An exposure-led approach to worker safety assessment of sodium 2- hydroxyethane sulphonate using New Approach Methodologies

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Introduction

As outlined by the European Commission's Scientific Committee on Consumer Safety, Next Generation Safety Assessment or Next Generation Risk Assessment (NGRA) is an exposure-led approach to safety assessment that employs the use of human-based New Approach Methdologies (NAMs) [1]. It is increasingly used to assure the consumer safety of cosmetic ingredients without the use of toxicology data generated in animals. The scientific principles of Next Generation Safety Assessment are also applicable to other areas of safety assessment including the safety of workers in factories.

This poster describes how NAMs can be used in a weight of evidence approach to understand whether any bioactivity is expected during/following worker exposure to sodium 2-hydroxyethane sulphonate (SI). The weight of evidence approach was constructed in accordance with the International Cooperation on Cosmetics Regulation (ICCR) principles underpinning the use of NAMs for the assessment of cosmetic ingredients [2], which form a framework for safety decision making without generating animal data. The overall strategy used was similar to two published examples of cosmetic ingredient Next Generation Safety Assessments (coumarin and phenoxyethanol [3, 4]). The objective is to generate a broad suite of human-relevant bioactivity data for molecular events that may occur upstream of an adverse health effect and to compare these in vitro points of departure (PoDs) with physiologically-based kinetic (PBK) model predictions of levels of human systemic exposure. This allows an assessment of the probability that human exposure will result in systemic bioactivity. If no bioactivity is expected during/following registered uses of SI, there can be no adverse effects.

Methods and Results

Exposure Estimation

The worst-case levels of exposure of workers to SI in several factory environments were estimated using factory-specific data and occupational exposure models including CHESAR and ART. These exposure values were then used to estimate worst-case levels of systemic exposure to SI following occupational exposure using Physiologically Based Kinetic (PBK) modelling [5]. Experimental ADME data from NAMs were also generated on SI for this PBK modelling.

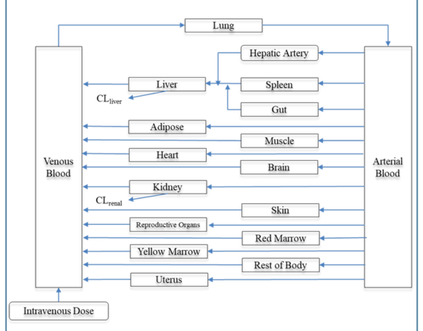
Worker Exposure Data

Data Generation

In vitro data on SI:

- **Dermal absorption**
- **Blood to plasma ratio**
- **Plasma protein binding**
- **Metabolic stability**

PBK Modelling



ART ADVANCED REACH TOOL chesar

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(12 different assays, 107 Experiments, 8 CROs)

The use of ERM as independent consultants throughout this work ensured appropriate protection of individual companies' confidential business information

In Vitro Biological Activity Characterisation

The bioactivity of SI was assessed in a battery of NAMs relevant to systemic [6], reproductive, and developmental toxicity [7]. Concentration-response curves were derived for 40 cell stress markers and High Throughput Transcriptomics was conducted in HepG2, HepaRG and MCF7 cells. Pharmacological profiling of SI against 73 targets was conducted as well as specific assays relating to developmental toxicity (Reprotracker, devTOX^{qP}).

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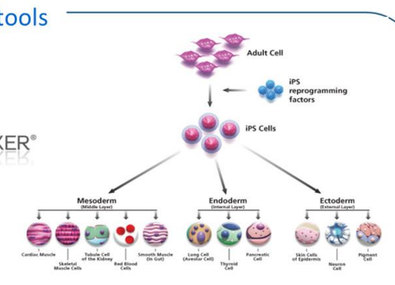
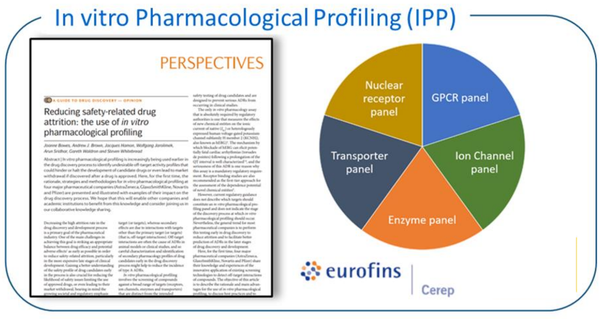


Toxicology in Vitro (2020), **63**, 104746

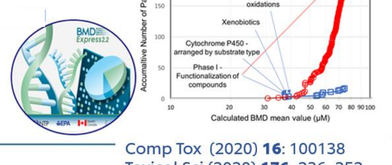
In vitro Pharmacological Profiling (IPP)



High-throughput Transcriptomics (HTTr)

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

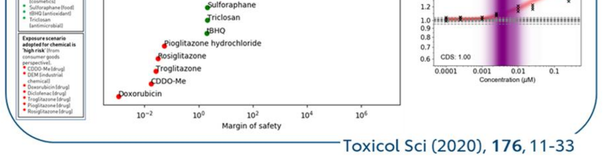
BMDExpress 2 and BIFROST



Comp Tox (2020) **16**: 100138
Toxicol Sci (2020) **176**, 236–252

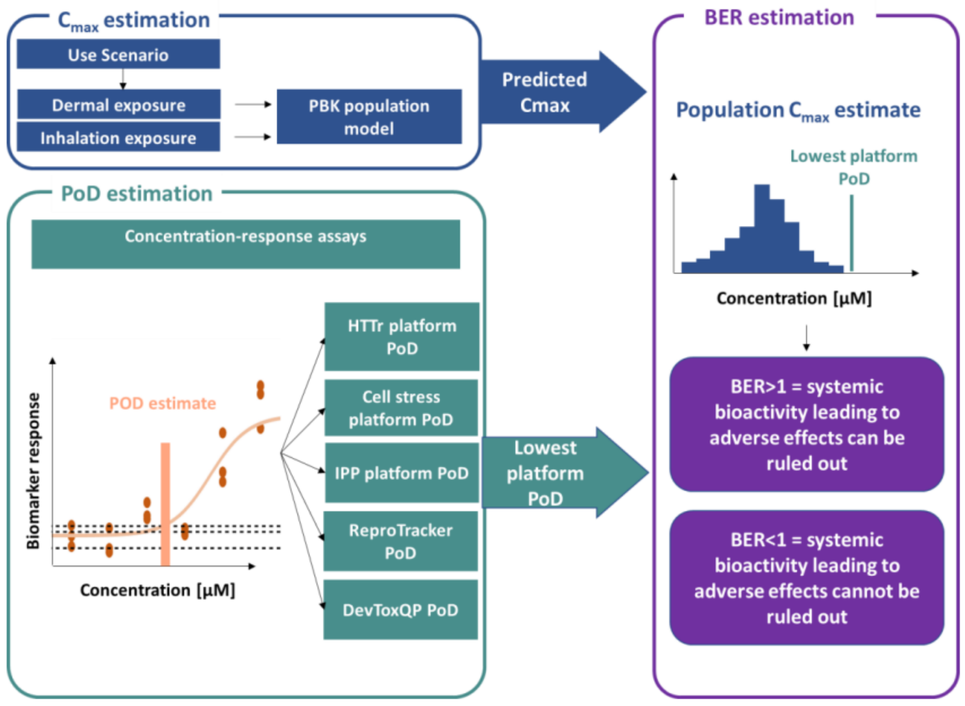
Cell Stress Panel (CSP)

36 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways



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

Bioactivity: Exposure Ratio (BER)



Results

- The PBK modelling indicated a worst-case plasma Cmax of 0.80 µM across the factory environments studied
- Points of Departure (PoDs) for SI in the *in vitro* assays ranged from 104-5044 µM.

	Cell Stress Panel	IPP	HTTr (MCF7)	HTTr (HepG2)	HTTr (HepRG)	DevTox Quickpredict	Reprotracker
			(BIFROST PoD)				
PoD (µM)	5044	>100	104	1728	829	>1000	>1000

- The lowest PoD of 104 µM was compared with the highest, worst case Cmax across all simulations (0.80 µM representing the 95th percentile pregnant female population simulation) covering the entire life cycle of SI, resulting in the most conservative BER for SI of 130.

Conclusions

- The principles of NGRA that have been established for use in assessing consumer safety of cosmetic ingredients [1, 6] were successfully applied to an occupational safety assessment for SI across several factory settings.
- PoDs for SI in these assays ranged from 104-5044 µM. Cmax values obtained from PBK modelling of occupational exposure to SI were compared to PoDs from the bioactivity assays to derive Bioactivity/Exposure Ratios (BER).
- Based on previous benchmarking, this BER allows us to confidently assign a low-risk conclusion for occupational exposure to SI, meaning that systemic bioactivity that could lead to an adverse outcome in the human body can be ruled out.
- This work provides additional evidence to support the application of NGRA for regulatory purposes such as REACH.

Acknowledgements: A big 'thank you' to everyone involved with this work

Alex Teixeira, Alistair Middleton, Andrea Gredelj, Annabel Rigarlsford, Ashraf Abdelkhaliq, Beate Nicol, Catherine Barratt, Chris Sparham, Chrissie Langley, Clarissa Donna, Danilo Basili, Dawei Tang, Elin Barrett, Ellen Edwards, Erica Vit, Erika Kunz, Fazila Bunglawala, Geoff Hodges, Gopal Pawar, Gordon Riley, Hequn Li, Hugh Barlow, Iris Muller, Jade Houghton, Jens Bietz, Joachim Eichhorn, Joe Reynolds, Karen Boness, Katie Przybylak, Lisa Ryder, Lucy Bull, Maria Baltazar, Matt Dent, Michael Seebach, Nathan Kenyon, Nicola Haywood, Paul Carmichael, Predrag Kukic, Ramya Rajagopal, Regiane Sanches-Natumi, Richard Cubberley, Richard Parry, Roger van Egmond, Ruth Pendlington, Sandrine Spriggs, Sarah Hatherell, Sharon Scott, Sophie Cable, Sophie Malcomber, Sue Martin, Wendy Simpson

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