredient, benzyl salicylate, after dermal exposure


OXFORD SOT Society of Toxicology academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 176(1), 2020, 236–252

A Next-Generation Risk Assessment Case Study for Coumarin in Cosmetic Products

Maria T. Baltazar,[1] Sophie Cable, Paul L. Carmichael, Richard Cubberley, Tom Cull, Mona Delagrange, Matthew P. Dent, Sarah Hatherell,


OECD Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)35

Unclassified — English - Or. English

27 October 2021

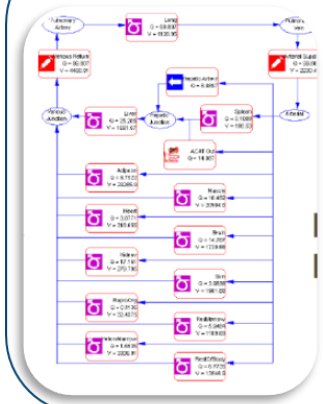
ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

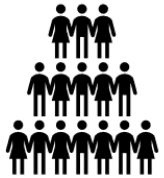
Case Study on use of an Integrated Approach for Testing and Assessment (IATA) for Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion

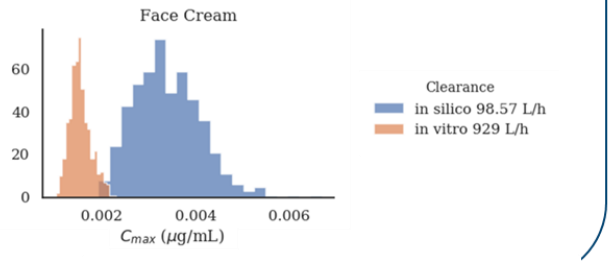
Baltazar *et al.*, (2020) *Tox Sci* Volume 176, Issue 1, 236–252

Key tools in our NGRA approach for Systemic Toxicity – Bioactivity assays

PBK Modelling

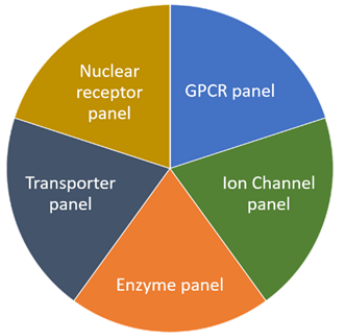






Toxicology in Vitro (2020), **63**, 104746

In vitro pharmacological profiling



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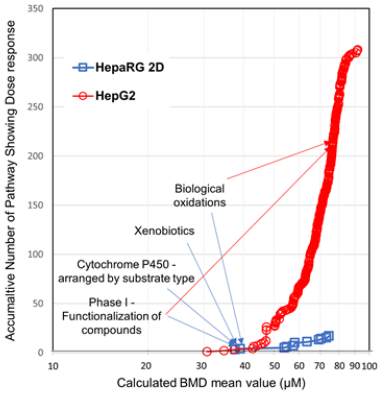
Transcriptomics

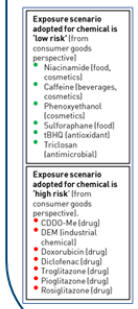
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

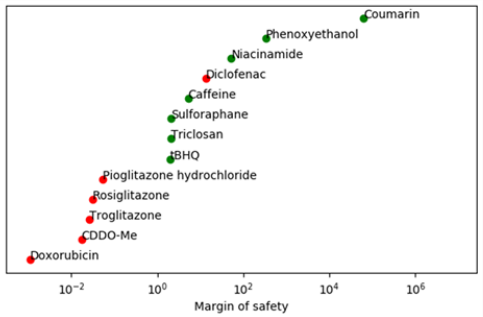
BMDExpress 2



Cellular Stress Pathways

13 chemicals, 36 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways





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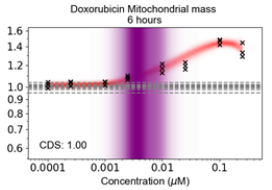

Toxicol Sci (2020), **176**, 11-33

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Muller et al., (2024) in preparation

Cable et al., (2024) in preparation

Middleton et al., (2022) Toxicol Sci, 189, 124-147

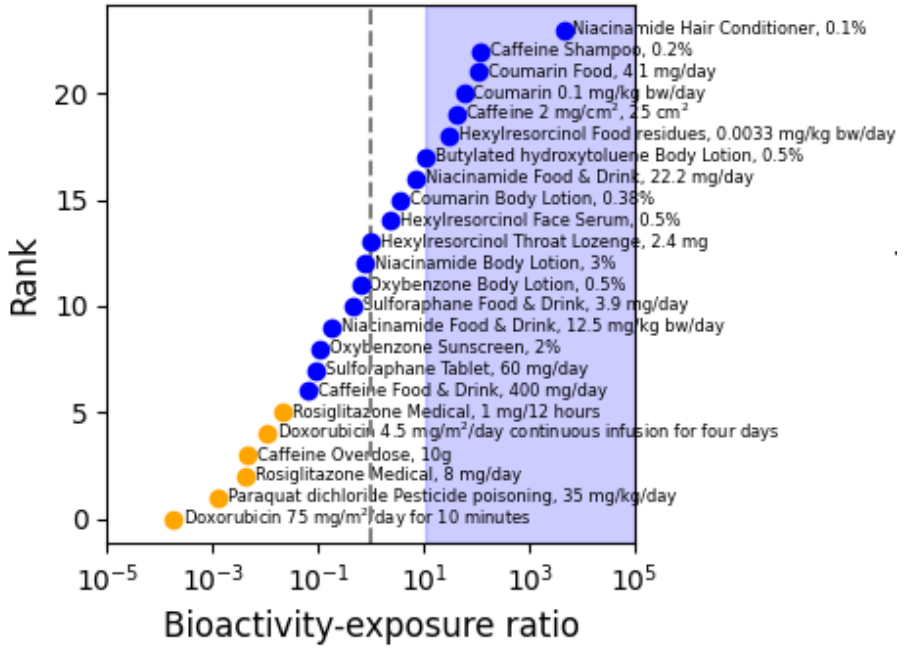
What about a larger subset of chemicals? (Part 1):

Selection of chemicals and exposure scenario

- Chemicals with well-defined human exposures
- Traditional safety assessment available
- High certainty in the risk classification for each chemical-exposure scenario
- Risk class is relative to consumer health

Chemical	Exposure scenario	Risk classification
Oxybenzone	**2 scenarios:** 0.5%; 2% sunscreen	Low risk
Caffeine	**2 scenarios:** 0.2% shampoo & coffee oral consumption 50 mg	Low risk
Caffeine	10g – fatal case reports	High risk
Coumarin	**3 scenarios:** 4 mg/d oral consumption; 1.6% body lotion (dermal); TDI 0.1 mg/kg oral	Low risk
Hexylresorcinol	**3 scenarios:** Food residues (3.3 ug/kg); 0.4% face cream; throat lozenge 2.4 mg	Low risk
BHT	Body lotion 0.5%	Low risk
Sulforaphane	**2 scenarios:** Tablet 60 mg/day; food 4.1-9.2 mg/day	Low risk
Niacinamide	**4 scenarios:** oral 12.5-22 mg/kg; dermal 3% body lotion and 0.1 % hair condition	Low risk
Doxorubicin	75 mg/m2 IV bolus 10 min; 21 days cycles; 8 cycles	High risk
Rosiglitazone	8 mg oral tablet	High risk
Paraquat	Accidental ingestion 35 mg/kg	High risk

10 chemicals – 25 exposure scenarios

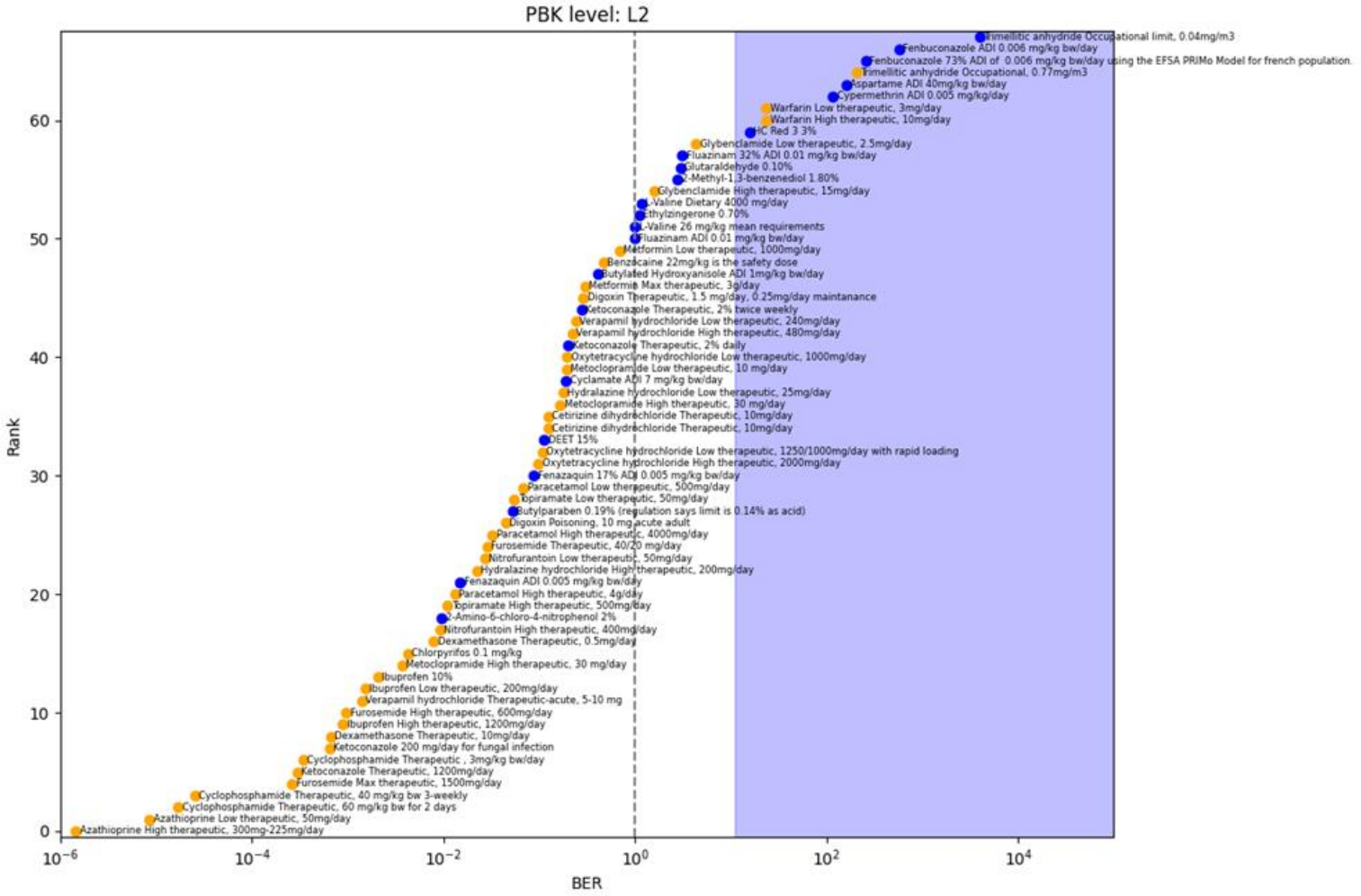


BER=lowest POD/Plasma Cmax
Blue: low risk chemical-exposure scenario
Yellow: high risk chemical-exposure scenario

Blue shaded region BER> 11

Middleton AM et al (2022). Are Non-animal Systemic Safety Assessments Protective? A Toolbox and Workflow. Toxicological Sciences, 189:124-147.

NAM Systemic toolbox remains protective (>90%) when 38 additional chemicals and 70 exposure scenarios were tested (Part 2):

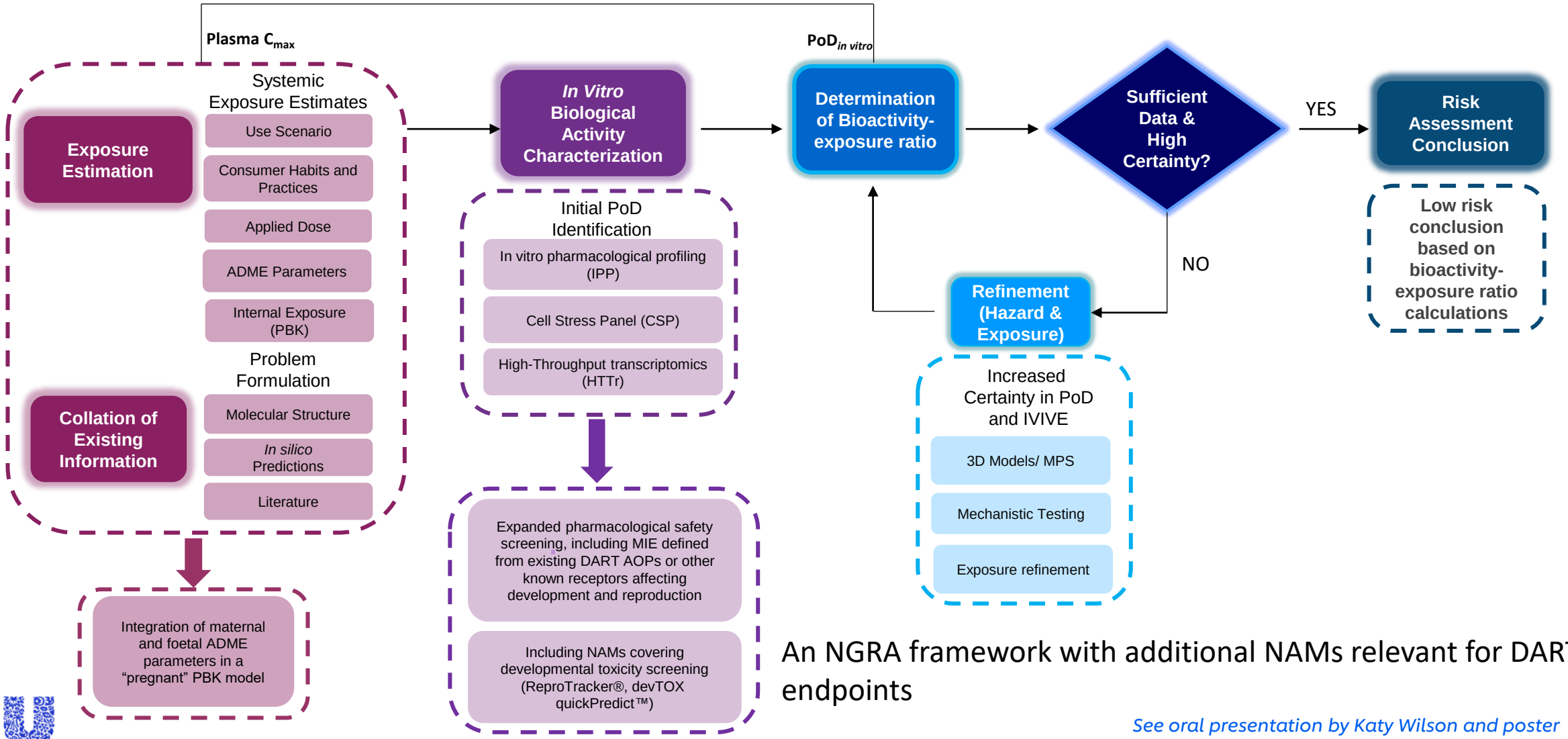


- **Toolbox not protective for 3/46 of the high-risk exposure scenarios**
- **Chemical- Exposure scenarios not protective for:**
  - Warfarin therapeutic oral dose
  - Trimellitic anhydride inhalation exposure
- **On a case-by-case basis** (e.g., depending on wider literature), **deviation may be possible.**

Cable et al (2024) – in preparation

See oral presentation by Sophie Cable for further details

Integrating DART Safety Assessment into Existing NGRA Framework:



An NGRA framework with additional NAMs relevant for DART endpoints

See oral presentation by Katy Wilson and poster presentation by Kathryn Wolton for current evaluation of DART NGRA framework

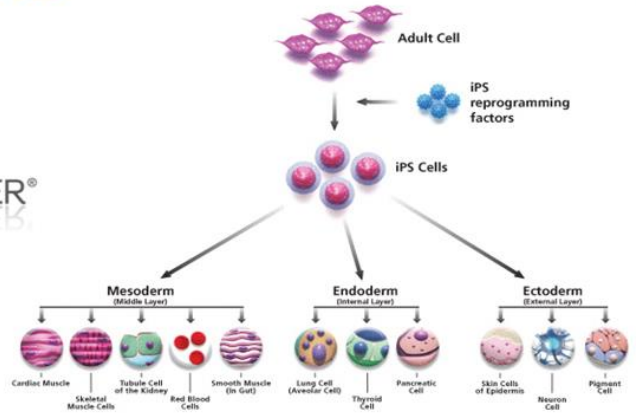
Rajagopal et al. Frontiers in Toxicology, Volume 4, March 2022,

Key tools in our NGRA approach for Systemic Toxicity – Bioactivity assays

iPSC based tools

devTOX qP quickPREDICT

REPROTRACKER®

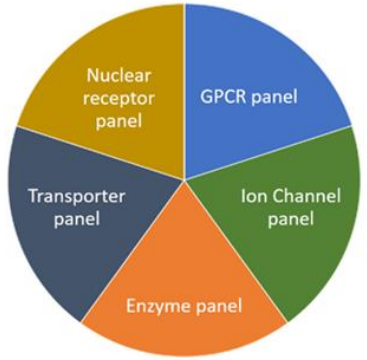


Toxicology in Vitro (2020), **63**, 104746

In vitro Pharmacological Profiling (IPP)


PERSPECTIVES

Reducing safety-related drug attrition: the use of *in vitro* pharmacological profiling



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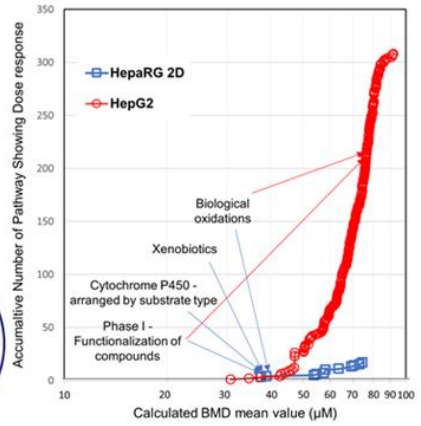
Toxicol Sci (2020), **176**, 11-33

High-throughput Transcriptomics (HTTr)

- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

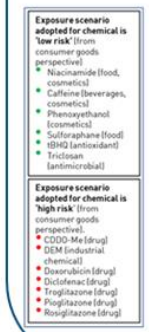
BMDExpress 2

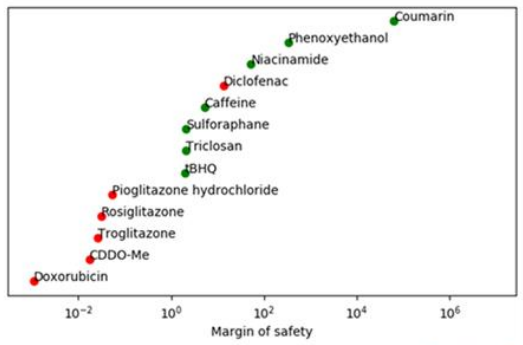


Muller et al., (2024) in preparation

Cell Stress Panel (CSP)

36 Biomarkers, 3 Timepoints, 8 Concentrations – 10 Stress Pathways





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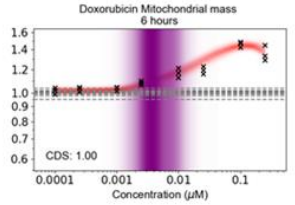

Cable et al., (2024) in preparation

Middleton et al., (2022) Toxicol Sci, 189, 124-147

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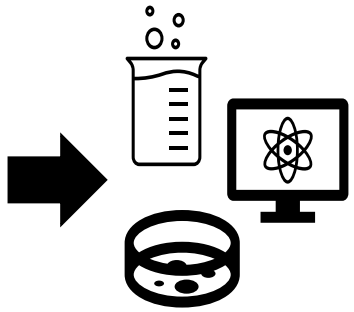
Points of Departure (PODs) from NAMs can be protective even if not predictive

AOPs (~500 in AOP wiki)



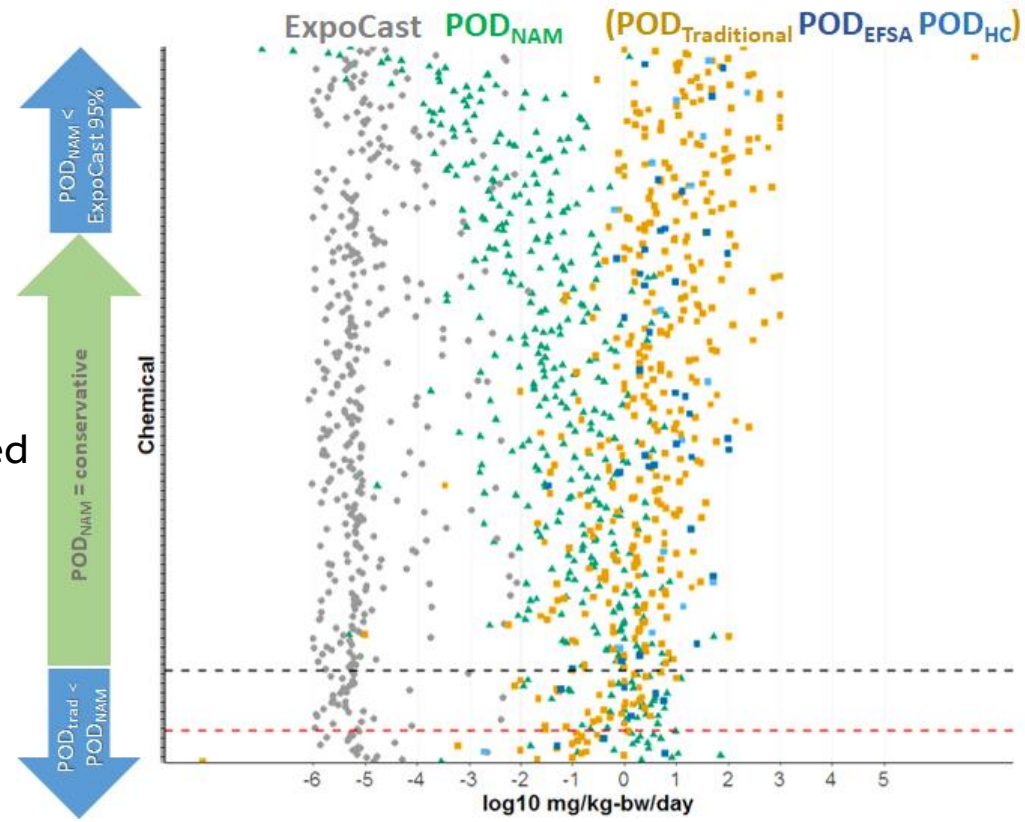
A-O-P-Wiki

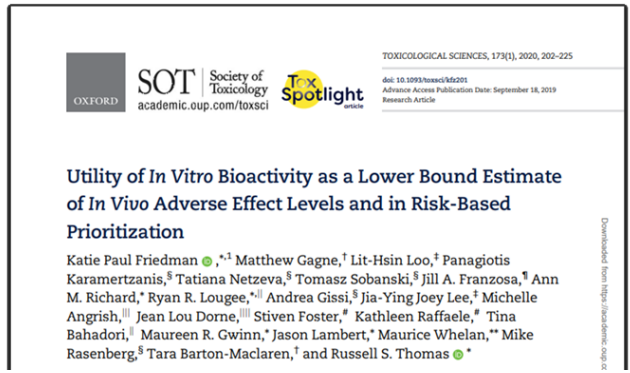
Development of battery of assays aligned to AOPs

~ 1000 of assays need to be performed if multiple AOPs are identified

Useful for Tier 2/bespoke safety assessment when differentiation between bioactivity & adversity is needed but assessment based on bioactivity is the feasible, current approach.

Human Exposure | PODs NAMs | Animal





TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman,*,1 Matthew Gagne,† Lit-Hsin Loo,‡ Panagiotis Karamertzanis,§ Tatiana Netzeva,§ Tomasz Sobanski,§ Jill A. Franzosa,¶ Ann M. Richard,* Ryan R. Lougee,*,|| Andrea Gissi,§ Jia-Ying Joey Lee,‡ Michelle Angrish,|| Jean Lou Dorne,|| Stiven Foster,# Kathleen Raffaele,# Tina Bahadori,‖ Maureen R. Gwinn,* Jason Lambert,* Maurice Whelan,** Mike Rasenberg,§ Tara Barton-Maclaren,† and Russell S. Thomas*

414/448 chemicals = *92% of the time this naïve approach appears conservative*

Case Studies Demonstrating Application of Bioactivity as a Protective POD

'... understanding how construction of NAM-based POD estimates may offer equivalent levels of public health protection as the PODs produced by animal methods ...' Paul Friedman *et al*, 2023, Computational Toxicology, 28, 10028

Unilever

APCRA ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

Paul Friedman et al., 2020. Toxicol. Sci **173**, 202-225

Application of NGRA to occupational safety assessment – challenges vs cosmetic sector

- Often simultaneous exposure over multiple routes (dermal and inhalation) and limited biomonitoring data to calibrate PBK models.
- Different exposure estimation models.
- Large number of scenarios to consider (factory, professional, cleaning etc).
- Complex supply chains and ways of working under worker safety regulations (lead registrant/confidential information).

Perceived industry challenges for uptake of occupational NGRA

↑ Complexity ↑ Resource

↑ Uncertainty ↓ Confidence

↓ Regulatory acceptance

↑ Conservatism

Case studies needed to improve confidence of chemical sector with NGRA and to address worker safety specific challenges that make its uptake more challenging from a (non) technical perspective.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The last resort requirement under REACH: From principle to practice

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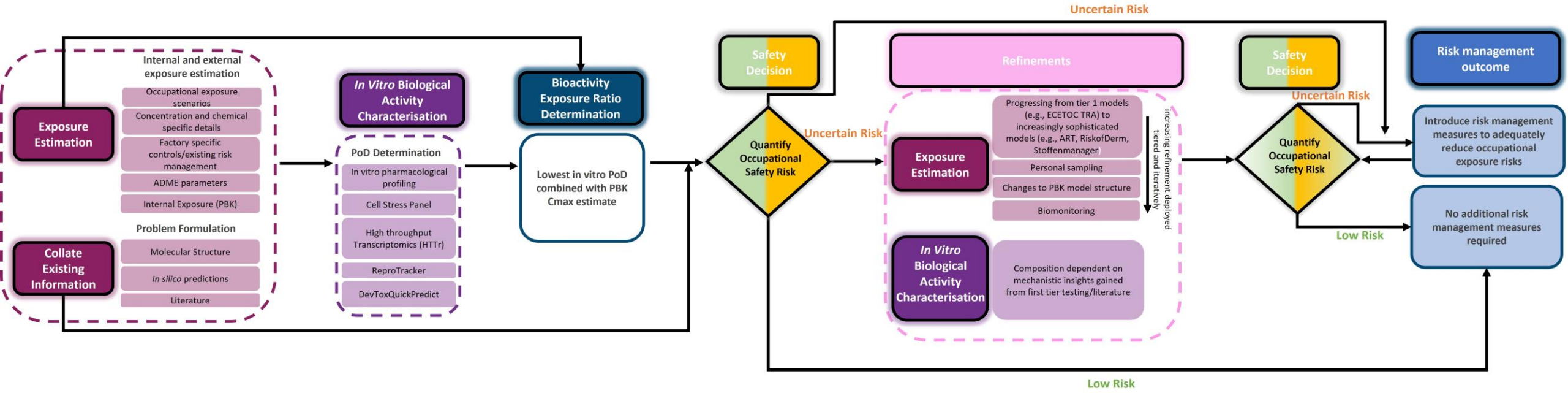
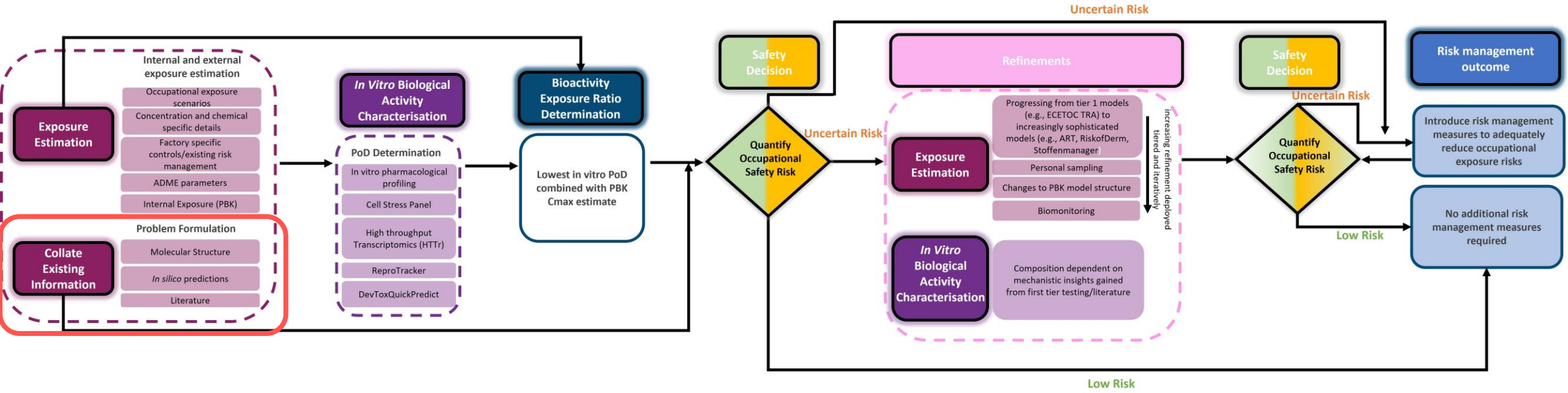
"there is a fear, or assumption, that non-animal methods will be rejected by regulators, borne out of experience that they must provide information directly equivalent to that of animal tests."

NGRA for occupational safety assessment



Wood *et al.*, (2024) *submitted*

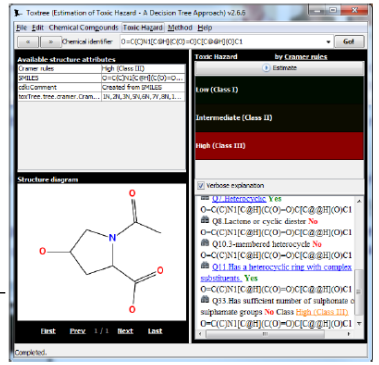
Problem formulation



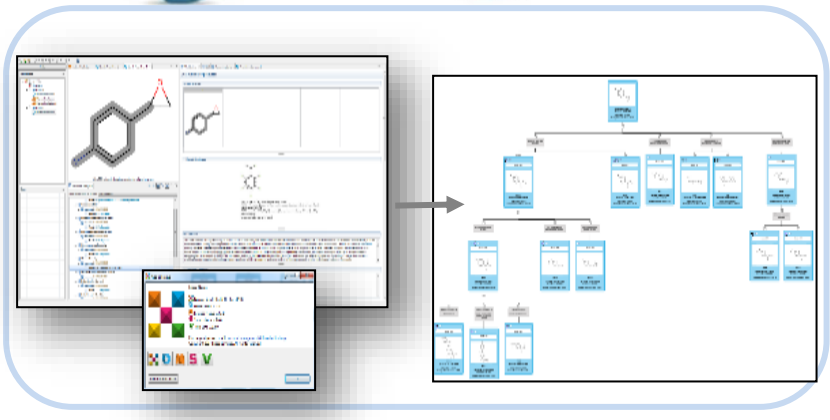
Problem formulation, in silico predictions and literature data

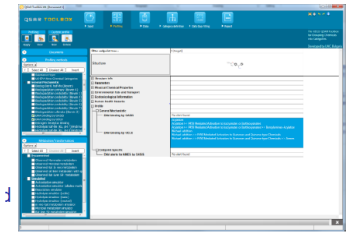
- Sodium-2-hydroxyethane sulfonate (SI) is widely used in the manufacture of alkyl isethionate surfactants.
- Historical toxicology studies: 90-day oral (NOAEL: 200 mg/kg bw/day) and developmental toxicity (rats) (NOAEL: 1000 mg/kg bw/day).
  - Comprehensive *in silico* profiling performed - Lack of any concerns.

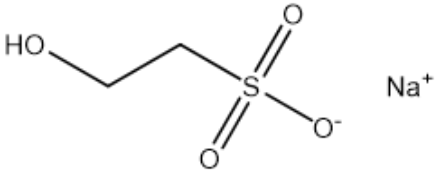
ToxTree



Derek nexus Meteor nexus OECD QSAR TOOLBOX

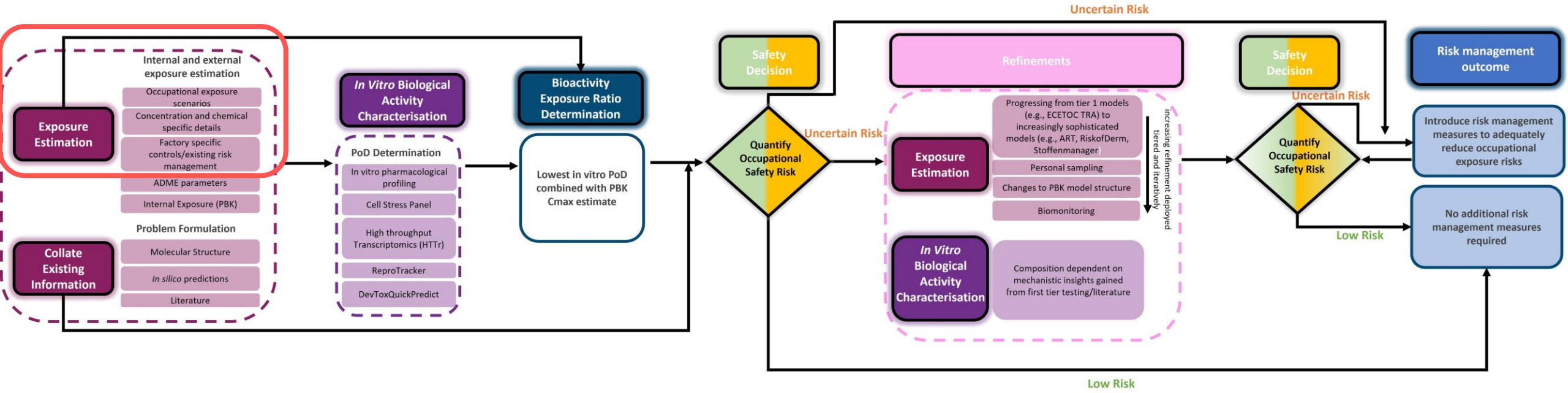




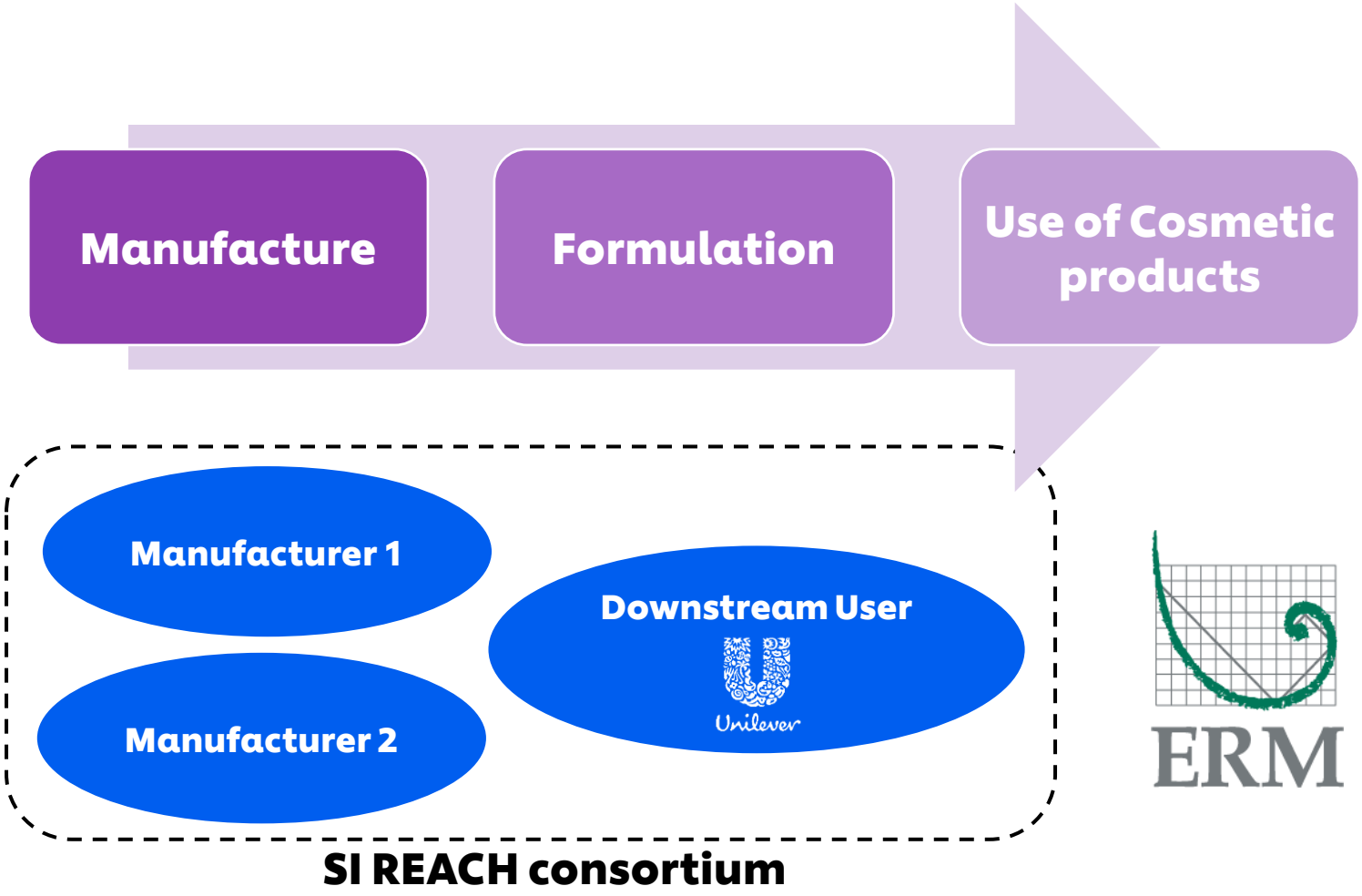


			General	ED		DART			Carcinogenicity		Genotoxicity				Irritation	Protein Binding	Chromosome Damage	DNA Binding
SMILES	**Biotransformation Name**	**Phase**	*Derek Nexus*	*OPERA*	*VEGA*	*Derek Nexus*	*VEGA*	*OECD QSAR Toolbox*	*Derek Nexus*	*OECD QSAR Toolbx*	*Derek Nexus*	OECD QSAR Toolbox	VEGA	TIMES	*Derek Nexus*	*OECD QSAR Toolbox*	*VEGA*	*OECD QSAR Toolbox*
OCCS(O)(=O)=O	SI parent	N/A	N	N	N	N	N	N	N	N	N	N	N*	N	N	N	N	N
OC(CS(O)(=O)=O)=O	Oxidation of Primary Alcohols	Phase I	N			N			N		N			N	N			
OC1C(OCCS(O)(=O)=O)OC(C(O)C1O)C(O)=O	Glucuronidation of Primary and Secondary Aliphatic and Benzylic Alcohols	Phase II	N			N			N		N			N	N			
OS(OCCS(O)(=O)=O)(=O)=O	O-Sulphonation of Aliphatic Alcohols	Phase II	N			N			N		N			N	N			

Exposure assessment – external:



Exposure Assessment within REACH consortium



- 3 consortium members covering the entire life cycle
- Confidential business information (CBI) seen as blocker to perform exposure led approach

Solution - independent consultant

1) To collect CBI (manufacturing process, volume…) and convert them to PROCs, ECS etc
2) To identify the **worst case** scenario(s) and refine them further with additional CBI
3) To provide the **worst case** exposure values (mg/kg/d) within the entire life cycle to the consortium for modelling.

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External exposure assessment:

- Life cycle assessment performed to identify relevant scenarios of use (process categories/PROCs).

- From these PROCs, exposures are typically estimated using variety of modelling software packages (e.g., ECETOC TRA, ART etc).

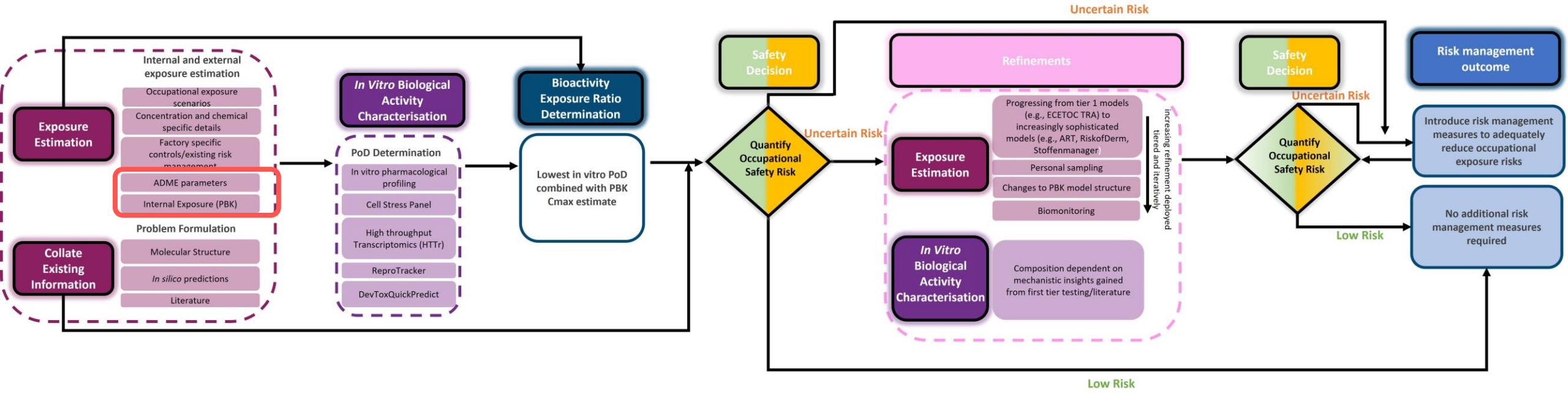
- Although worker exposure to SI occurs from a limited number of scenarios, approach can still be followed for more complex supply chains.

- External exposure estimates serve as inputs to SI specific PBK model.

PROC number:	Description:
PROC 1	Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions.
PROC 2	Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
PROC 3	Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition
PROC 4	Chemical production where opportunity for exposure arises
PROC 5	Mixing or blending in batch processes
PROC 7	Industrial spraying
PROC 8a	Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
PROC 8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
PROC 9	Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
PROC 13	Treatment of articles by dipping and pouring
PROC 14	Tabletting, compression, extrusion, pelletisation, granulation
PROC 15	Use as laboratory reagent
PROC 21	Low energy manipulation and handling of substances bound in/on materials or articles
PROC 28	Manual maintenance (cleaning and repair) of machinery

Exposure Scenario	PROC 1	PROC 2	PROC 3	PROC 4	PROC 5	PROC 7	PROC 8a	PROC 8b	PROC 9	PROC 13	PROC 14	PROC 15	PROC 21	PROC 28
Manufacture of substance	☑	☑	☑					☑				☑		☑
Use as Intermediate	☑	☑	☑					☑	☑			☑		☑
Formulation	☑	☑	☑	☑	☑	☑	☑	☑	☑		☑	☑		
Repacking		☑						☑						
Use in Printing inks							☑			☑			☑	
Use as processing aid	☑	☑	☑	☑			☑	☑						
Service Life of fabrics													☑	

Exposure assessment – internal:



Internal exposure assessment - PBK

- Worst-case exposures were selected by consultant using simple procedure.
- Procedure converts inhalation and dermal exposures into an intravenous infusion.
- Inherently conservative (e.g., 100% inhalation bioavailability)

Worker contributing scenario	Dermal exposure estimate	Inhalation exposure estimate	Max total time per day (TT)	Duration per occasion	Frequency	Exposure rate dermal	Exposure rate inhalation	Rate of systemic exposure from dermal	Rate of systemic exposure from inhalation	Total systemic exposure rate	Total dose/day	GastroPlus infusion dose/occasion
PROC 8b 'Transfer into drums – indoor'	mg/kg bw/day	mg/m^3	h	h	per day	mg/h	mg/h	mg/h	mg/h	mg/h	mg	mg
	0.034	0.38	8	8	1	0.26	0.47	0.00043	0.47	0.47	3.75	3.75

Step 1	Exposure rate dermal = Dermal exposure estimate * 60 kg bw/ 8 h/day = 0.26 mg/h
Step 2	Exposure rate inhalation = inhalation exposure estimate * 10 m3/day / 8 h/day = 0.47 mg/h
Step 3	Rate of systemic exposure from dermal = Exposure rate dermal * Potentially absorbable dose (PAD) = 0.26 * 0.17/100 = 0.00043 mg/h
Step 4	Rate of systemic exposure from inhalation = Exposure rate inhalation * inhalation bioavailability = 0.47 * 100/100 = 0.47 mg/h
Step 5	Total systemic exposure rate = dermal + inhalation rate of exposure = 0.00043 + 0.47 = 0.47
Step 6	Total dose/day = total systemic exposure rate * 8 h/day = 0.47* 8 = 3.75 mg/day

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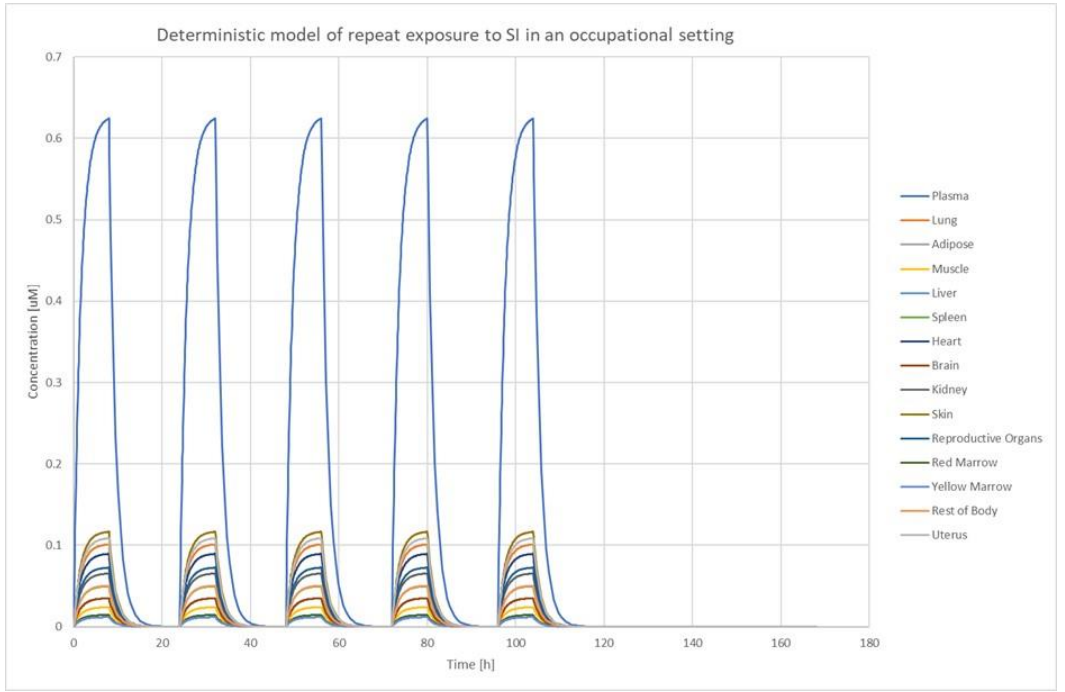
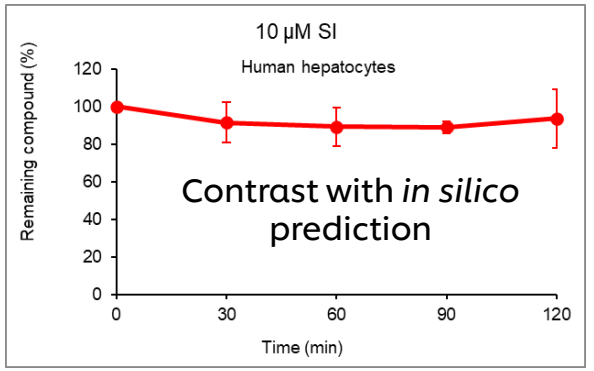
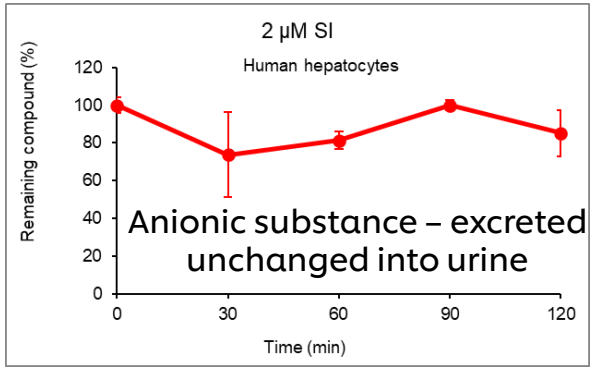
Procedure is described in detail in Wood et al (2024) - submitted

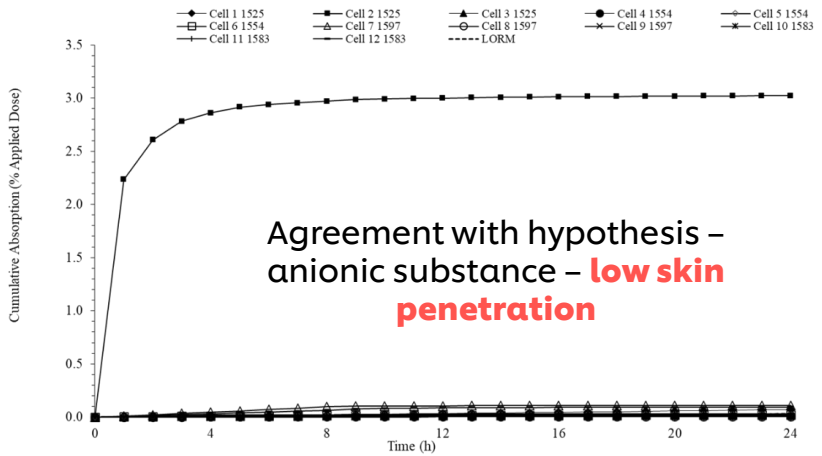
Internal exposure assessment - PBK

- 3 PBK simulation types – deterministic (pregnant individual), probabilistic (1: general worker, 2: pregnant).
- Models built using SI specific ADME data, e.g., hepatic metabolism.
- Probabilistic models included ranges for uncertain parameters (e.g., fraction unbound) and variable population parameters (e.g., blood flows).



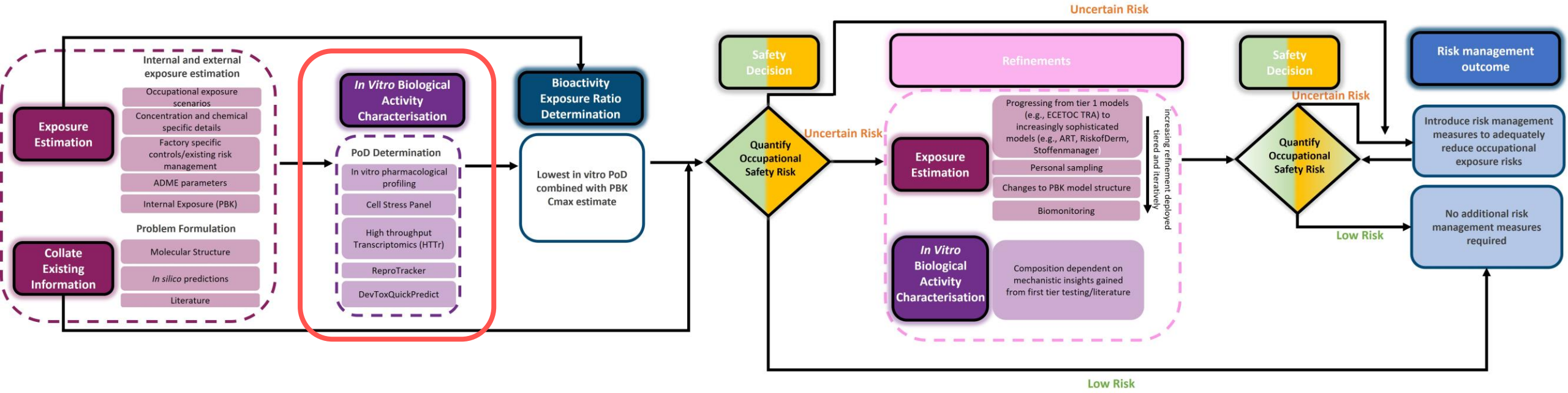






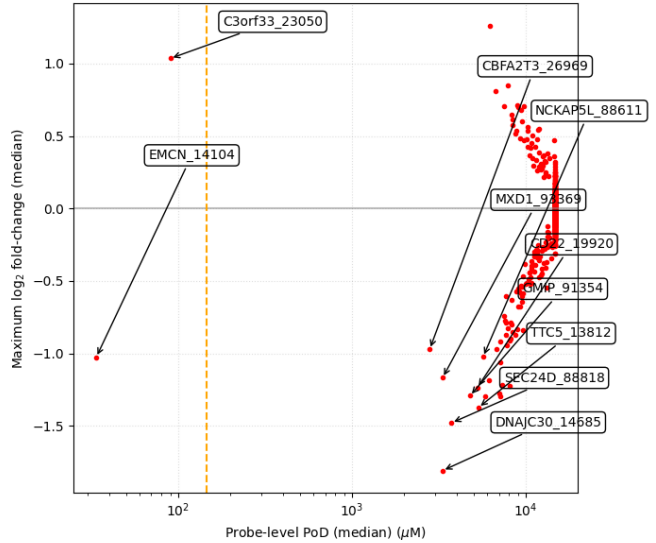
PBK simulation	C_{max} (µM)	Mean C_{max} (µM)	95th percentile C_{max} (µM)
Single person, deterministic	0.62	-	-
General workforce, probabilistic	-	0.61	0.74
Pregnant population, probabilistic	-	0.58	0.80

In Vitro Biological Activity Characterisation



Limited bioactivity demonstrated across 5 NAM assays:

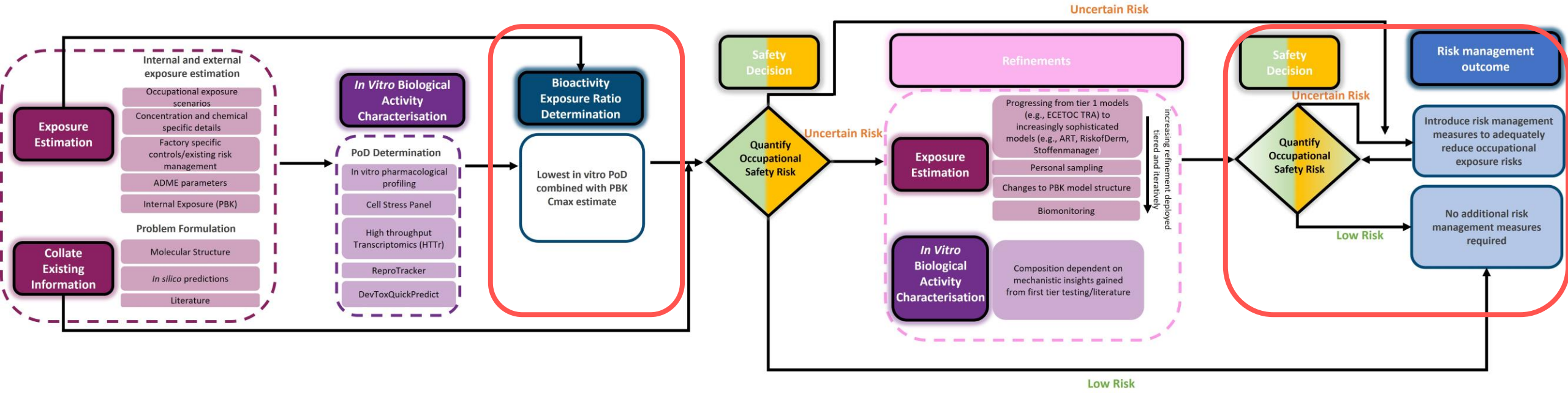
- SI showed limited bioactivity across all assays.
- Lowest PoD came from the high throughput transcriptomics assay (MCF-7 cell line), based on a single probe significantly more sensitive than others.
- Some deviation from nominal concentration was observed in dose-confirmation assays due to a dosing error.
- **Final PoD taken forward for risk characterisation = 104 µM**.



Platform	CSP (Global PoD)	*IPP*	HTTr (MCF-7) (BIFROST)	HTTr (HepG2) (BIFROST)	HTTr (HepaRG) (BIFROST)	HTTr (MCF-7) (BMDExpress)	HTTr (HepG2) (BMDExpress)	HTTr (HepaRG) (BMDExpress)	Stemina/ devTox quickpredict	Reprotracker
PoD (µM) (Nominal)	7300	>100	150	2500	1200	2860	4210	1040	>1000	>1000
Corrected PoD (µM) ★	5044	>100	104	1728	829	1976	2909	719	>1000	>1000

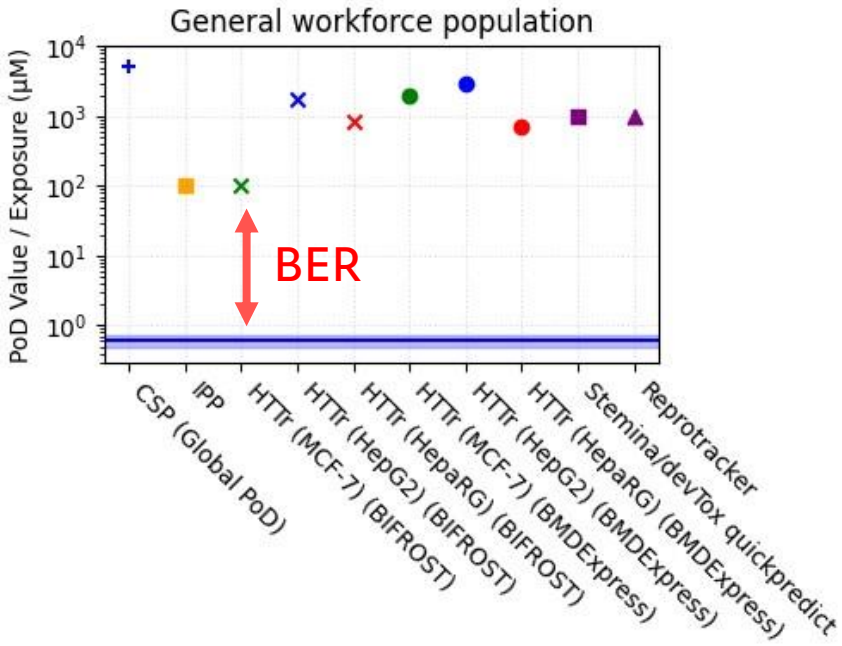
PoDs adjusted based on achieved concentrations to increase confidence in QIVIVE.

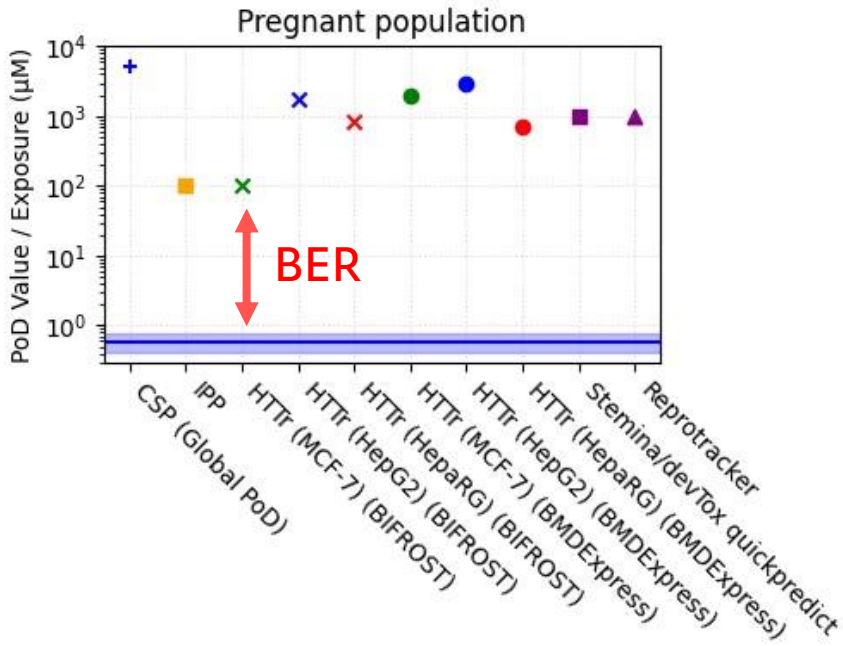
Bioactivity Exposure Ratio Determination and Safety Decision



Bioactivity Exposure Ratio Determination and Safety Decision

- Lowest PoD compared with exposure estimates.
- Most conservative BER (calculated from lowest PoD and 95th percentile pregnant population Cmax) was 130.
- In combination with existing data and lack of *in silico* alerts, current occupational exposures to SI are a low risk.
- Decision consistent with one that could be made using historical animal data (RCRs <1).





Route	Type of effect	Risk characterisation type	DNEL	PROC 8B Exposure estimate (ECETOC TRA)	RCR (ECETOC TRA)	Worst-case BER (ECETOC TRA)
Inhalation	Systemic effects - long term	Quantitative	4.9 mg/m3	0.38 mg/m3	0.078	
Dermal	Systemic effects - long term	Quantitative	294 mg/kg bw/day	0.034 mg/kg bw/day	<0.001	130
Combined routes, systemic long term					0.078	

RCR = risk characterisation ratio = Exposure/DNEL

Wrap up

- Current lack of published examples of application of NGRA to worker safety.
- Framework developed here includes multiple options for refinement and is applicable to large subset of substances to which worker exposure occurs.
- Simple procedure to convert external inhalation/dermal exposures to infusion dose can be used by consultants to manage feasibility of PBK modelling and NGRA under REACH WoW.
- NGRA frameworks such as this can be implemented to address shortcomings of tonnage driven testing requirements.

For SI:

- Limited bioactivity across a broad range of bioactivity assays. Consistent with *in silico* profiling results and existing knowledge on the substance.
- Current occupational exposures (and any RMM already in place) is sufficient for protection of workers.
- Performance of additional animal testing would not provide any human health benefit.

Acknowledgements:

NGRA (especially this one) is a multidisciplinary exercise requiring the involvement of a multitude of individuals across a broad range of expertise areas.

- SEAC safety scientists: Richard Cubberley, Matt Dent, Jade Houghton, Predrag Kukic, Sophie Malcomber, Sue Martin, Beate Nicol, Joe Reynolds, Gordon Riley, Sharon Scott, Carl Westmoreland, Mesha Williams, Kathryn Wolton
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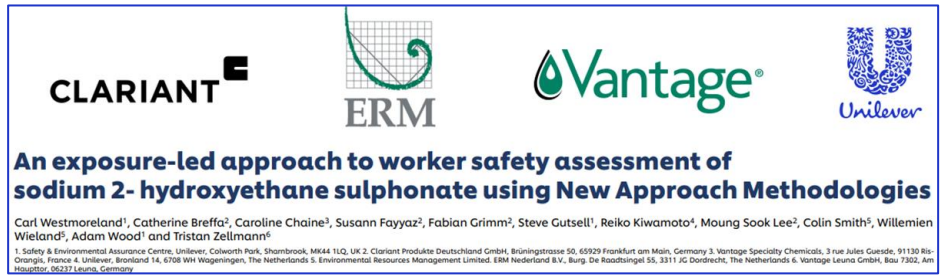
- ERM: Willemien Wieland, Colin Smith
- Bibra: Chris Waine, Dan Threlfall
- Vitis regulatory: Peter Sladen, Mike Crookes
- The numerous CROs where data is generated (Charles River, Toxys, Cyprotex, Bioclavis, Stemina, Eurofins, Pharmacelsus).



https://seac.unilever.com/files/c52d0ce8-0fbd-44a4-867b-fa4f7c1260d4/si-poster-for-wc12-final.pdf

Contents of talk today form the basis of a paper titled *"Next Generation Risk Assessment for Occupational Chemical Safety – a Real World Example with Sodium-2-hydroxyethane sulfonate"* submitted last week – watch this space!

See (poster/oral) presentations from SEAC colleagues at BTS 2024: Katy Wilson, Sophie Cable, Julia Fentem, Kathryn Wolton.

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