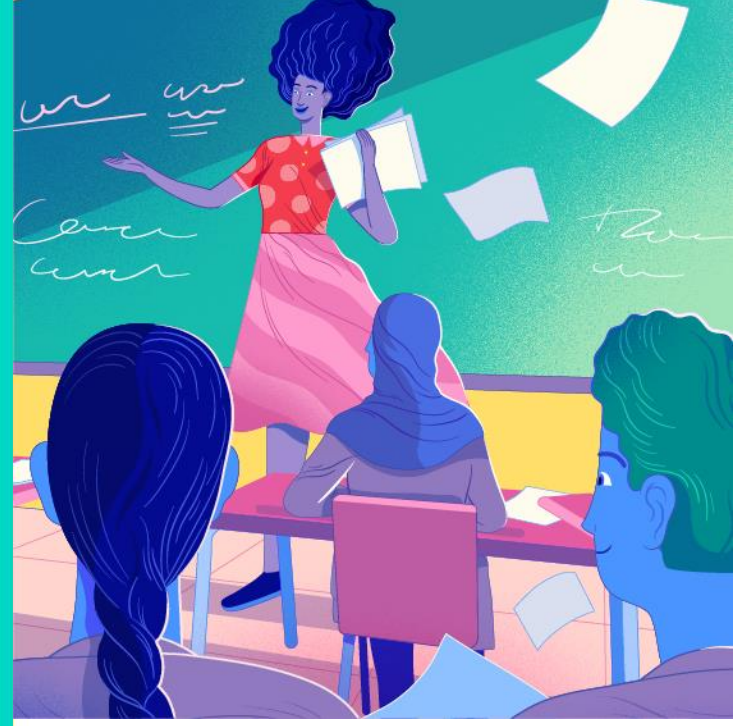
Evaluating new approach methodologies for consumer-based risk assessments: challenges and future perspectives

Alistair Middleton



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Our products must be safe

Can we make robust, reproducible decisions on these people's safety?

Recognition of Next Generation Risk Assessment (NGRA) in cosmetic safety assessment

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

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ABSTRACT

Consumer safety is a prerequisite for any cosmetic product. Worldwide, there is an ever-increasing desire to bring safe products to market without animal testing, which requires a new approach to consumer safety. 'Next Generation Risk Assessment' (NGRA), defined as an exposure-led, hypothesis driven risk assessment approach that integrates *in silico*, *in chemico* and *in vitro* approaches, provides such an opportunity. The customized nature of each NGRA means that the development of a prescriptive list of tests to assure safety is not possible, or appropriate. The International Cooperation on Cosmetics Regulation (ICCR) therefore tasked a group of scientists from regulatory authorities and the Cosmetic industry to agree on and outline the principles for incorporating these new approaches into risk assessments for cosmetic ingredients. This ICCR group determined the overall goals of NGRA (to be human-relevant, exposure-led, hypothesis-driven and designed to prevent harm); how an NGRA should be conducted (using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies); and how the assessment should be documented (transparent and explicit about the logic of the approach and sources of uncertainty). Those working on the risk assessment of cosmetics have a unique opportunity to lead progress in the application of novel approaches, and cosmetic risk assessors are encouraged to consider these key principles

International Cooperation on Cosmetics Regulation

SCCS/1628/21

Scientific Committee on Consumer Safety

SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION

11TH REVISION

Scientific Committees on Consumer Safety and on Health, Environmental and Emerging Risks

The SCCS adopted this guidance document at its plenary meeting on 30-31 March 2021

3-4 RELEVANT TOXICOLOGICAL TOOLS FOR THE SAFETY EVALUATION OF COSMETIC INGREDIENTS

The SCCS has been closely following the progress made with regard to the development and validation of alternative methods and updated its NoG on a regular basis taking progress into consideration.

Besides validated alternatives, the SCCS may also accept, on a case-by-case basis, methods that are scientifically valid as new tools (*e.g.*, "-omics" technology) for the safety evaluation of cosmetic substances. Such valid methods may not have necessarily gone through the complete validation process, but the Committee may consider them acceptable when there is a sufficient amount of experimental data proving relevance and reliability and including positive and negative controls.

According to the Cosmetics Regulation, the experimental studies have to be carried out in accordance with the principles of Good Laboratory Practice (GLP)laid down in Council Directive 87/18/EEC. All possible deviations from this set of rules should be explained and scientifically justified (SCCNFP/0633/02).

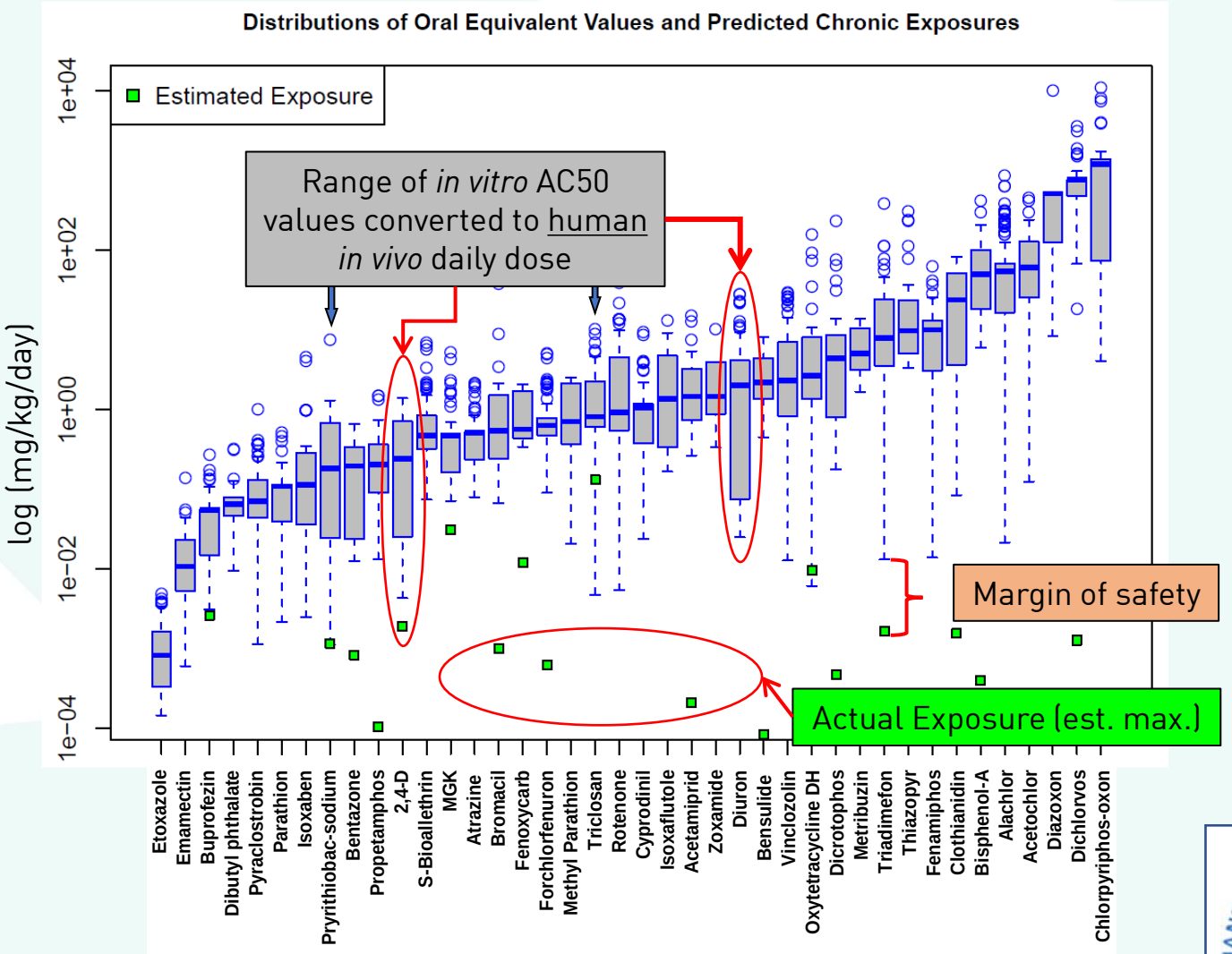
3-4.1 NEW APPROACH METHODOLOGY (NAM) AND NEXT-GENERATION RISK ASSESSMENT (NGRA)

Whereas the terminology of "Alternative Test Methods (ATMs)" does not cover all available tools *e.g.*, *in silico* methodology, the more general term, New Approach Methodology (NAM) has been introduced. As for cosmetics and their ingredients, testing and marketing bans apply with respect to animal use and also the obligation exists to only use validated replacement alternatives, the need for validated non-animal alternative methods for chemical hazard assessment is much more important in Europe for compliance with the Cosmetics Regulation than for other regulatory frameworks. NAMs may include *in vitro*, *ex vivo*, *in chemico and in silico* methods, read-across, as well as combinations thereof. Therefore, before any testing is carried out for safety evaluation, all information on the substance under consideration should be gathered from different available means. A set of criteria, universal across initiatives, to evaluate NAMs fit-for-purpose was developed by a multi-stakeholder group and may support greater consistency across different initiatives (Parish *et al.*, 2020).

Many efforts are ongoing to modernise toxicological safety evaluation and to look for non-animal methodology that can be used for the risk assessment of compounds that after long-term exposure could be at the origin of systemic toxicity. One of these approaches is referred to as NGRA (USEPA, 2014). The principles underpinning the application of an NGRA to cosmetics have been defined by the International Cooperation on Cosmetics Regulation (ICCR), a platform of regulators and cosmetics industry from the EU, the US, Japan, Canada and Brazil (Dent *et al.*, 2018). NGRA is a human-relevant, exposure-led, hypothesis-driven risk assessment designed to prevent harm. It integrates several NAMs to deliver safety decisions relevant to human health without the use of experimental animals. An NGRA should be conducted using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies. Given the novelty of NGRA and the current lack of regulatory guidance on the use of a variety of NAMs in decision-making, it is important that the assessment should be transparently documented and explicit about the logic of the approach and sources of uncertainty (Dent *et al.*, 2018). A general NGRA workflow is described in **Figure 5** (Berggren *et al.*, 2017). The tools useful for safety evaluation of cosmetic ingredients, which could also be used in case NGRA would be taken as a possible workflow in the future, are described in chapters 3-4.2 to 3-4.14. Treshold of Toxicological Concern (TTC) and internal TTC (iTTC) approaches as a risk assessment tools are described in 3-5.2.

European Commission: Scientific Committee on Consumer Safety (2021)

NGRA: The assessment is designed to prevent harm



Slide from Dr Rusty Thomas, EPA, with thanks

Rotroff, *et al.* Tox.Sci 2010

The philosophy behind this type of risk assessment aimed at preventing harm is **based on the premise of "Protection not Prediction".**

The hypothesis underpinning this type of NGRA is that **if there is no bioactivity observed at consumer-relevant concentrations, there can be no adverse health effects.**

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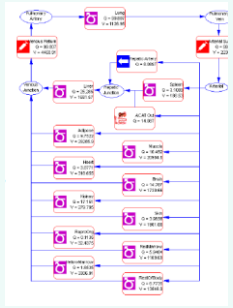
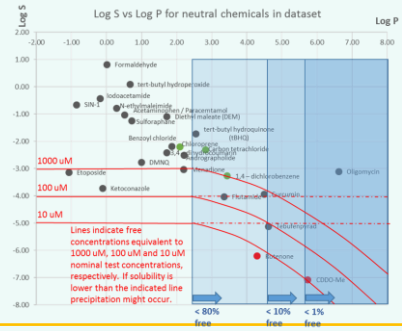
Overview of core toolbox

Exposure Estimation

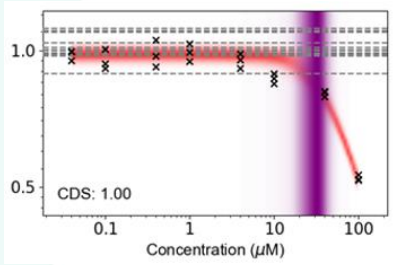
PBK models



Free concentration

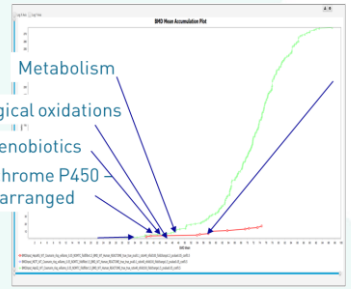


Concentration Response Models



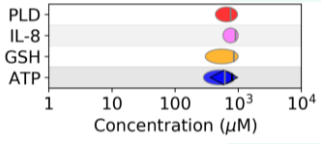
In Vitro Biological Activity Characterization

HTTr



- MCF7
- HepG2
- HepaRG

CSP

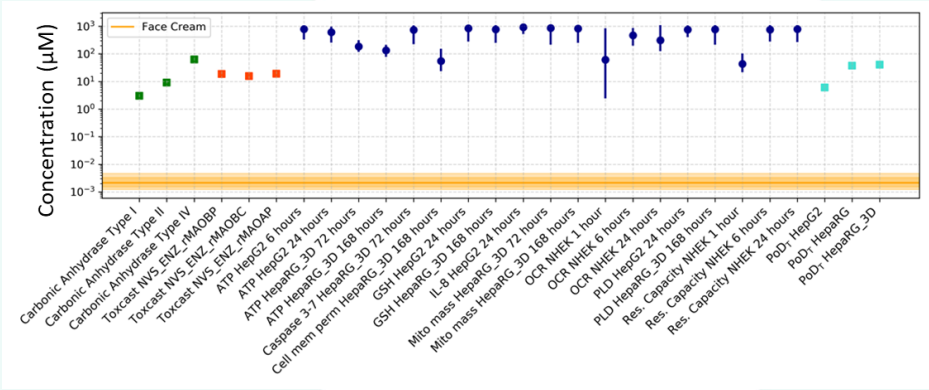


- HepG2

IPP

- All binding and enzymatic assay results were **negative at 10 μM, including COX-1 and COX-2**.
- Highest inhibition (22%) was for MAO-A

Bioactivity exposure ratio estimate



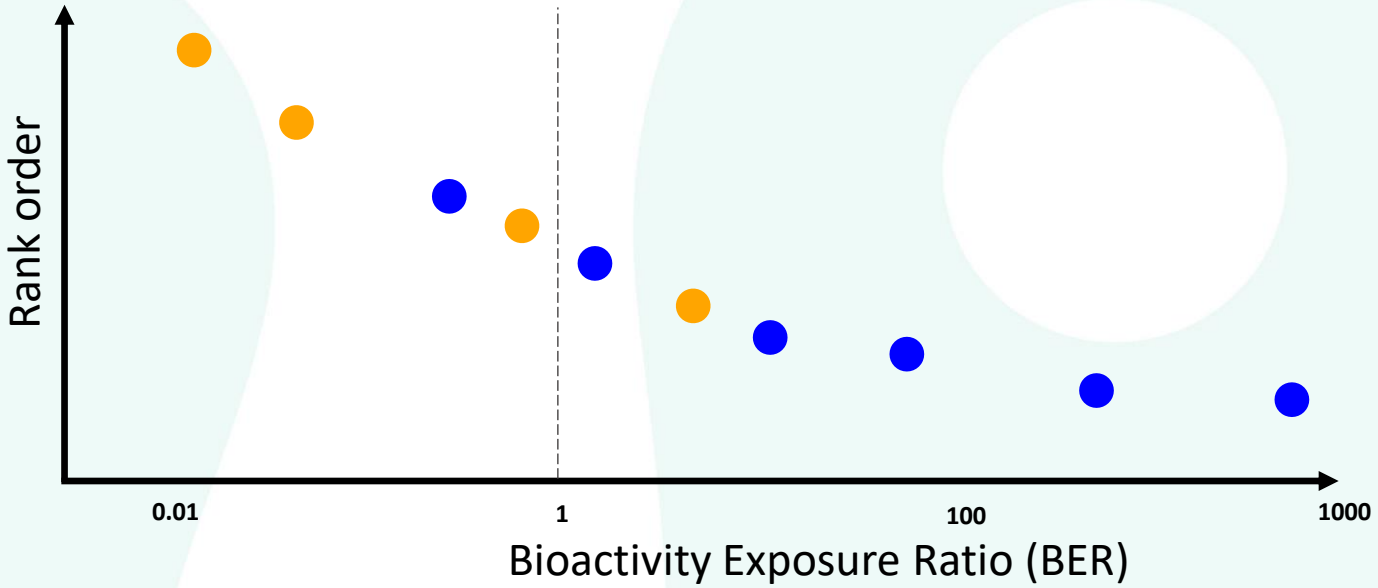
Inform safety decision

HTTr: High-throughput transcriptomics **CSP:** Cell Stress Panel **IPP:** In vitro pharmacological profiling

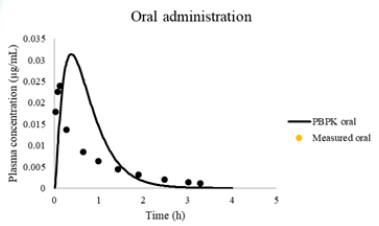
Evaluating the toolset for risk assessment

Chemical exposures scenarios

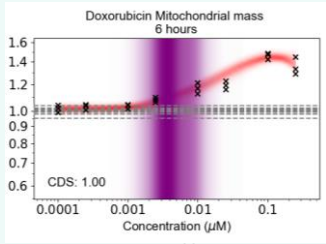
- ‘Low’ risk (from consumer goods perspective) – e.g. foods, cosmetics
- ‘High’ risk (from consumer goods perspective) – e.g. drugs



Define typical use-case scenarios benchmark chemical-exposures



PBK models of systemic exposure



In-vitro cell assays, estimate PoDs

Calculate the bioactivity exposure ratio

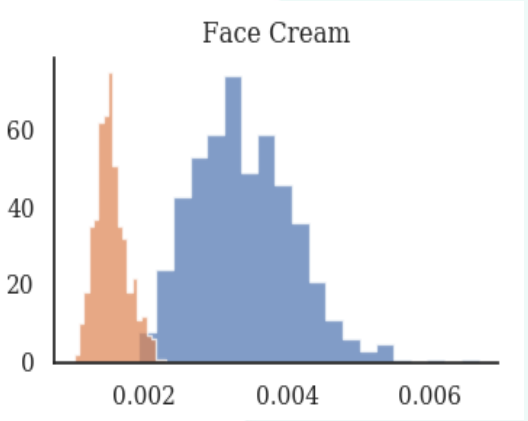
Can the toolset successfully **distinguish between low and high risk** chemical exposure scenarios up to a certain BER?

Challenges and potential solutions

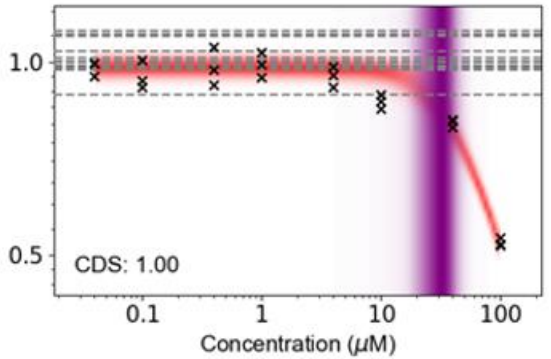
Benchmark chemical selection

Orginal_ID	List_CName	CASRN	DTXSID	List_Source	ferred_na	x_structu	ndard_In	dard_InCh
1838	R-(-)-Carvone;-;	6485-40-1	DTXSID70	HTTR chemcial master list with p	R-(-)-Carv	DTXCID50	InChI=1S/	ULDHMXU
2400	3-Oxobutanamide;-;	5977-14-0	DTXSID10	ECHA EU-TOXrisk 2nd compound	3-Oxobut	DTXCID90	InChI=1S/	GCPWJFK
2061	Undecane;-;	1120-21-4	DTXSID90	HTTR chemcial master list with p	Undecane	DTXCID30	InChI=1S/	RSJKGSCJ
1566	N,N-Dimethyldecylamine oxide;-;	2605-79-0	DTXSID70	HTTR chemcial master list with p	N,N-Dime	DTXCID50	InChI=1S/	ZRKZFNZP
905	C.I. Acid Blue 74;-;	860-22-0	DTXSID10	HTTR chemcial master list with p	C.I. Acid B	DTXCID80	InChI=1S/	KHLVKKO
1583	N-Cyclohexyl-N-methylcyclohexanamin	7560-83-0	DTXSID60	HTTR chemcial master list with p	N-Cyclohe	DTXCID40	InChI=1S/	GSCCALZH
703	6:2 Fluorotelomer alcohol;-;	647-42-7	DTXSID50	HTTR chemcial master list with p	6:2 Fluoro	DTXCID30	InChI=1S/	GRJRKPMI
388	1-Undecanol;-;	112-42-5	DTXSID00	HTTR chemcial master list with p	1-Undecar	DTXCID70	InChI=1S/	KJIOQYGW
2303	2,2'-Dibenzoylaminodiphenyl disulfide;-	135-57-9	DTXSID70	HTTR_2019_Screening_List_for_L	2,2'-Diben	DTXCID50	InChI=1S/	ZHMIOPLN
1620	Nonane;-;	111-84-2	DTXSID90	HTTR chemcial master list with p	Nonane	DTXCID00	InChI=1S/	BKIMMITL
970	cis-3,7-Dimethyl-2,6-octadien-1-yl aceta	141-12-8	DTXSID20	HTTR chemcial master list with p	cis-3,7-Dir	DTXCID00	InChI=1S/	HIGQPQR
1160	Diphenhydramine hydrochloride;-;	147-24-0	DTXSID40	HTTR chemcial master list with p	Diphenhy	DTXCID20	InChI=1S/	PCHPORC
1123	Dihexyl phthalate;-;	84-75-3	DTXSID60	HTTR chemcial master list with p	Dihexyl pl	DTXCID50	InChI=1S/	KCXZNSG
2448	4-(3-Phenylpropyl)pyridine;-;4-(3-pheny	2057-49-0	DTXSID50	EUTOXRISK Chem set 1 - pass 3 fi	4-(3-Phen	DTXCID30	InChI=1S/	AQIIVEIS
1668	Panthenol;-;	16485-10-	DTXSID30	HTTR chemcial master list with p	Pantheno	DTXCID10	InChI=1S/	SNPLKNR
300	1,2-Diphenylethanone;-;	451-40-1	DTXSID60	HTTR chemcial master list with p	1,2-Diphe	DTXCID40	InChI=1S/	OTKCEEW
1958	Tetradecane;-;	629-59-4	DTXSID10	HTTR chemcial master list with p	Tetradeca	DTXCID70	InChI=1S/	BGHCVCJ
821	Benzoin;-;	119-53-9	DTXSID10	HTTR chemcial master list with p	Benzoin	DTXCID10	InChI=1S/	ISAOCJYI
581	3-Ethoxy-4-hydroxybenzaldehyde;-;	121-32-4	DTXSID50	HTTR chemcial master list with p	3-Ethoxy-	DTXCID90	InChI=1S/	CBOQJAN
516	2-Methoxy-4-vinylphenol;-;	7786-61-0	DTXSID70	HTTR chemcial master list with p	2-Methox	DTXCID80	InChI=1S/	YOMSJEA

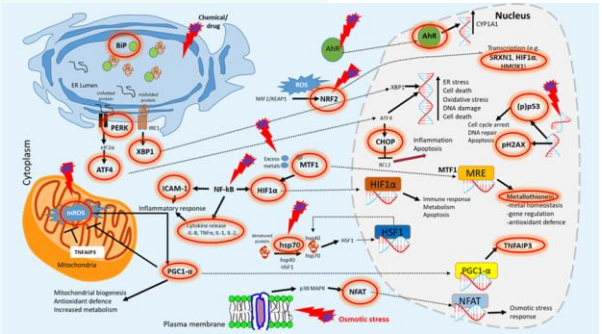
Uncertainty in exposure estimates (inc metabolism)



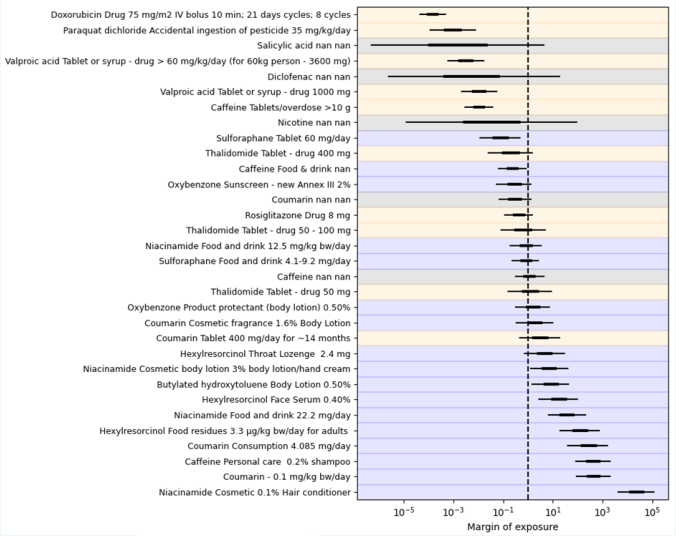
Uncertainty in PoD estimates and free concentration



Sufficient biological coverage (assays, cell models)



Robust decision-making based on the BER



Moxon TE, Li H, Lee MY, et al. Application of physiologically based kinetic (PBK) modelling in the next generation risk assessment of dermally applied consumer products. *Toxicol In Vitro*. 2020;63:104746. doi:10.1016/j.tiv.2019.104746

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Concluding remarks

- NGRA aims to be protect of human health at defined exposures.
- Evaluation needs to be based on how the different bioactivity and exposure estimates can be combined to make robust, reliable decisions on consumer safety.
- Quantifying the degree of uncertainty in the tools is key ensuring that they can be used with confidence.
- There is a need to increase confidence amongst many risk assessors with the use of mathematical approaches in NGRA used to combined different types of in vitro data (PBK modelling, PoD modelling etc)

Session 24 (30th September, 16:30-18:30):
Building confidence in the use of new approach methodologies for safety decision-making

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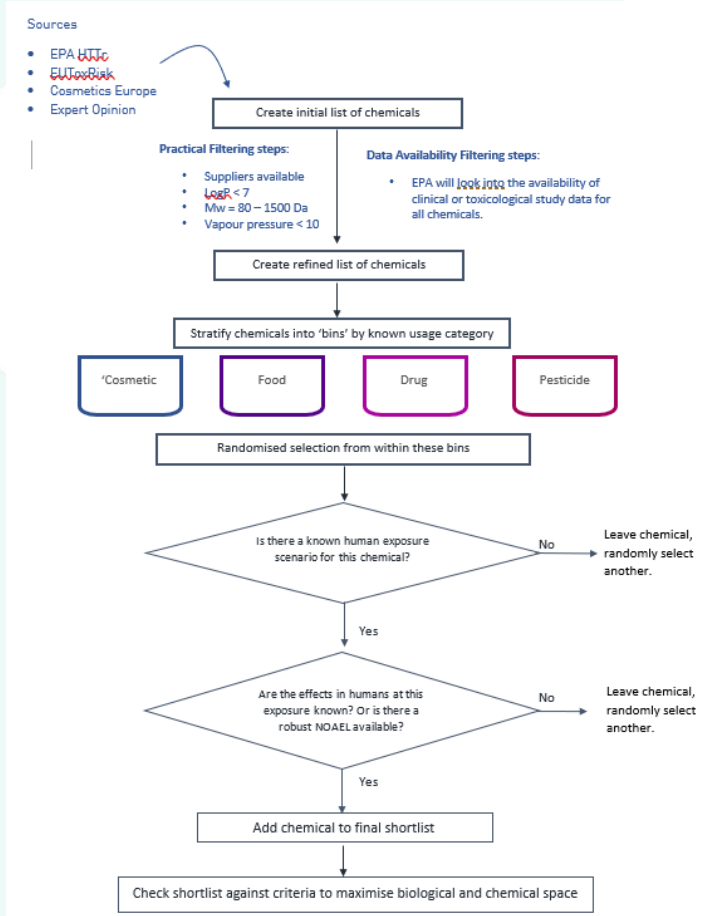
What we're doing to address these challenges (1/3)

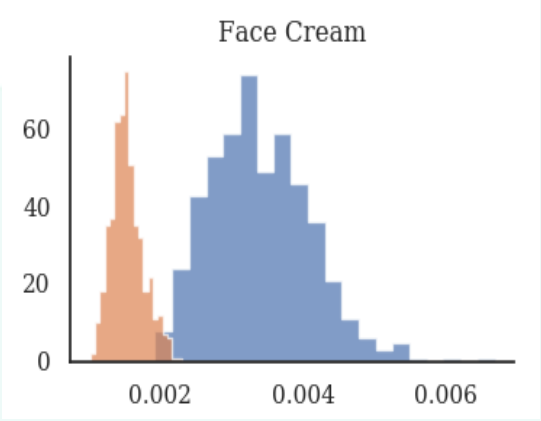
Identification of appropriate chemical-exposures

Orginal_ID	List_CName	CASRN	DTXSID	List_Source	ferred_na	ox_structu	ndard_In	ndard_InCh
1838	R-(-)-Carvone;-;	6485-40-1	DTXSID70	HTTR chemcial master list with p	R-(-)-Carv	DTXCID50	InChI=1S/	ULDHMXU
2400	3-Oxobutanamide;-;	5977-14-0	DTXSID10	ECHA EU-TOXrisk 2nd compound	3-Oxobut	DTXCID90	InChI=1S/	IGCPWJFK
2061	Undecane;-;	1120-21-4	DTXSID90	HTTR chemcial master list with p	Undecane	DTXCID30	InChI=1S/	RSJKGSCJ
1566	N,N-Dimethyldecylamine oxide;-;	2605-79-0	DTXSID70	HTTR chemcial master list with p	N,N-Dime	DTXCID50	InChI=1S/	ZRKZFNZP
905	C.I. Acid Blue 74;-;	860-22-0	DTXSID10	HTTR chemcial master list with p	C.I. Acid B	DTXCID80	InChI=1S/	KHLVKKO
1583	N-Cyclohexyl-N-methylcyclohexanamin	7560-83-0	DTXSID60	HTTR chemcial master list with p	N-Cyclohe	DTXCID40	InChI=1S/	GSCCALZH
703	6:2 Fluorotelomer alcohol;-;	647-42-7	DTXSID50	HTTR chemcial master list with p	6:2 Fluoro	DTXCID30	InChI=1S/	GRJRKPMI
388	1-Undecanol;-;	112-42-5	DTXSID00	HTTR chemcial master list with p	1-Undecar	DTXCID70	InChI=1S/	KJIOQYGW
2303	2,2'-Dibenzoylaminodiphenyl disulfide;-	135-57-9	DTXSID70	HTTR_2019_Screening_List_for_L	2,2'-Diben	DTXCID50	InChI=1S/	ZHMIOPLN
1620	Nonane;-;	111-84-2	DTXSID90	HTTR chemcial master list with p	Nonane	DTXCID00	InChI=1S/	BKIMMITL
970	cis-3,7-Dimethyl-2,6-octadien-1-yl aceta	141-12-8	DTXSID20	HTTR chemcial master list with p	cis-3,7-Dir	DTXCID00	InChI=1S/	HIGQPQR
1160	Diphenhydramine hydrochloride;-;	147-24-0	DTXSID40	HTTR chemcial master list with p	Diphenhy	DTXCID20	InChI=1S/	PCHPORC
1123	Dihexyl phthalate;-;	84-75-3	DTXSID60	HTTR chemcial master list with p	Dihexyl pl	DTXCID50	InChI=1S/	KCXZNSG
2448	4-(3-Phenylpropyl)pyridine;-;4-(3-phen	2057-49-0	DTXSID50	EUTOXRISK Chem set 1 - pass 3 fi	4-(3-Phen	DTXCID30	InChI=1S/	AQIIVEISJ
1668	Panthenol;-;	16485-10-	DTXSID30	HTTR chemcial master list with p	Pantheno	DTXCID10	InChI=1S/	SNPLKNR
300	1,2-Diphenylethanone;-;	451-40-1	DTXSID60	HTTR chemcial master list with p	1,2-Diphe	DTXCID40	InChI=1S/	OTKCEEW
1958	Tetradecane;-;	629-59-4	DTXSID10	HTTR chemcial master list with p	Tetradeca	DTXCID70	InChI=1S/	BGHCVCJ
821	Benzoin;-;	119-53-9	DTXSID10	HTTR chemcial master list with p	Benzoin	DTXCID10	InChI=1S/	ISAOCJYI
581	3-Ethoxy-4-hydroxybenzaldehyde;-;	121-32-4	DTXSID50	HTTR chemcial master list with p	3-Ethoxy-	DTXCID90	InChI=1S/	CBOQJAN
516	2-Methoxy-4-vinylphenol;-;	7786-61-0	DTXSID70	HTTR chemcial master list with p	2-Methox	DTXCID80	InChI=1S/	YOMSJEA

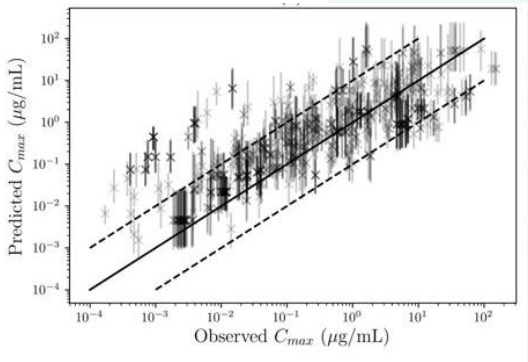
Systematic selection of different chemicals with defined human-use scenarios (cosmetics, drugs, etc)



Uncertainty in exposure estimates (how 'wrong' are the PBK models?)



Evaluation of 'how wrong' PBK models can be by comparing human Cmax/AUC data to model predictions



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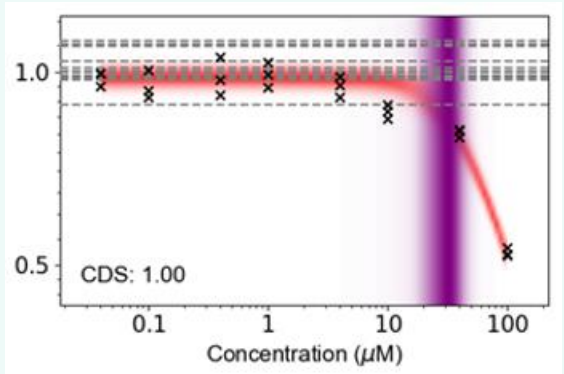
What we're doing to address these challenges (2/3)

Uncertainty in PoD estimates



PoD variability across cell models and replicates

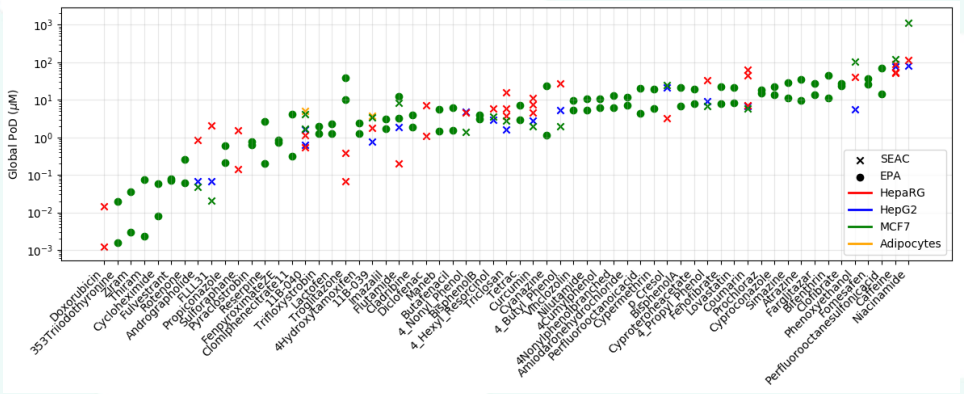
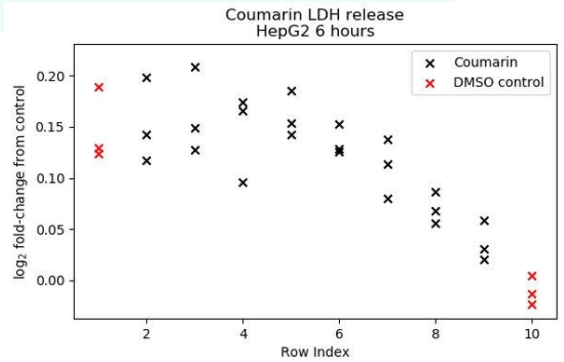
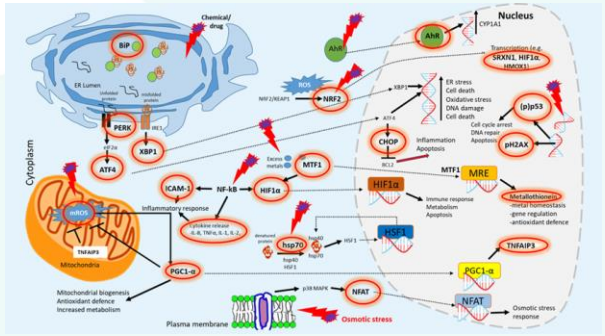


Plate effect example



Sufficient biological coverage (assays and cell models)



- Optimising experimental design of our assays (number of replicates, plate layout, appropriate controls etc)
- Compare different PoD calculation approaches (BMDexpress etc)
- Analysing biological pathway coverage across large numbers of compounds and cell types.
- Evaluating other broad-spectrum assays (e.g. phenotypic profiling).

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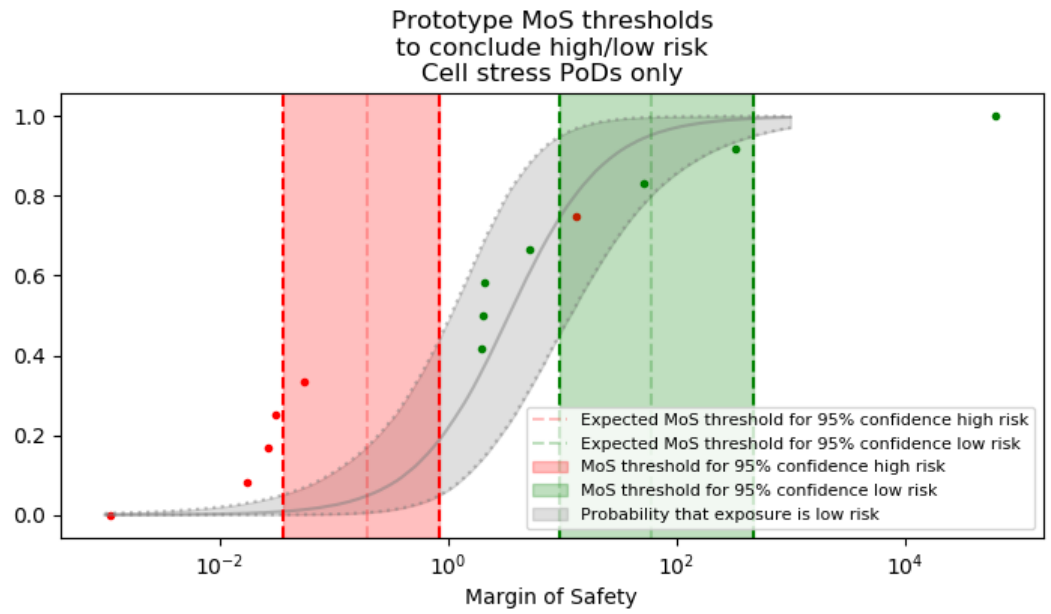
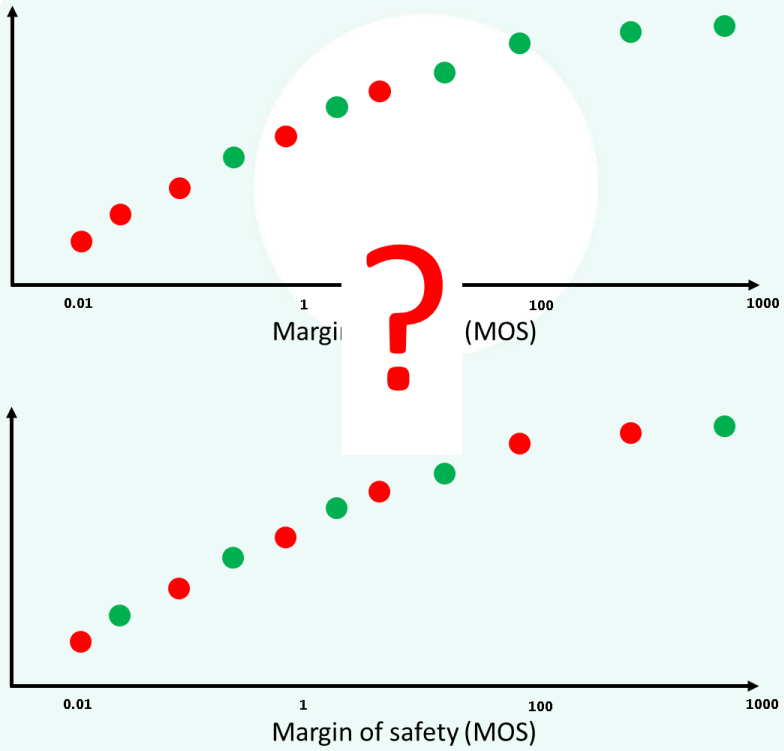
What we're doing to address these challenges (3/3)

Robust decision-making based on the MOS using e.g. Bayesian logistic regression





Using the toolbox data, deploy probabilistic models that quantify the (un)certainty that a given exposure scenario is low-risk based on the margin-of-safety.

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