

Use of IATA for Next Generation Risk Assessment (NGRA) decision-making

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Unilever

We make many of the world's favourite brands



Many products means many ingredients=

potential for impact on the health of consumers & environment=

Need for robust safety assessment of ingredients in consumer products

Can we safely use X% of ingredient Y in product Z?



All safety assessments of cosmetic ingredients are exposure-driven:



Consumer
Exposure

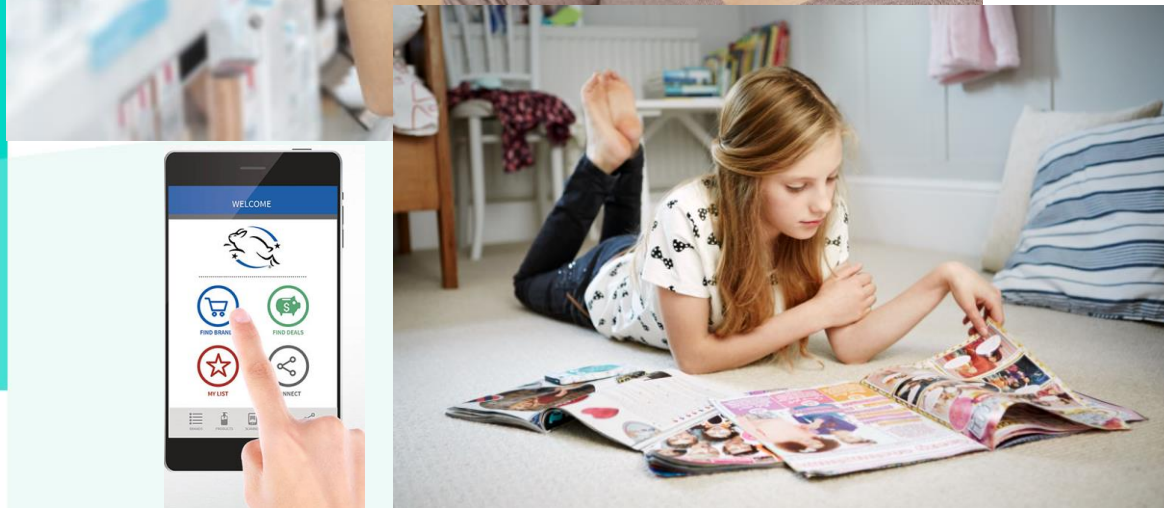
Potential hazards
of the ingredients

Risk Assessment

Increasing numbers of global consumers want their consumer products not tested on animals + transparency



Scientific, societal, regulatory and ethical reasons are demanding change; calls for non-animal, next generation risk assessments



Integrated Approach to Testing and Assessment (IATA)

- are **pragmatic, science-based approaches** for chemical hazard characterisation that rely on an **integrated analysis** of existing information coupled with the generation of new information using testing strategies
- follow an **iterative approach to answer a defined question** in a specific regulatory context, taking into account the acceptable level of uncertainty associated with the decision context
- **range from more flexible**, non-formalised judgment-based approaches (e.g. grouping and read-across) **to more structured, prescriptive**, rule based approaches [e.g. integrated testing strategy (ITS)]
- can **include a combination of methods** and can be informed by integrating results from one or many methodological approaches

www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

Skin Sensitisation: useful case study to consider

First human health AOP to be defined (2012)

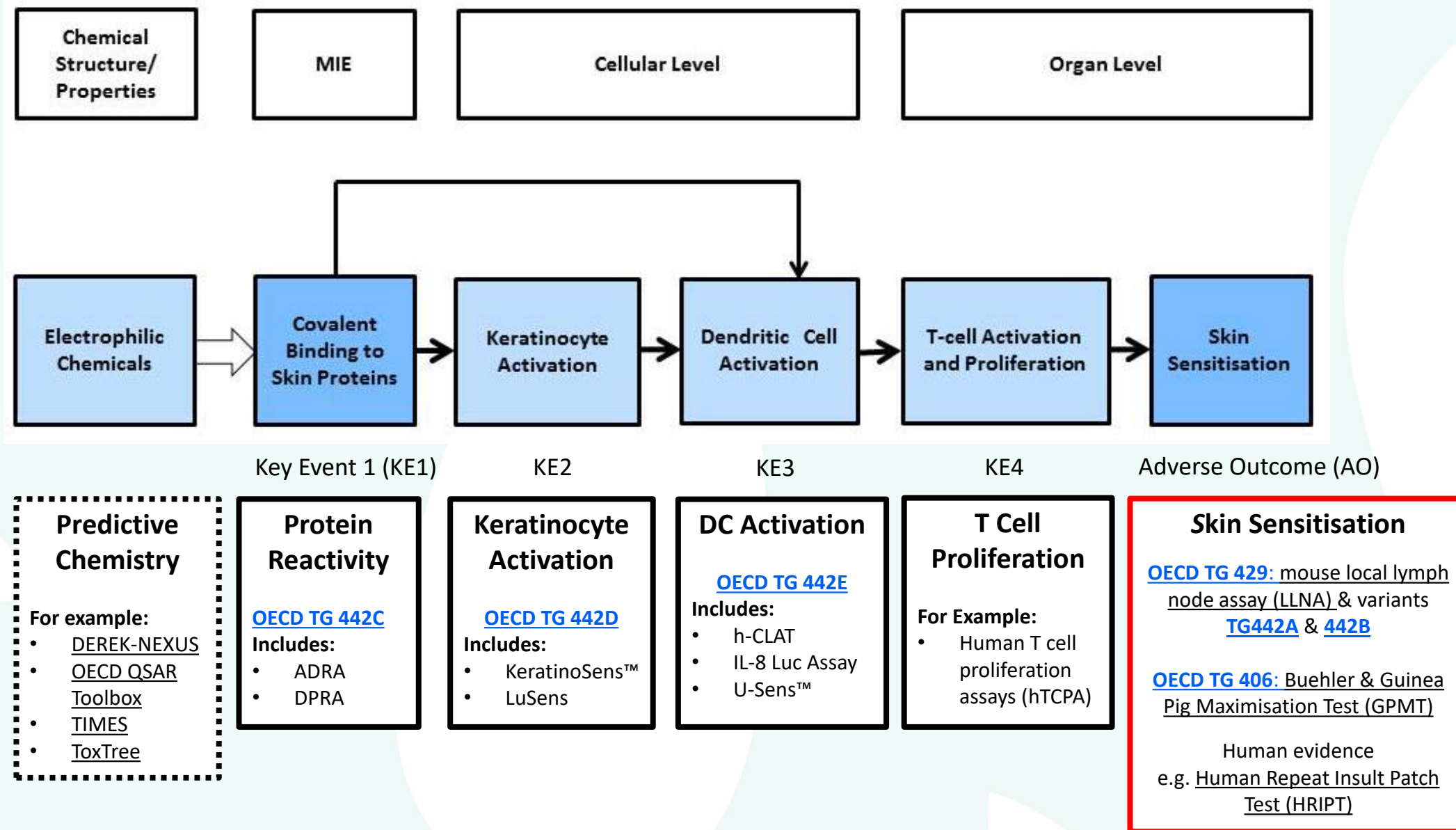
- <https://aopwiki.org/aops/40>

Used by OECD to develop IATA (2014-16) and Defined Approach (DA) (2017-present) concepts

- No. 255: Reporting of Defined Approaches to be used within Integrated Approaches to Testing and Assessment
 - [www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)28&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)28&doclanguage=en)
- No. 256: Reporting of Defined Approaches and Individual Information Sources to be Used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation
 - [www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)29&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)29&doclanguage=en)
 - Annex 1: [www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)29/ann1&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)29/ann1&doclanguage=en)
 - Annex 2: [www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)29/ann2&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)29/ann2&doclanguage=en)

Many published examples demonstrating the value of the AOP for driving the application of New Approach Methodologies (NAMs)

Covalent Protein Binding leading to Skin Sensitisation AOP <https://aopwiki.org/aops/40>



in silico NAM

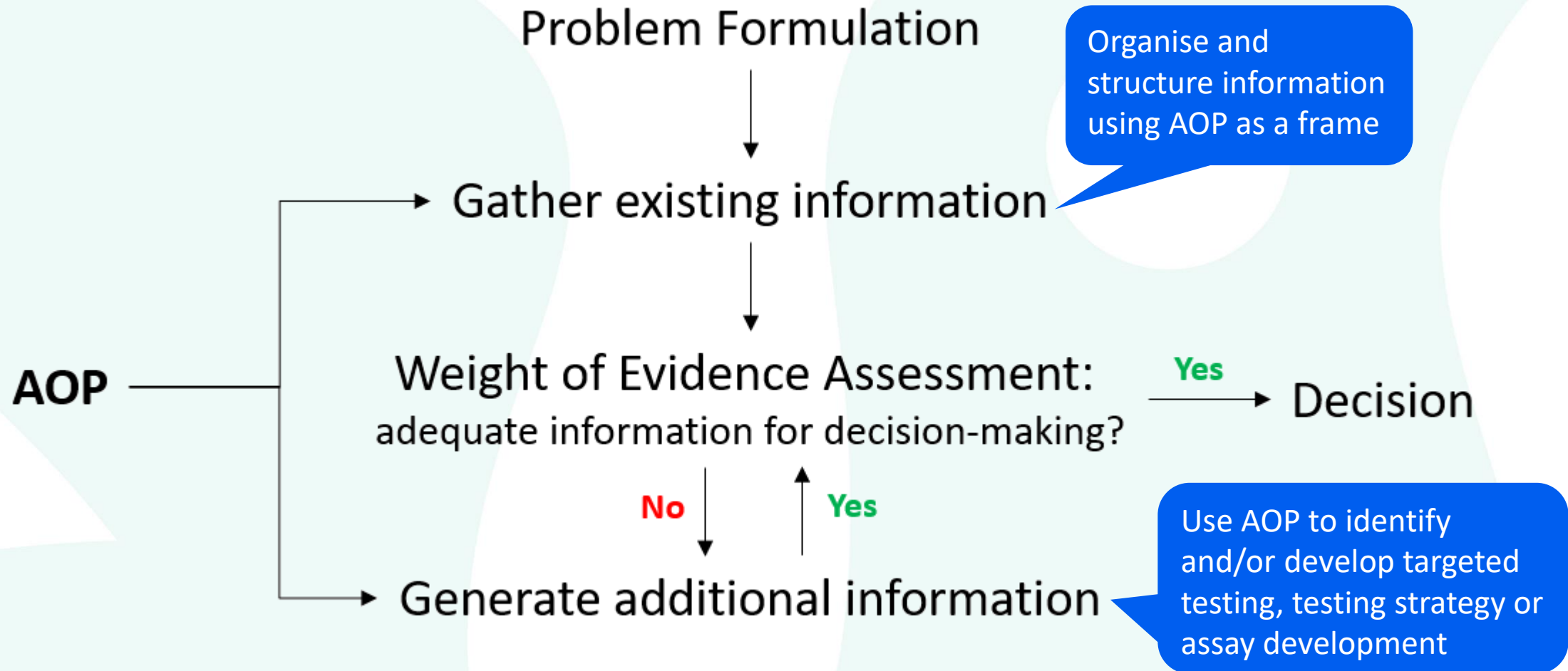


in chemico/vitro NAM



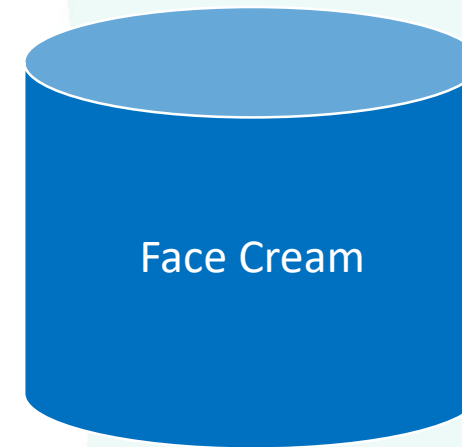
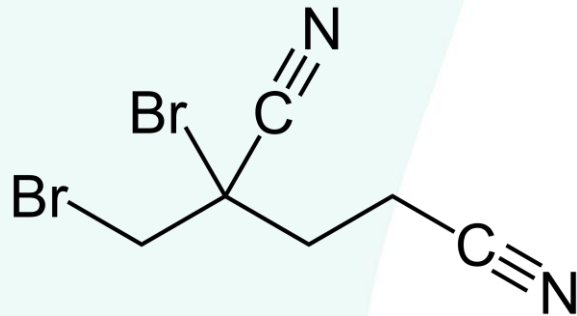
in vivo evidence

IATA General Workflow: applied to Next Generation Risk Assessment of Skin Sensitisation



Question: Is 0.2% Methyldibromoglutanitrile (MDBGN) safe for use in a face cream?

- Assume MDBGN is a new ingredient and no *in vivo* data or read-across candidates exist to illustrate an *ab initio* Next Generation Risk Assessment scenario



Problem Formulation

Gather existing information

Weight of Evidence Assessment:
adequate information for decision-making?

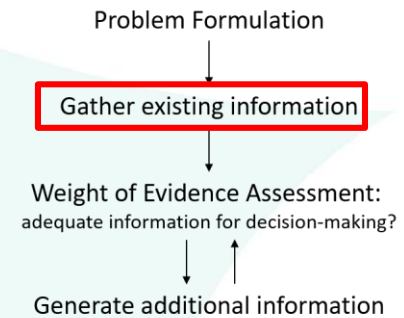
Generate additional information

Question: Is 0.2% Methyldibromoglutanitrile (MDBGN) safe for use in a face cream?

- Predict skin exposure to MDBGN at 0.2% inclusion in face cream as follows:

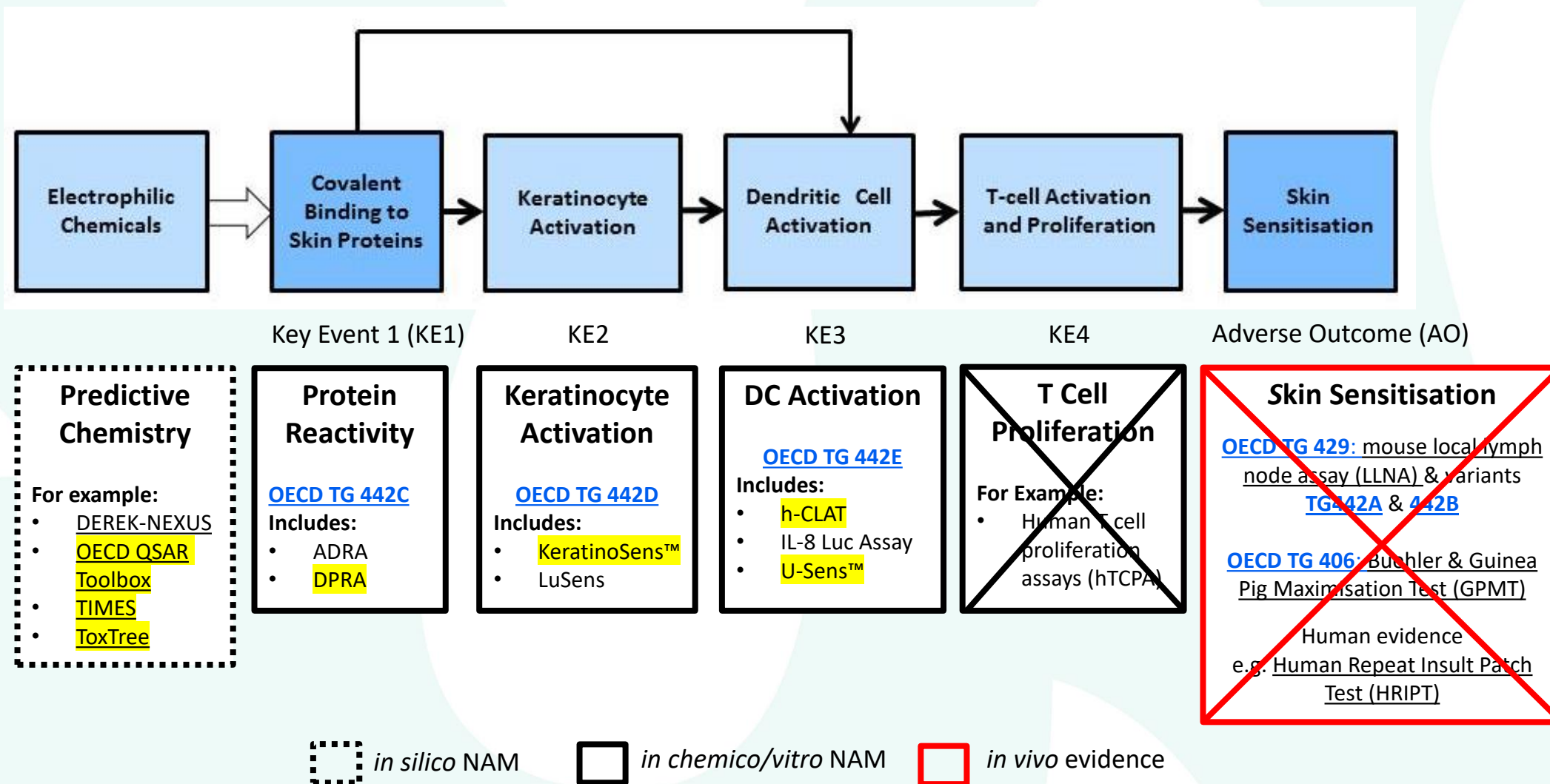
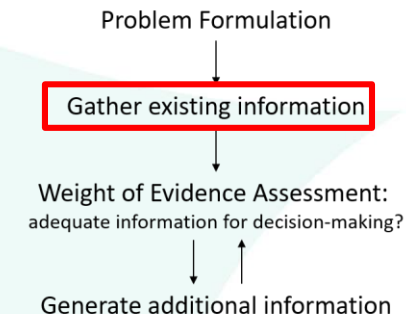
Exposure Parameter	Face cream
Amount of product used per day (g/day)	1.54
Retention factor	1
Skin surface area (cm ²)	565
Amount of product in contact with skin (mg)	1536
Percentage ingredient in product (%)	0.2
Amount of ingredient in contact with skin (µg)	3072
Local dermal exposure (µg/cm ²)	5

* Deterministic worse case (90th percentile) for Europe based upon SCCS notes of guidance (SCCS/1602/18)

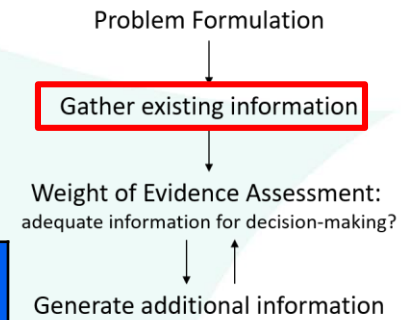


Question: Is 0.2% Methyldibromoglutanitrile (MDBGN) safe for use in a face cream?

- Gather existing hazard information for MDBGN



Question: Is 0.2% Methyldibromoglutanitrile (MDBGN) safe for use in a face cream?



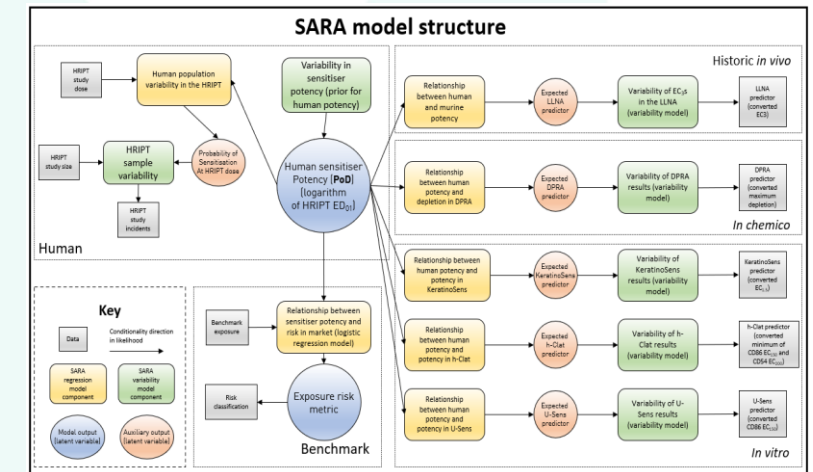
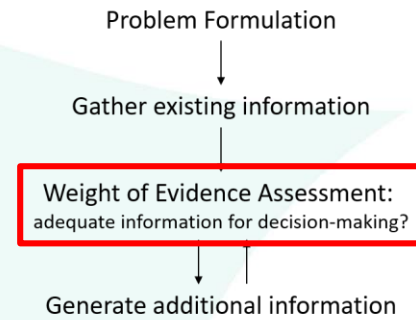
Line of evidence	MDBGN
Chemistry expert view	Sensitiser, Pro-MA mechanism
TIMES	Sensitiser, Pre/Pro-SN2 mechanism
OECD QSAR Toolbox	Sensitiser, SN2 mechanism
ToxTree	Sensitiser, MA/SN2 mechanism
DPRA (Literature data*) - % cys / lys depletion	Sensitiser, 100 / 28.6
DPRA (Unilever data) - % cys / lys depletion	Sensitiser, 100/24.7
KeratinoSens (Lit. data*) - EC1.5 µM	Sensitiser, 7.8
KeratinoSens (Unilever data) - EC 1.5µM	Sensitiser, 9.45, 3.7, 12.4, 7.2, 10.9, 6.7
h-CLAT (Lit. data*) - CD54 EC200/CD86 EC150 (µg ml ⁻¹)	Sensitiser, 10.8 / 9.4
U-SENS (Lit. data*) - CD86 EC150 (µg ml ⁻¹)	Sensitiser, 3.0
U-SENS (Unilever data) - CD86 EC150 (µg ml ⁻¹)	Sensistier, 1.0, 1.0, 2.0, 2.0, 1.0

*Hoffmann et al. 2018: <https://doi.org/10.1080/10408444.2018.1429385>

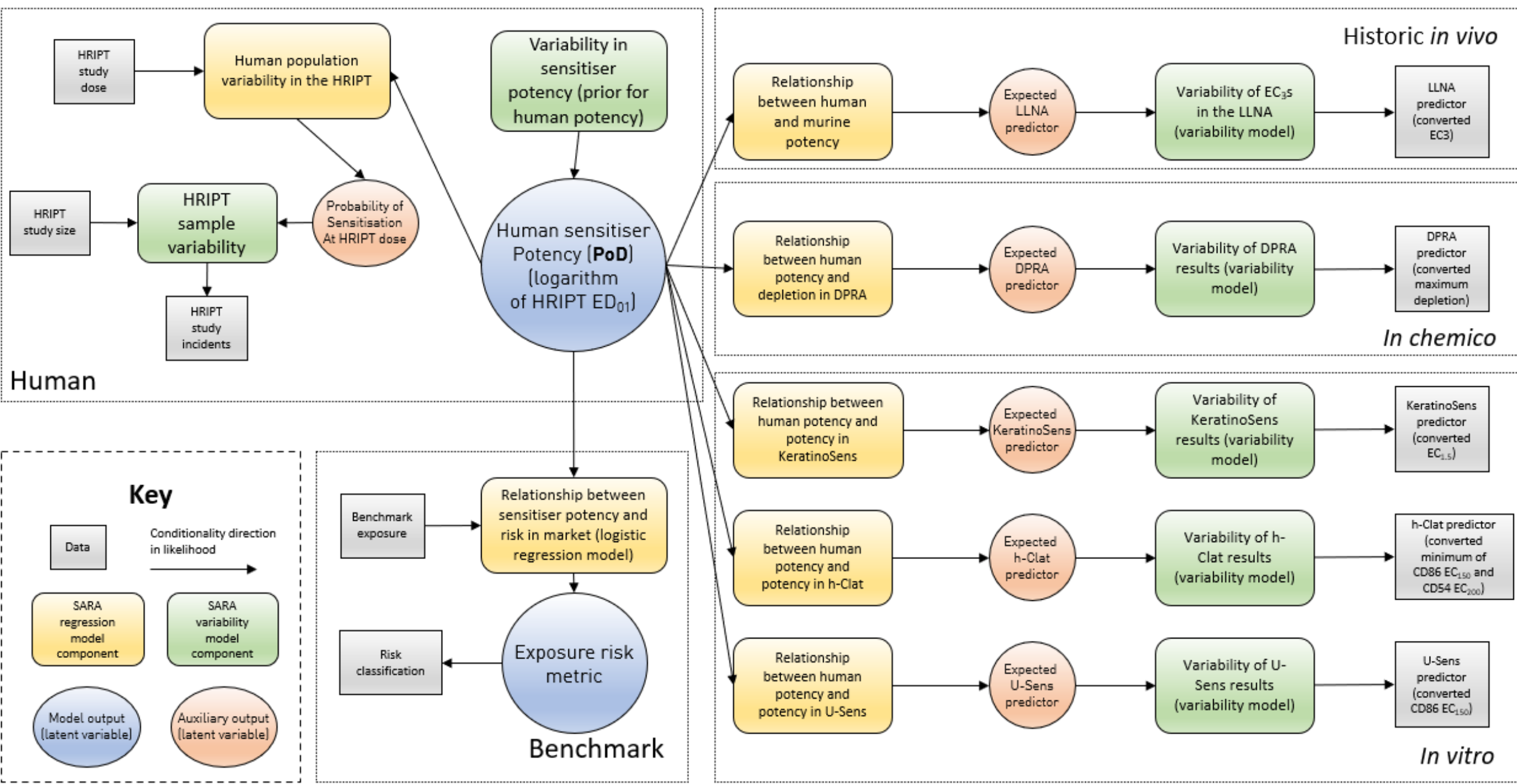
Question: Is 0.2% Methyldibromoglutanitrile (MDBGN) safe for use in a face cream?

Weight of Evidence summary:

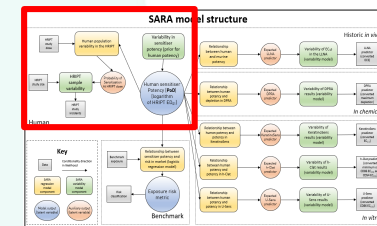
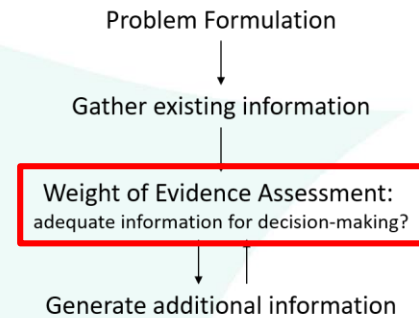
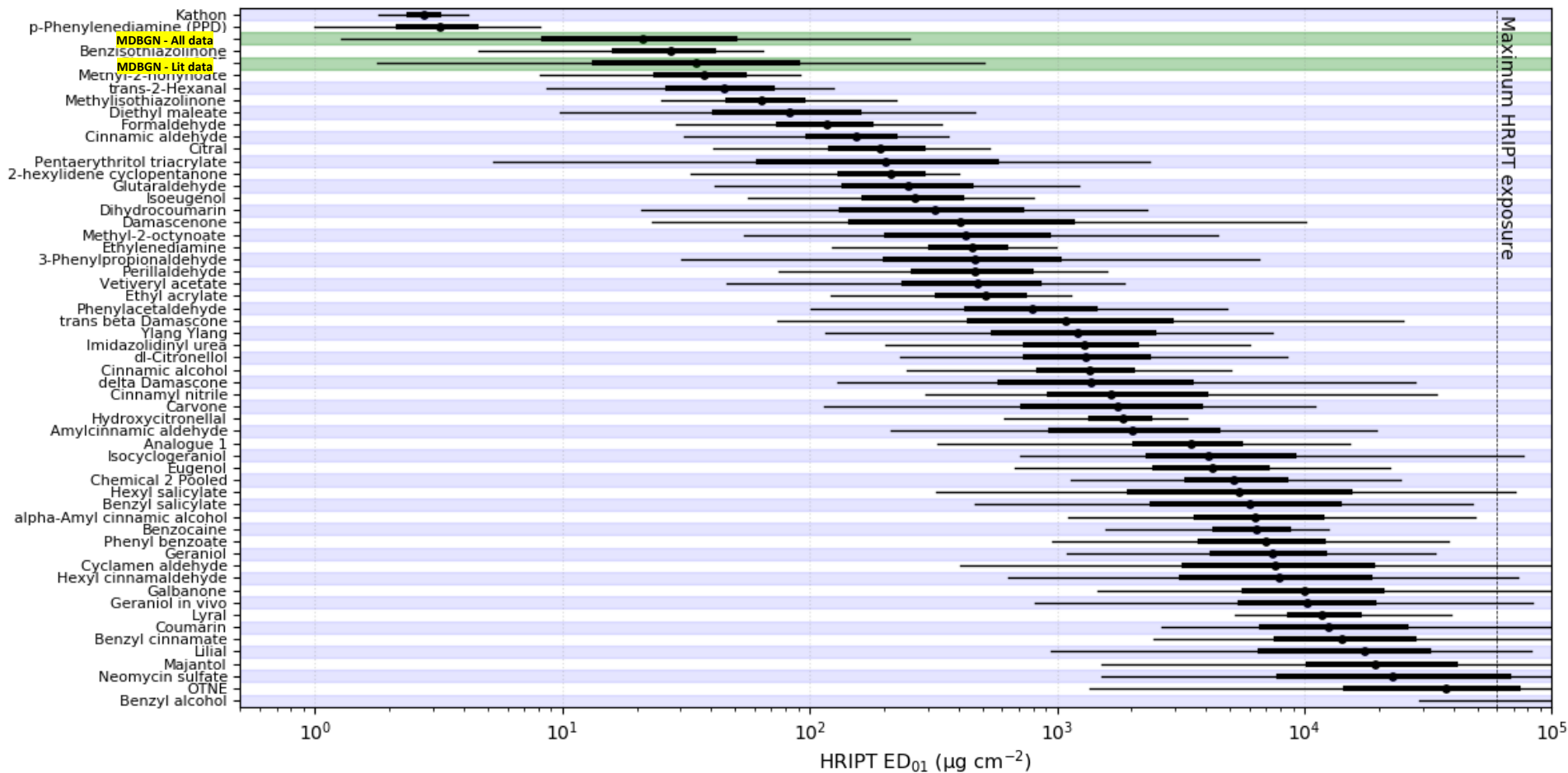
- Significant skin exposure predicted: $5\mu\text{g}/\text{cm}^2$
- Significant evidence of MDBGN skin sensitisation potential
- Use Skin Allergy Risk Assessment (SARA) defined approach (DA) to predict human potency and benchmark risk
 - SARA is a Bayesian probabilistic model, which estimates human sensitiser potency for use in risk assessment decision-making
 - uses a 100 cosmetic ingredient database of public data spanning the Skin Sensitisation AOP
 - risk benchmarking module uses clinical evidence for 62 cosmetic ingredient/exposure to benchmark low or high risk of skin sensitisation
 - published and shared with OECD as a DA example: [Reynolds et al. 2019](#)



SARA model structure

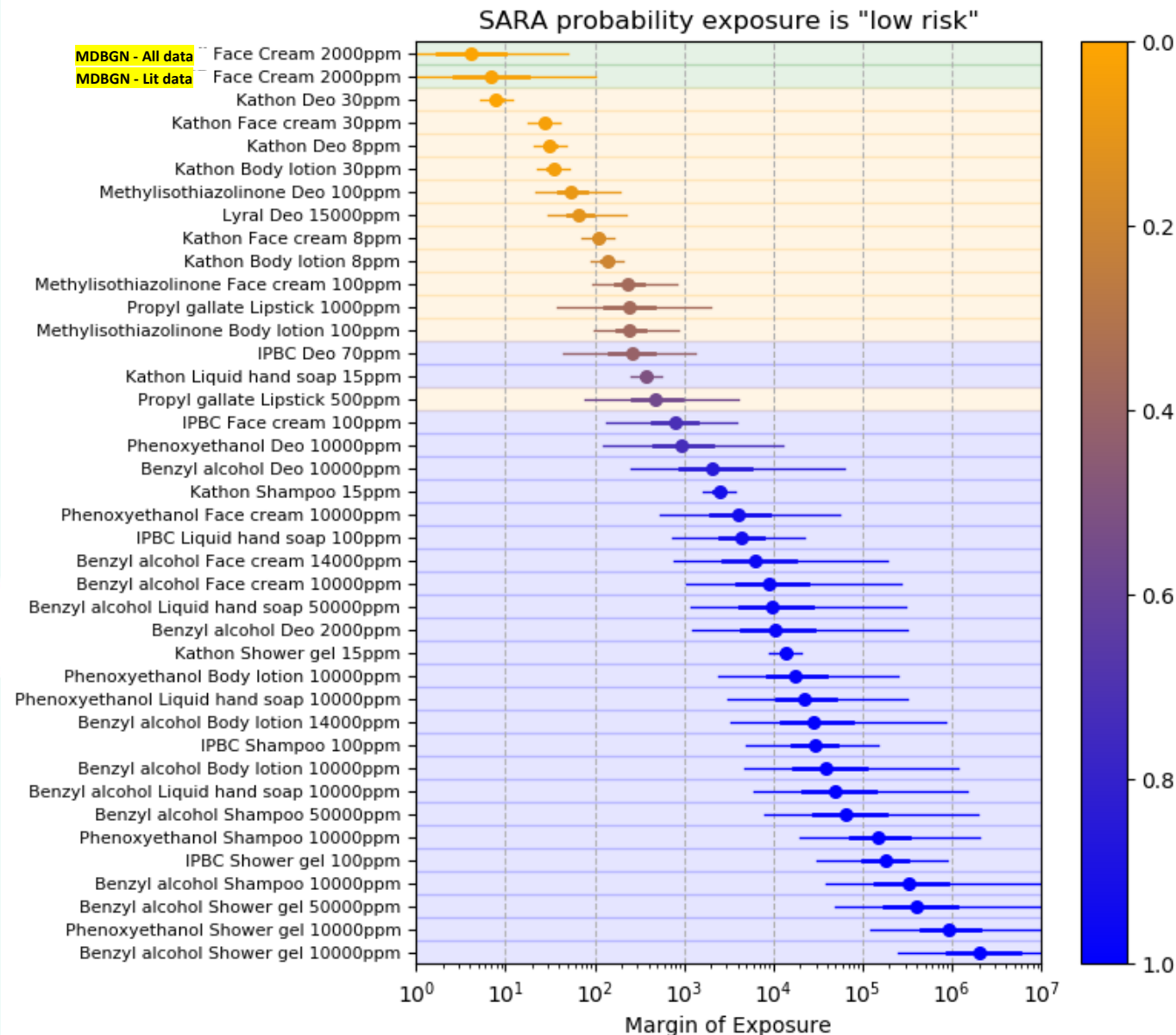


Question: Is 0.2% Methyldibromoglutanitrile (MDBGN) safe for use in a face cream?



MDBGN	Expected ED ₀₁ (µg/cm ²)	ED ₀₁ 2.5 th % (µg/cm ²)	ED ₀₁ 97.5 th % (µg/cm ²)
Literature data	34	2	485
All data	21	1	257

Question: Is 0.2% Methyldibromoglutanitrile (MDBGN) safe for use in a face cream?

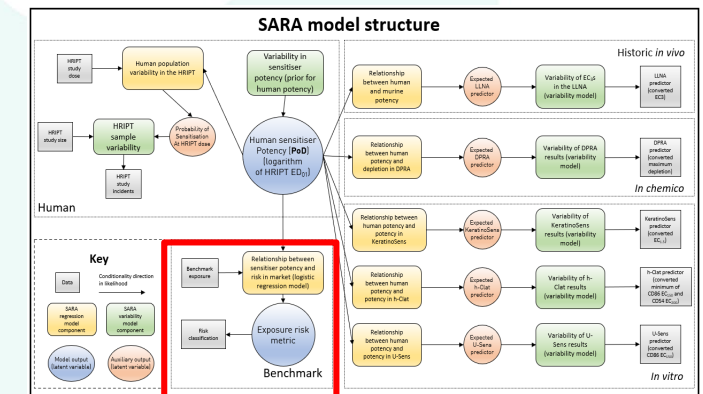


Problem Formulation

Gather existing information

Weight of Evidence Assessment:
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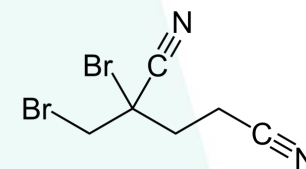
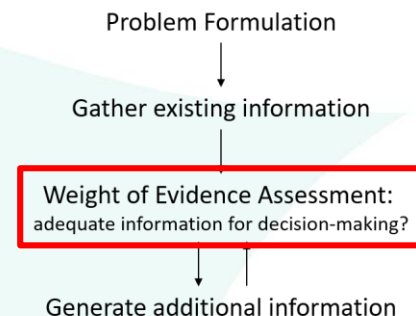
Generate additional information



Question: Is 0.2% Methyldibromoglutanitrile (MDBGN) safe for use in a face cream?

Weight of Evidence summary (updated):

- Significant skin exposure predicted: $5\mu\text{g}/\text{cm}^2$
- Evidence of MDBGN skin sensitisation potential
- Using available *in vitro* data the SARA DA prediction for MDBGN human potency is $21\mu\text{g}/\text{cm}^2$ (strong/extreme sensitiser)
- SARA predicts that 0.2% MDBGN in face cream is very unlikely to be low risk (1% probability) and benchmarks the risk as similar to use of Kathon in leave-on cosmetics (high risk benchmark)
- Consequently we conclude based on these data that 'no' it's not safe to use 0.2% MDBGN in a face cream
- *Note: similar result would be reached if a traditional quantitative risk assessment was performed using in vivo data*



Summary:

1. **IATA concept** has allowed mechanistic and clinical understanding (i.e. AOP) to be directly applied to weight of evidence safety decisions
2. **IATA framework** has helped facilitate communication and adoption of new non-animal decision-making approaches (e.g. Skin Sens. NAMs, NGRA application) across industry sectors/regulatory use-cases
3. **IATA concept & framework** are increasingly enabling a more clinically relevant evaluation of new non-animal decision-making approaches (e.g. use of human benchmark data in OECD DA Skin Sens. WG)
4. **IATA** enable us to discuss and debate how to better protect people using new non-animal decision-making approaches

Acknowledgements

SEAC, Unilever – Skin Allergy team

Maja Aleksic, Nora Aptula, Maria Baltazar, Bobbie Bradford, Richard Cubberley, Beate Nicol, Katarzyna Przybylak, Ramya Rajagopal, Georgia Reynolds, Joe Reynolds, Sandrine Spriggs, Charlotte Thorpe, Carl Westmoreland & Sam Windebank

In vitro Data Generation Partners


charles river


COVANCE

 gentronix


IVS
Institute for In Vitro Sciences

 XCellR8
Redefining testing

The Integrated Case Studies Project was launched in 2015 to increase experience with the use of IATA by developing case studies, which constitute examples of predictions that are fit for regulatory use. The aim is to create common understanding of using novel methodologies and the generation of considerations/guidance stemming from these case studies.

Eight new cases have been published that illustrate diverse read-across approaches based on various type of data from New Approach Methodologies. A [considerations document](#) includes considerations topics such as Margins of Internal Exposure, Coverage of the key events in AOP, uncertainty on the use of non-endorsed AOPs and advantage of the use of AOP networks.

The OECD released the following new cases:

- [No. 1](#): Case Study on the use of an Integrated Approach to Testing and Assessment (IATA) and New Approach Methods to inform a Theoretical Read-Across for Dermal Exposure to Propylparaben from Cosmetics
- [No. 2](#): Case Study on the use of Integrated Approaches for Testing and Assessment for Systemic Toxicity Arising from Cosmetic Exposure to Caffeine
- [No. 3](#): Case Study on the Use of Integrated Approaches for Testing and Assessment for 90-Day Rat Oral Repeated-Dose Toxicity of Chlorobenzene-Related Chemicals
- [No. 4](#): Case Study on the Use of Integrated Approaches for Testing and Assessment to Inform Read-across of p-Alkylphenols: Repeated-Dose Toxicity
- [No. 5](#): Prediction of a 90 day repeated dose toxicity study (OECD 408) for 2-Ethylbutyric acid using a read-across approach from other branched carboxylic acids
- [No. 6](#): Read-across based filling of developmental and reproductive toxicity data gap for methyl hexanoic acid
- [No. 7](#): Identification and characterisation of parkinsonian hazard liability of deguelin by an AOP-based testing and read across approach
- [No. 8](#): Mitochondrial Complex-III-mediated neurotoxicity of - Read-Across to other strobilurins

[Learn more on the IATA project](#)