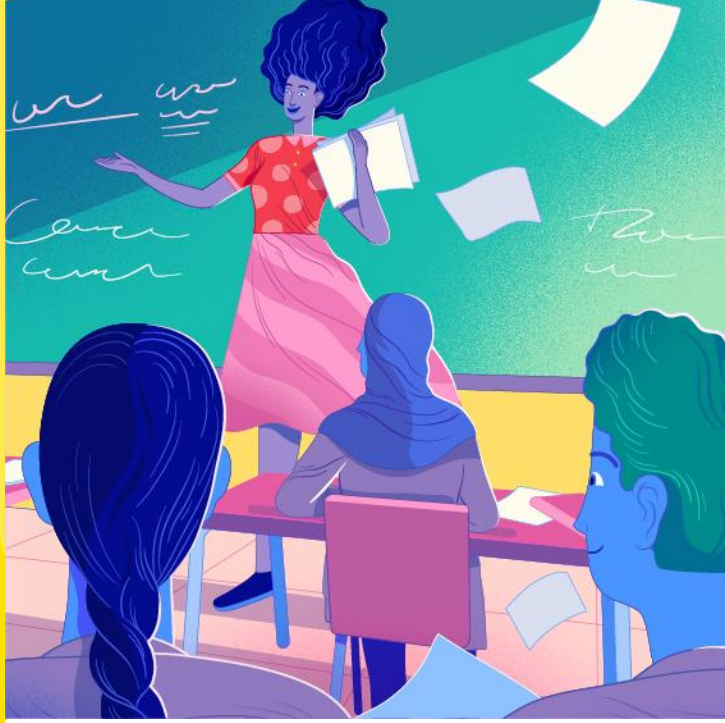
Utilization of Human Evidence for Testing and Assessment of Chemical Sensitizers



SOT, 2021
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Physicians Committee for Responsible Medicine

AEROTOX Consulting Services, LLC

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Outline

- Insights from human data are key contributors to the weight of evidence in development of AOP frameworks
- Human data are valuable in evaluation or benchmarking of *in silico* or *in vitro* approaches in hazard identification and enable development of Integrated Approaches to Testing and Assessment (IATA)
- However, clinical and epidemiological data can be riddled with variability mainly due to lack of standardized guidelines
- We present two approaches in the systematic use of human data on chemical sensitizers:
  - ***To build a reference list of putative respiratory sensitizers that can be used for regulatory purpose and development of IATA for chemical respiratory allergy***
  - ***To benchmark the risk of skin sensitizer exposures that can be further combined with Next Generation Risk Assessment (NGRA) methodologies for the predicting risk of allergic contact dermatitis for novel chemicals***

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Utilization of Human Data: Chemical Respiratory Allergy

- A list of 120 chemicals, with human clinical evidence of respiratory sensitization, was developed from Enoch et al. *Chem Res Toxicol* 2012, 25:2490-2498.
- A systematic and phased approach was developed for utilization and curation of human data towards validating this reference list of putative respiratory sensitizers
- EPA-developed Abstract Sifter tool, that automates broad literature searching via PubMed, was utilized to standardize the search for human data related to asthma or respiratory allergy for the list of chemicals (Baker N et al. *F1000Research* 2017, 6(Chem Inf Sci):2164)
- The objective was to identify those chemicals in the list with definitive human evidence of respiratory sensitization
- Additionally, those chemicals in the list with equivocal evidence or evidence for dermal sensitization or respiratory/dermal irritation were identified for use as discriminatory controls in the assays within the IATA to be developed

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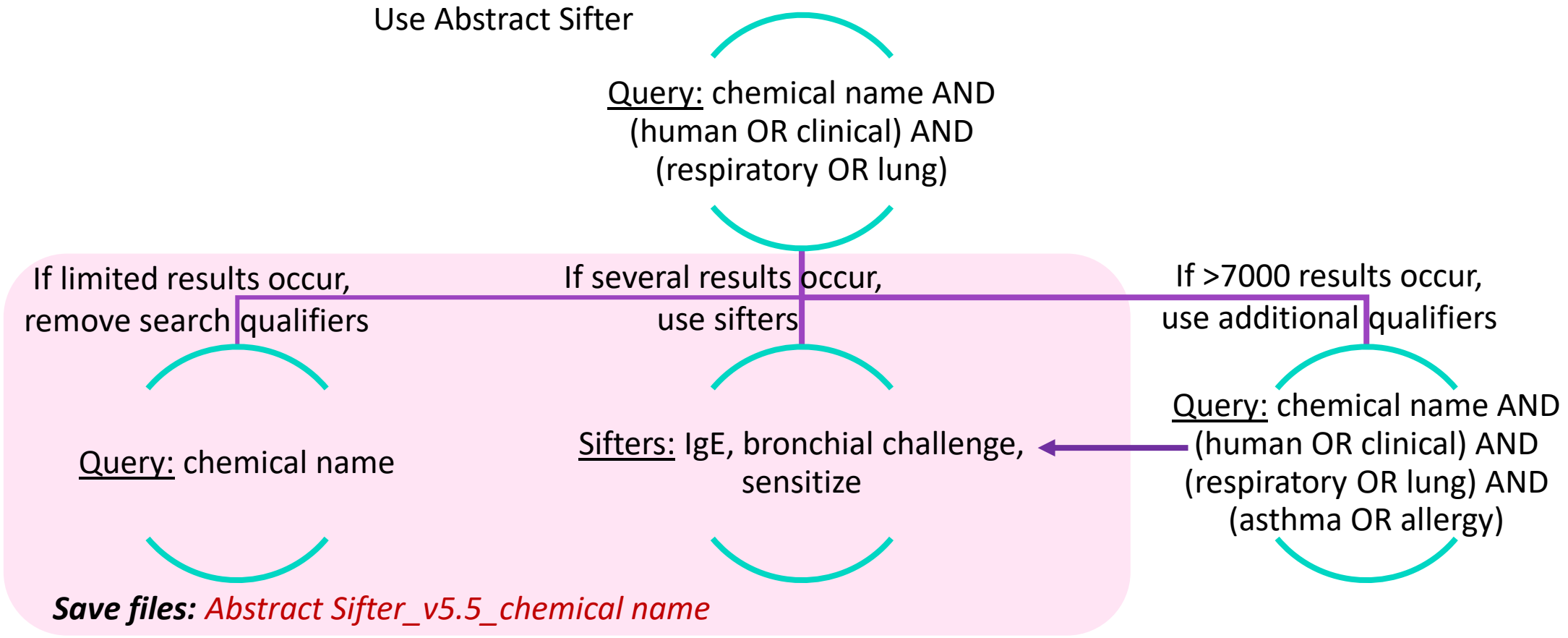
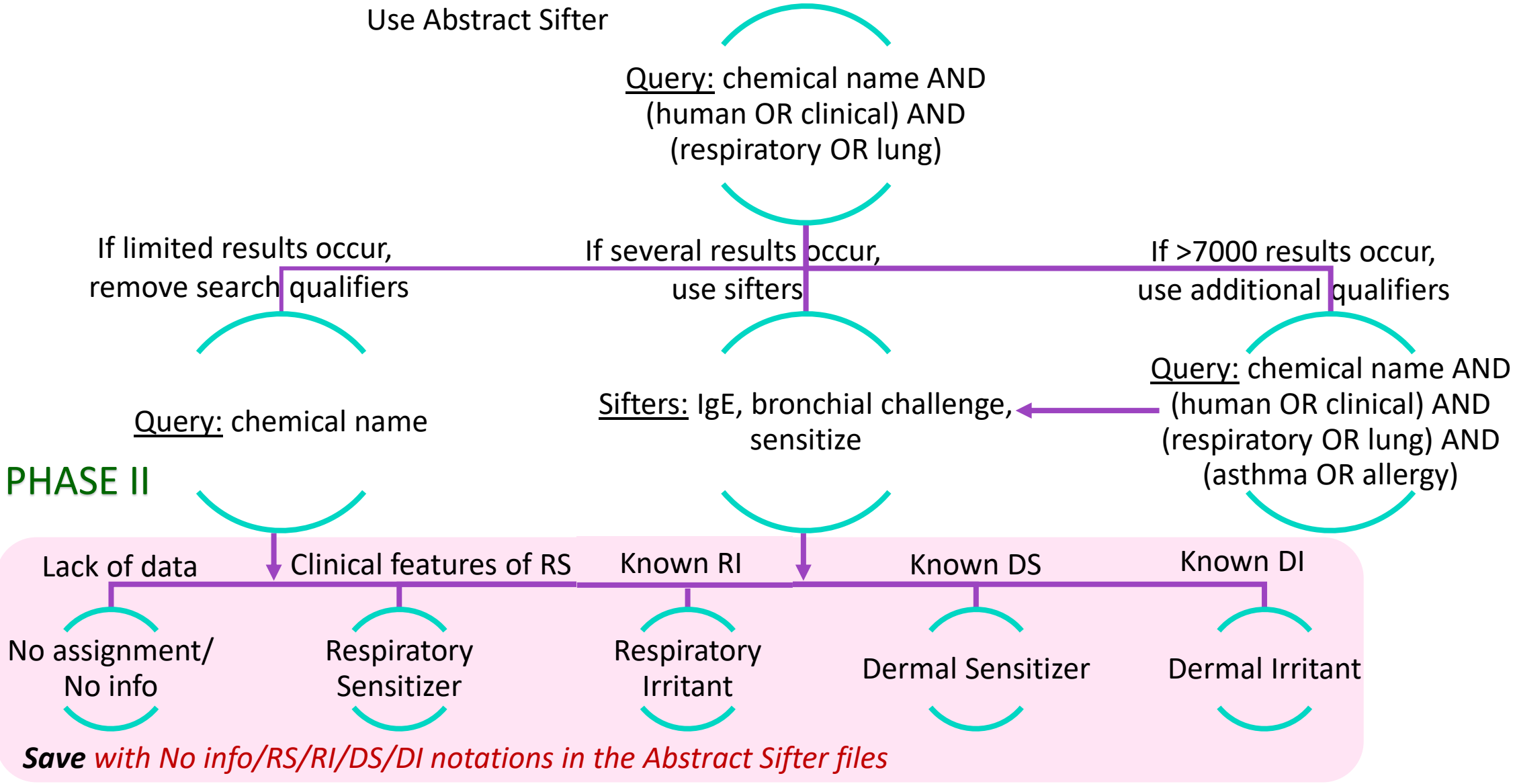
Utilization of Human Data: Chemical Respiratory Allergy

PHASE I



Utilization of Human Data: Chemical Respiratory Allergy



Utilization of Human Data: Chemical Respiratory Allergy

Criteria for classification of human data:

No information	***There is no information to evaluate the compound***
	Either absent from the literature
	Or the available literature is irrelevant to human respiratory symptoms
No	***The clinical literature demonstrates that the compound is not a respiratory sensitizer in humans***
	Either significant occupational exposure and investigation of asthmatic symptoms rules out immune-mediated occupational asthma/respiratory allergy caused by the compound
	Or significant literature demonstrates that the compound is used to prevent asthma by reducing symptoms or effects of exposure to allergens
Equivocal	***There is clinical evidence of respiratory symptoms after exposure, but available evidence does not conclusively demonstrate sensitization***
	Either there is no evidence of immune-mediated response to distinguish respiratory sensitization from respiratory irritation
	Or there is conflicting evidence of immune-mediated response or significant confounding exposure

(continued....)

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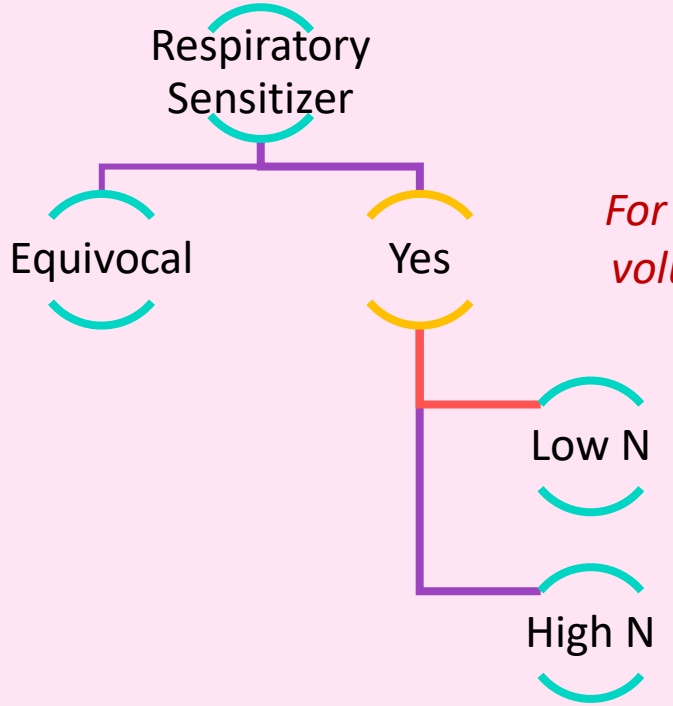
Utilization of Human Data: Chemical Respiratory Allergy

Criteria for classification of human data:

Yes	***There is significant clinical evidence that the compound has caused respiratory sensitization in at least one patient, as defined by one of the following scenarios:***	
	Patient history of exposure with positive specific bronchial challenge, combined with evidence of specific IgE and/or IgG immune-mediated response as determined by exposure to the compound:	Skin-prick test (SPT) Radioallergosorbent test (RAST) Enzyme-linked immunosorbent assay (ELISA)
	Patient history of exposure with positive nonspecific bronchial challenge, combined with evidence of IgE and/or IgG immune-mediated response paired with negative controls to eliminate confounding exposures	
	Additionally, the quantity of patients identified in the available literature is indicated for all compounds in this category:	$1 \leq N \leq 10$: **Low N** $N > 10$: **High N**

Utilization of Human Data: Chemical Respiratory Allergy

PHASE III



*For all RS compounds, **score** based on volume of cases and reports found in literature*

At least one report that fits the criteria

Several reports consistent with exposure, fit the criteria

PHASE IV

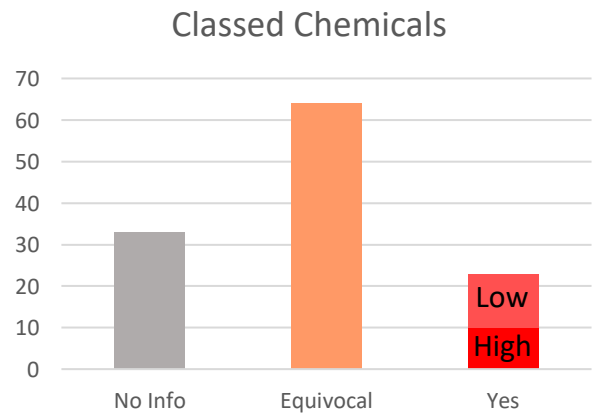
Peer review of all classed compounds

PHASE V

Align classifications with *in vitro* and *in vivo* datasets

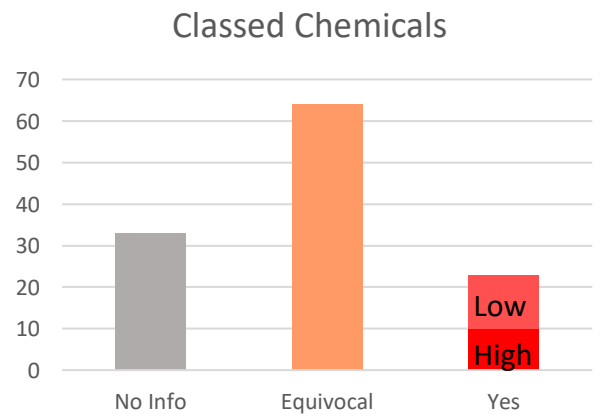
Utilization of Human Data: Chemical Respiratory Allergy

Chemical	Exposure	Reports of asthma or rhinitis	Evidence of specificity of symptoms	Evidence of specific IgG	Evidence of specific IgE	Evidence of other mechanisms	Potential for confounding exposure	Comments	Respiratory sensitizer	RI/DS/ DI
1,3-Bis(isocyanatomethyl)cyclohexane	Diisocyanate oligomer used in automobile paint factory	Yes, <10 reports	Workers administered methacholine bronchial challenge, led to decrease in FEV1	Not tested	Not tested	Not reported	None	Could be an irritancy effect, no information available on mechanism	**No info**	Possible RI
1,2-Benzisothiazolin-3-one	Additive in detergent manufactur-ing	Yes, <10 reports	Worker reported OA and rhinitis, FEV1 decreased by 26% when challenged with unconjugated BIT	Not tested	Test for IgE against formaldehyde negative	Not reported	None	Mechanistic information not available	**Equivocal**	



Utilization of Human Data: Chemical Respiratory Allergy

Chemical	Exposure	Reports of asthma or rhinitis	Evidence of specificity of symptoms	Evidence of specific IgG	Evidence of specific IgE	Evidence of other mechanisms	Potential for confounding exposure	Comments	Respiratory sensitizer	RI/DS /DI
Pauli's reagent (4-diazobenzenesulfonic acid)	Exposure through chromatographic reagent	Yes, only one report	Medical school lab technician reported OA, close to 20% decrease in with challenge using Pauli's reagent.	Not tested	SPT positive when challenged with Pauli's reagent	Not reported	None	Lymphocytic infiltration of thickened alveolar walls, occasional desquamated type 2 alveolar cells	**Yes – Low N**	
Glutaraldehyde	Healthcare workers, endoscopy and x-ray departments; cleaning industry	Yes, >100 reports	7 of 8 workers with complaints of OA showed ≥20% decrease in FEV1 with SIC	Not tested	Specific IgE seen in seven patients (29.1%, a cutoff value of 0.88% RAST binding.	Not reported	None		**Yes – High N**	



Utilization of Human Data: Chemical Respiratory Allergy

- Using a systematic approach, identified chemicals for which there is unequivocal clinical evidence of respiratory sensitization and asthma, with an underlying immunological mechanism
- For the rest of the chemicals in the list (developed using mechanism-based structural alerts), current knowledge of clinical evidence related to induction of respiratory sensitization through immunological mechanism or lack thereof was documented
- The variability in clinical tests as well as gaps that can be considered within the testing regimen for occupational asthma were identified
- As a next step, the human evidence was viewed in comparison with other *in vitro* and *in vivo* data either as a weight of evidence towards or as an indication for specific IATA for identifying chemical respiratory sensitizers

Please visit: ***2830: Poster Board - P296 Utilization of Human Evidence for Testing and Assessment of Chemical Respiratory Sensitizers***

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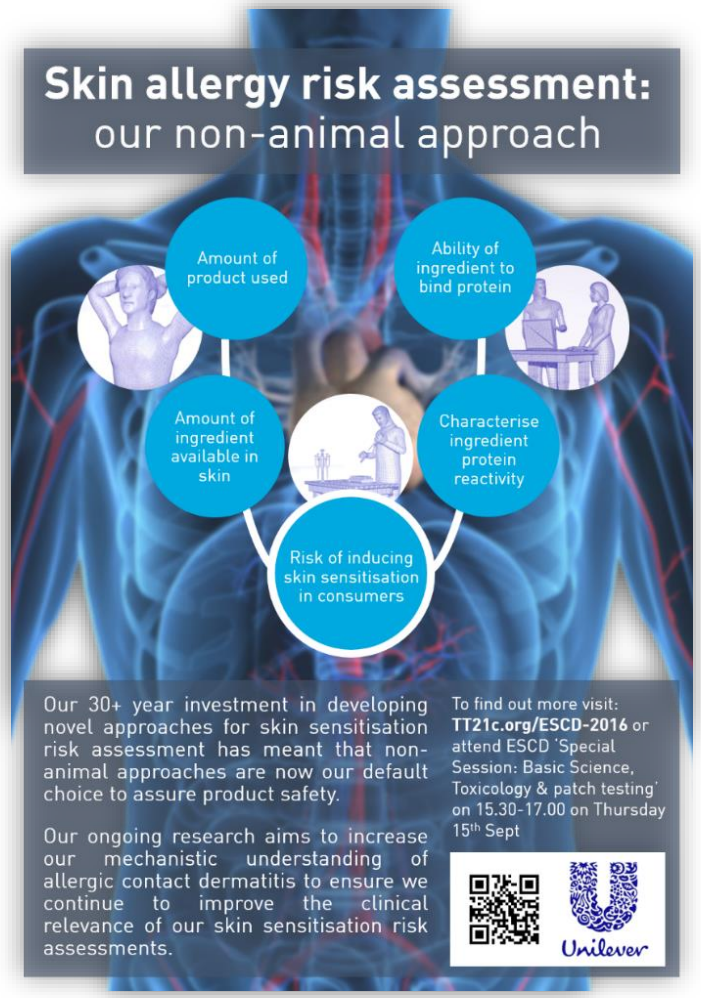
Next Generation Skin Sensitisation Risk Assessment



- We need a risk assessment approach for skin allergy that…
  - doesn't require new animal test data
  - addresses novel exposure scenarios
  - better characterises our uncertainty
  - fully utilises available human data…
- NexGen Risk Assessment (NGRA) is an exposure-led, hypothesis-driven approach integrating new approach methodologies (NAMs) to ensure safety without generating animal data

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Next Generation Skin Sensitisation Risk Assessment

In silico prediction tools	• ToxTree • TIMES • DEREK • OECD QSAR Toolbox • METEOR NEXUS
*Animal Studies**	• *LLNA (local lymph node assay)* • *GPMT (guinea pig maximisation test)*
*Human Clinical**	• *HRIPT (human repeat insult patch test)*
In chemico/in vitro assays	• DPRA (OECD TG 442C) • Peptide reactivity profiling / kinetics (Aleksic et al. *Toxicological Sciences*, 2009, 108(2), 401–411) • KeratinoSens™ (OECD TG 442D) • h-CLAT, U-SENS™ (OECD TG 442E)

* **Historical information, we do not conduct these studies. Historical animal data only used if pre-2010.**

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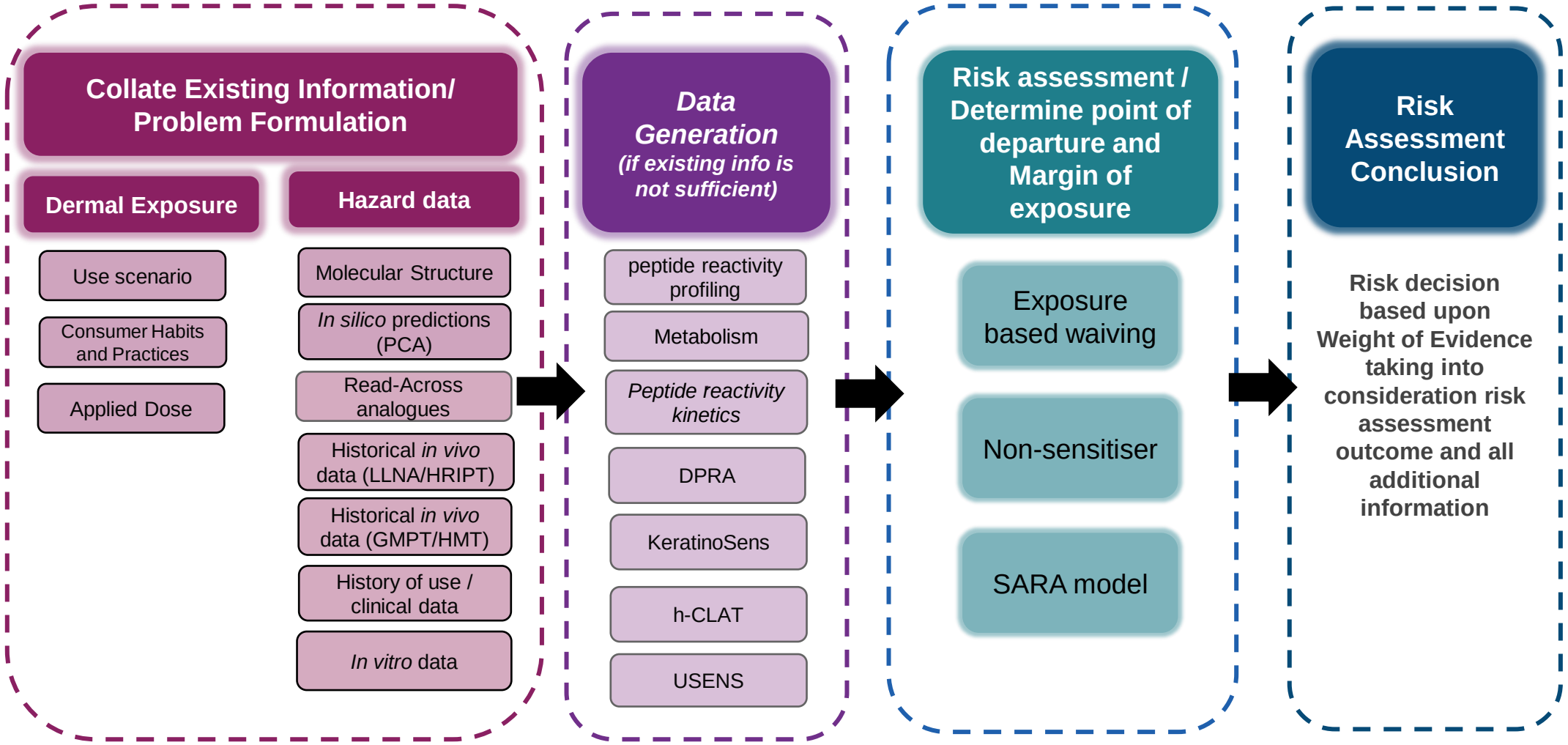
Next Generation Skin Sensitisation Risk Assessment



Utilization of Human Data: Skin Allergy

Key objectives were to ***a) collate a series of benchmark consumer exposures to skin sensitizing chemicals, assign high or low risk category, based on clinical evidence*** and ***b) incorporate the benchmark exposures into Skin Allergy Risk Assessment (SARA) model and evaluate its performance against these exposures***

Ten materials chosen based on the following criteria:

- They should be established contact allergens (based upon human / clinical experience)
- They should have an established history of use in cosmetic products
- The exposure can be quantified with respect to use levels / actual consumer exposure

Three representative leave on (underarm products, face cream and body lotion) and three rinse off (liquid hand soap, shampoo, and shower gel) product types selected for calculating consumer dermal exposure

Terms [chemical name] and [contact allergy] used to search Pubmed for clinical evidence

High or low risk assigned to an exposure based on the following premise:

- Strong association of a chemical exposure (in a specific body part/ product type) with high prevalence of contact allergy – **High Risk**
- Wide-spread exposure to a chemical and yet not a high prevalence of contact allergy – **Low Risk**

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Utilization of Human Data: Skin Allergy

Methylchloroisothiazolinone/ Methylisothiazolinone (MCI/MI)

- 30 ppm in leave-on and rinse-off → • High prevalence
- 7.5 ppm in leave-on and 15 ppm in rinse-off → • High prevalence
- Banned in leave-on and 15 ppm in rinse-off → • Decrease in prevalence

Material	Product type	Use level (ppm)	Consumer exposure to benchmark product (ng cm $^{-2}$)	Induction risk
MCI/MI	Deo	30	350	HIGH
		7.5	87.8	HIGH
	Face cream	30	100	HIGH
		7.5	25	HIGH
	Body lotion	30	80	HIGH
		7.5	20	HIGH
	Liquid hand soap	15	7.3	LOW
	Shampoo	15	1.1	LOW
	Shower gel	15	0.2	LOW

Hydroxyisohexyl 3-cyclohexane carboxaldehyde (HICC)

- 15000 ppm in leave-on (underarm products) → • High prevalence
- 1500 ppm in leave-on (underarm products) → •Decrease in prevalence, lag between reduction in exposure and contact allergy cases
- 200 ppm in leave-on (underarm products) → •Decrease in prevalence, lag between reduction in exposure and contact allergy cases

Material	Product type	Use level (ppm)	Consumer exposure to benchmark product (ng cm $^{-2}$)	Induction risk
HICC	Deo	15000	175581.4	HIGH
		1500	17558.1	UNCLASSIFIABLE
		200	2341.1	UNCLASSIFIABLE

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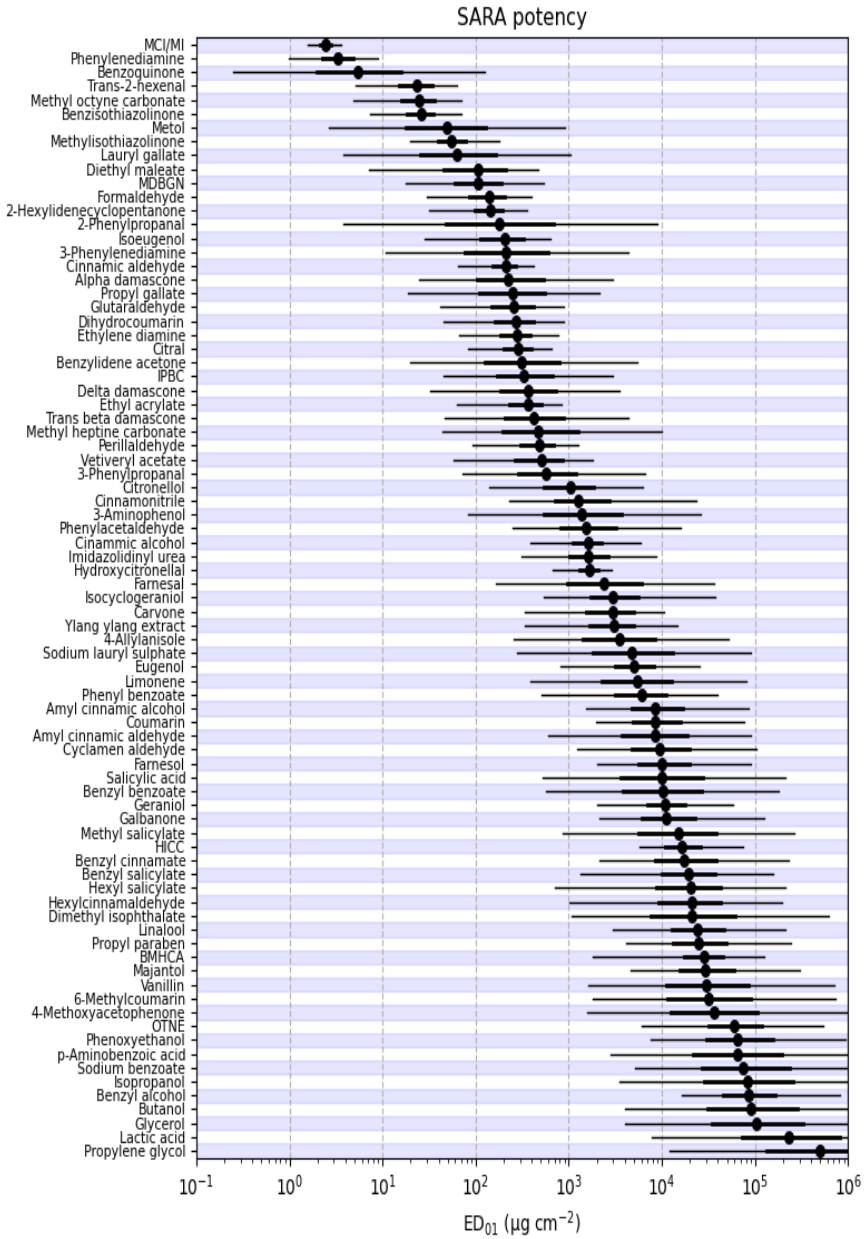
Utilization of Human Data: Skin Allergy



- SARA model: A model, defined using Bayesian statistics, to infer a human-relevant metric of sensitiser potency, with inputs into the model from any combination of HRIPT, LLNA, DPRA, KeratinoSens, h-Clat or U-Sens data (Reynolds et al. *Computational Toxicology,* 2019, 9:36–49)

- Probabilistic estimate of the ED_{01} (HRIPT dose with a 1% chance of sensitisation) obtained for all chemicals in the SARA database. For example:
  - Mean of the distribution for MCI/MI, PPD and benzoquinone is less than 10 µg cm-2
  - Mean of the distribution for benzyl alcohol, isopropanol and lactic acid is greater than the maximum possible HRIPT exposure of 60,000 µg cm^{-2}

- Varying levels of precision in estimates reflect the varying numbers and concordance of studies/assays available for each chemical

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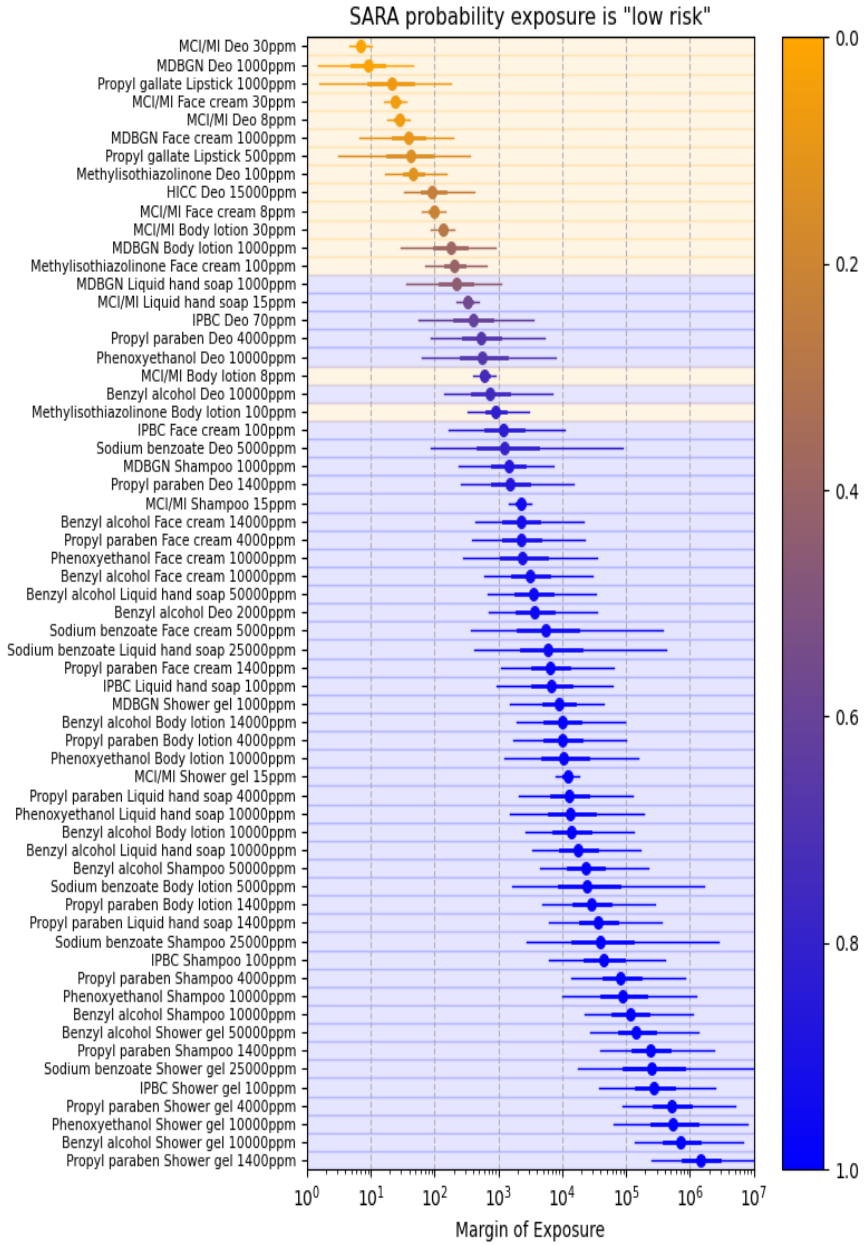
Utilization of Human Data: Skin Allergy



- A distribution generated for the margin of exposure (MoE) (ED_{01} divided by exposure) for every benchmark exposure, where the risk can be defined as either high or low, based on clinical evidence

- Background colours indicate the assigned risk category for each exposure (orange indicating high risk and blue low risk)

- SARA model also infers a probability that a certain exposure is low risk and the line colours indicate this model inferred probability

Using the SARA model, an almost full separation of risk categories based on ranking of the MoE observed

Utilization of Human Data: Skin Allergy

Validation of SARA predictive performance and calibration using the benchmark exposures

- SARA probability (that exposure is low risk) was calculated for each chemical with benchmark exposure available (after removing its risk classification). Metrics computed for these SARA predictions from different sets of inputs (in vivo, NAM or all) and compared with QRA

Metric	SARA in vivo	SARA all	SARA NAM	QRA
Sensitivity	73%	80%	53%	80%
Specificity	97%	89%	83%	91%
Accuracy	90%	86%	75%	88%
Balanced accuracy	85%	84%	68%	86%

- Assessment of calibration of SARA-derived probabilities was done by assigning risk category to each probability of every benchmark chemical exposure, generated over a range of probability intervals

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Utilization of Human Data: Skin Allergy

- Using the human benchmarks, the performance of the SARA model was measured, and key insights were drawn on NAM data usage and the accuracy of the resulting predictions
- Historically used Safety Assessment Factors (SAFs) incorporated in Quantitative Risk Assessment (QRA) approach rely on weight of evidence-based judgement and are not empirically derived
- Benchmarks based on clinical evidence are more specific and relevant to humans and may be an alternate approach
- Increasing the number of benchmarks by collaborating with dermatologist and tapping into surveillance data to further improve the risk assessment of novel chemical exposures are amongst the next steps

Please visit: ***2796: Poster Board - P262 Application of clinical benchmarks to NexGen Risk Assessment (NGRA) decision making for skin allergy: use of historical clinical experience to define low risk cosmetic product market exposures***

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Summary

- Shared two approaches for evaluating and applying human clinical data either as part of the weight of evidence towards generating a reference list of sensitizers or evaluating NAMs and defined approaches
- Clinical data, where available, can serve as a gold-standard tool, to validate mechanisms in adverse outcomes or its predictions from *in silico* or *in vitro* methodologies
- Current limitations include unavailability of certain types of data, lack of standardization in clinical data collection, and unexplored or underutilized clinical evidence
- Opportunities for toxicologists and clinicians to work together to maximize the learnings from clinical experience

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Acknowledgements

Chemical Respiratory Allergy

Stella Cochrane

Kristie Sullivan

Jessica Ponder

Madhuri Singal

Skin Allergy

Nicola Gilmour

Joe Reynolds

Maria Baltazar

Georgia Reynolds

Gavin Maxwell