

Developing a Respiratory Sensitization IATA

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NURA Nix the Six , 7th Oct 2021



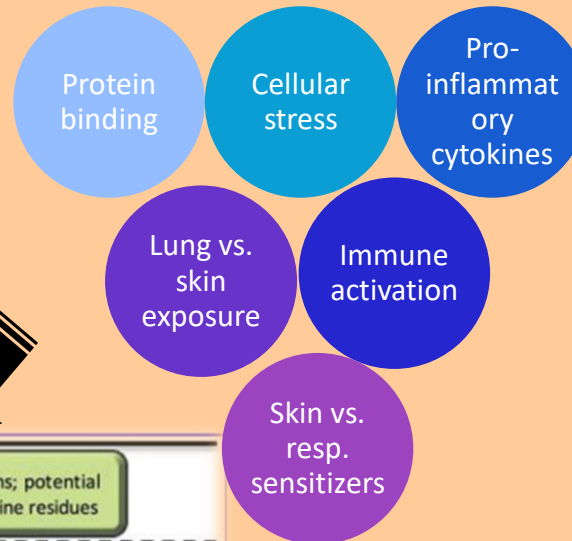
Unilever

Adverse Outcome Pathway - Chemical Respiratory Sensitization

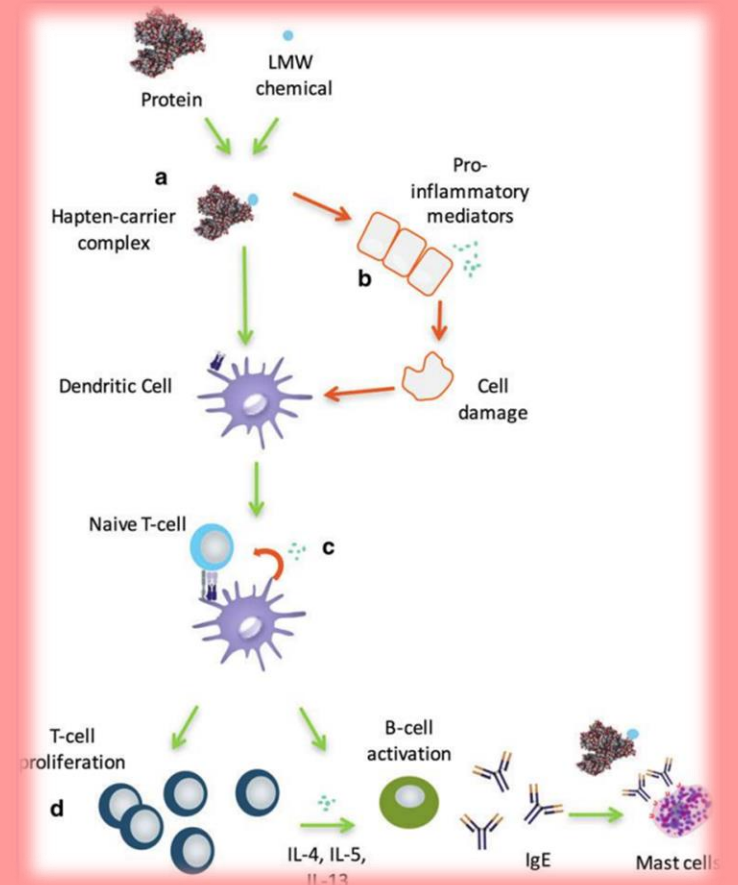
OCCUPATIONAL & CONSUMER HEALTH CHALLENGE

- WORK PLACE EXPOSURE
- IMMUNOLOGICAL & NON-IMMUNOLOGICAL MECHANISMS
- LACK OF SPECIFIC TESTS
- CONSUMER EXPOSURE & RISK

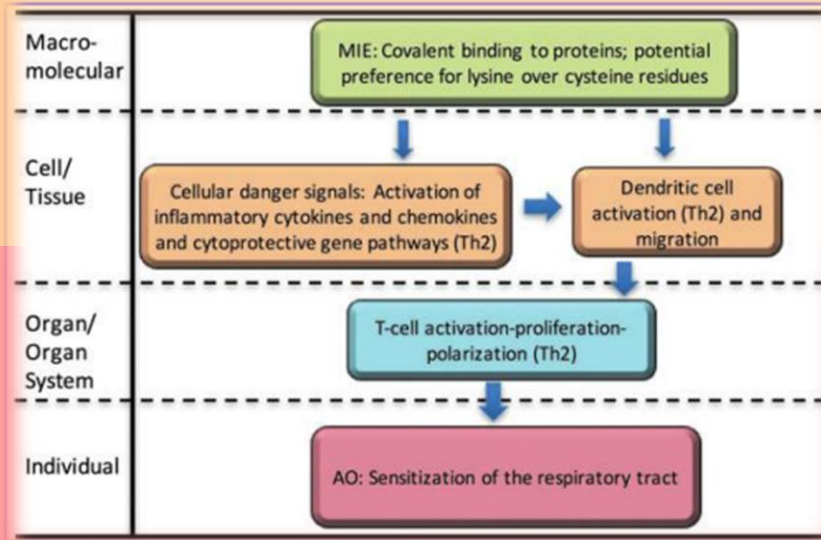
WHAT IS THE IMMUNOLOGICAL MECHANISM?



BASIS FOR DEVELOPING PREDICTIVE TESTS



Adverse Outcome Pathway



(Sullivan et al., 2017; AOP 39, under development)

Reference list of chemicals for testing

Reference List of Chemicals & Human Data Uncertainties

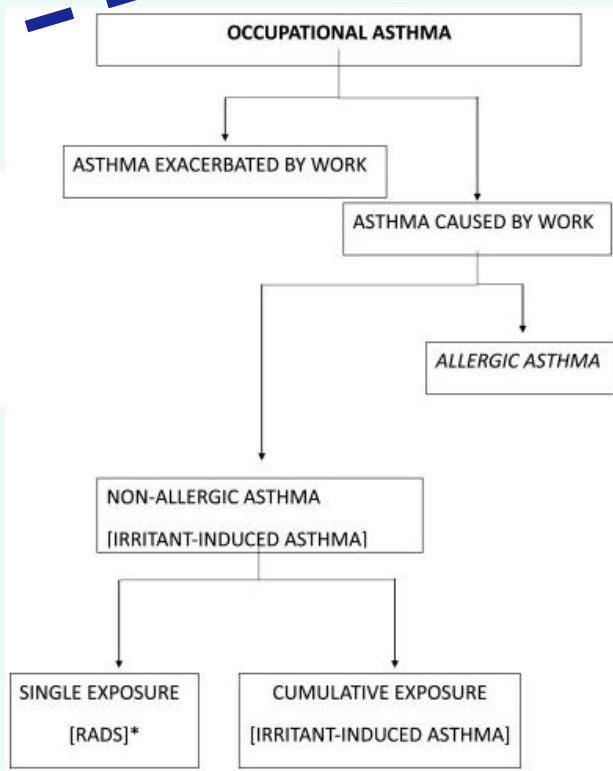
Is there evidence of asthma for the chemicals?

A list of 104 low molecular weight (LMW) organic compounds was developed by Enoch et al. *Chem Res Toxicol* 2012, 25:2490-2498, using 52 structural alerts

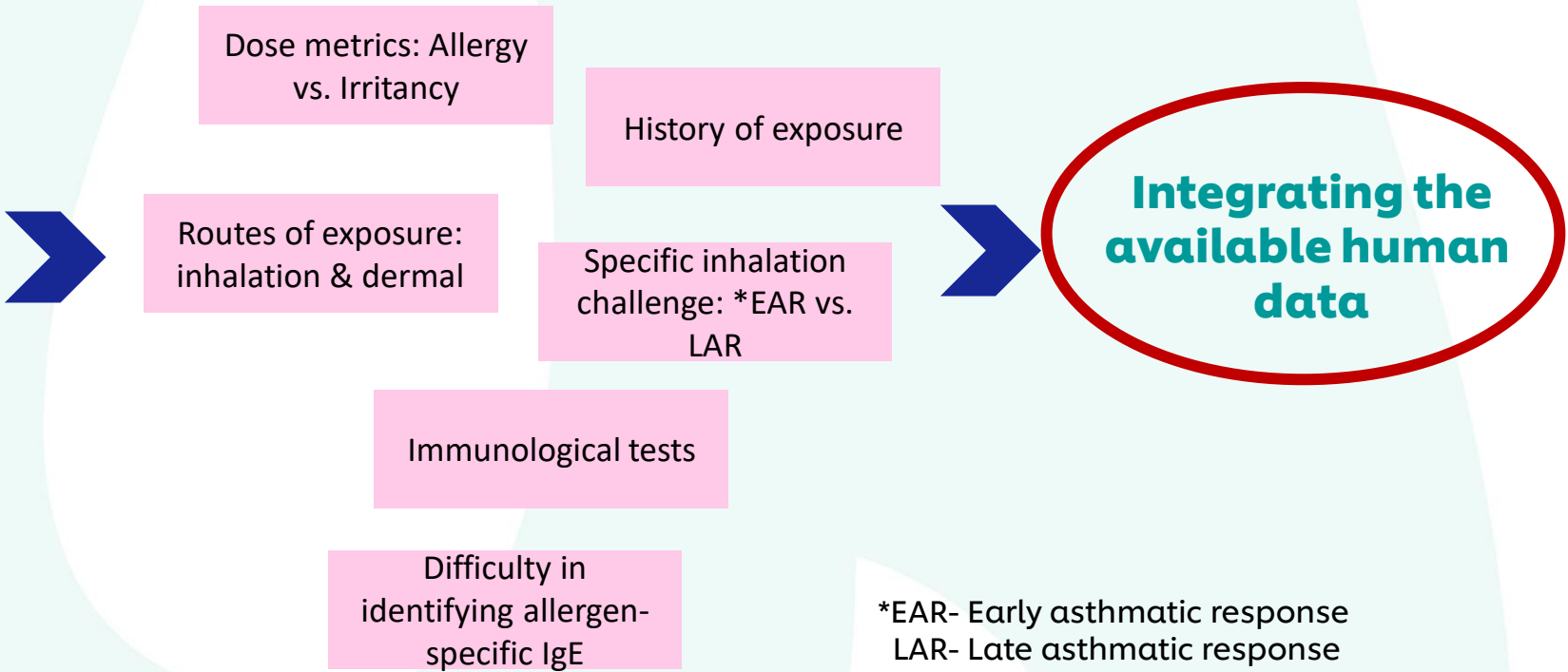
Human clinical evidence of respiratory sensitization considered based on peer-reviewed reports of asthma

There are several mechanisms and phenotypes of occupational asthma. Multiple test data, not always defined acceptance criteria or defined thresholds

What are the available data & are they robust enough?



(Pemberton & Kimber, 2021)



*EAR- Early asthmatic response
 LAR- Late asthmatic response
 +RADS- Reactive airways dysfunction syndrome



Reference List of Chemicals & Human Data Uncertainties

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What data are considered gold standard?

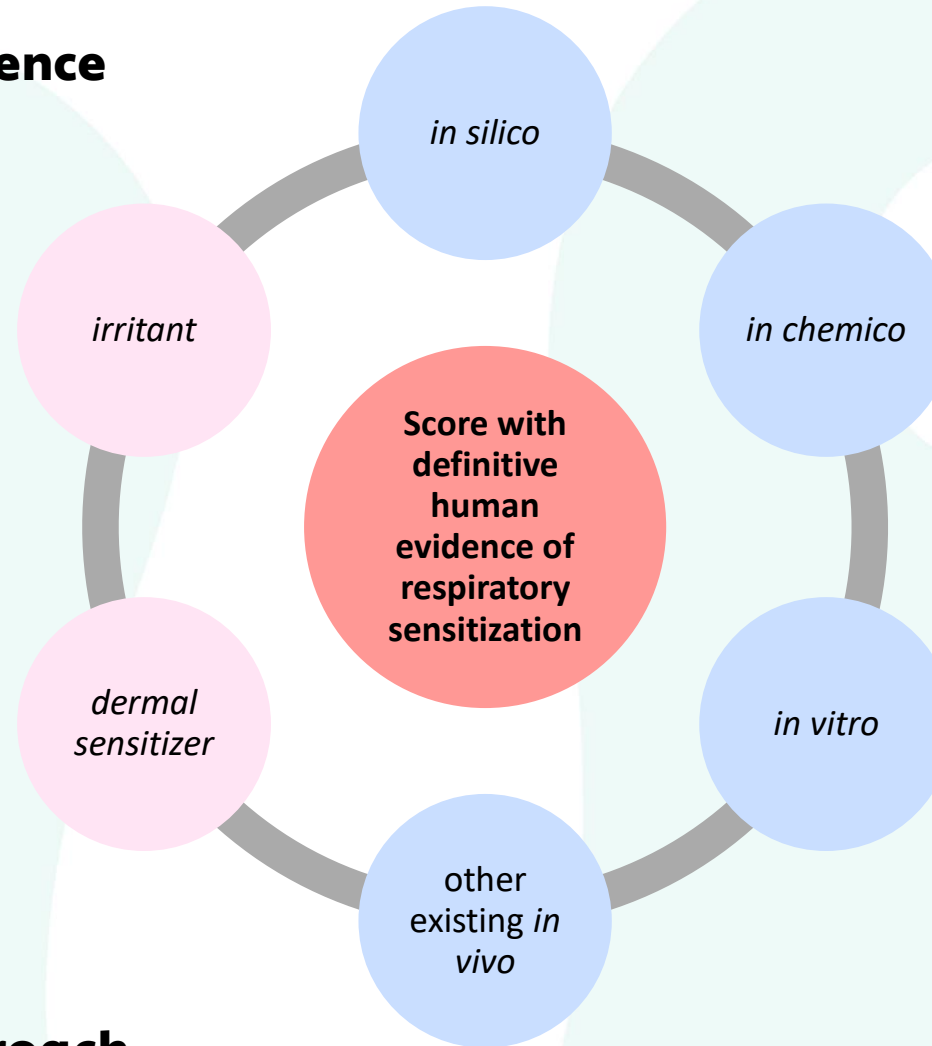
Specific bronchial challenge considered to be the gold-standard test for asthma, specific IgE data is further weight of evidence for immunological mechanism

A systematic and phased approach was developed for utilization and curation of human data towards validating this reference list of putative respiratory sensitizers

What is a good approach to validate the reference list?

Validation of the List of Putative Respiratory Sensitizers

Primary Input: Human Evidence



'*in litero*' Human Data Approach

EPA-developed Abstract Sifter tool, that automates broad literature searching via PubMed, 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)

Literature Search & Classification

PHASE I

Use Abstract Sifter

Query: chemical name AND
(human OR clinical) AND
(respiratory OR lung)

If limited results occur,
remove search qualifiers

If several results occur,
use sifters

If >7000 results occur,
use additional qualifiers

Query: chemical name

Sifters: IgE, bronchial challenge,
sensitize

Query: chemical name AND
(human OR clinical) AND
(respiratory OR lung) AND
(asthma OR allergy)

PHASE II

Lack of data

Clinical features of RS

Known RI

Known DS

Known DI

No assignment/
No info

Respiratory
Sensitizer

Respiratory Irritant

Dermal Sensitizer

Dermal Irritant

Save with No info/RS/RI/DS/DI notations in the Abstract Sifter files

Criteria for Classification

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

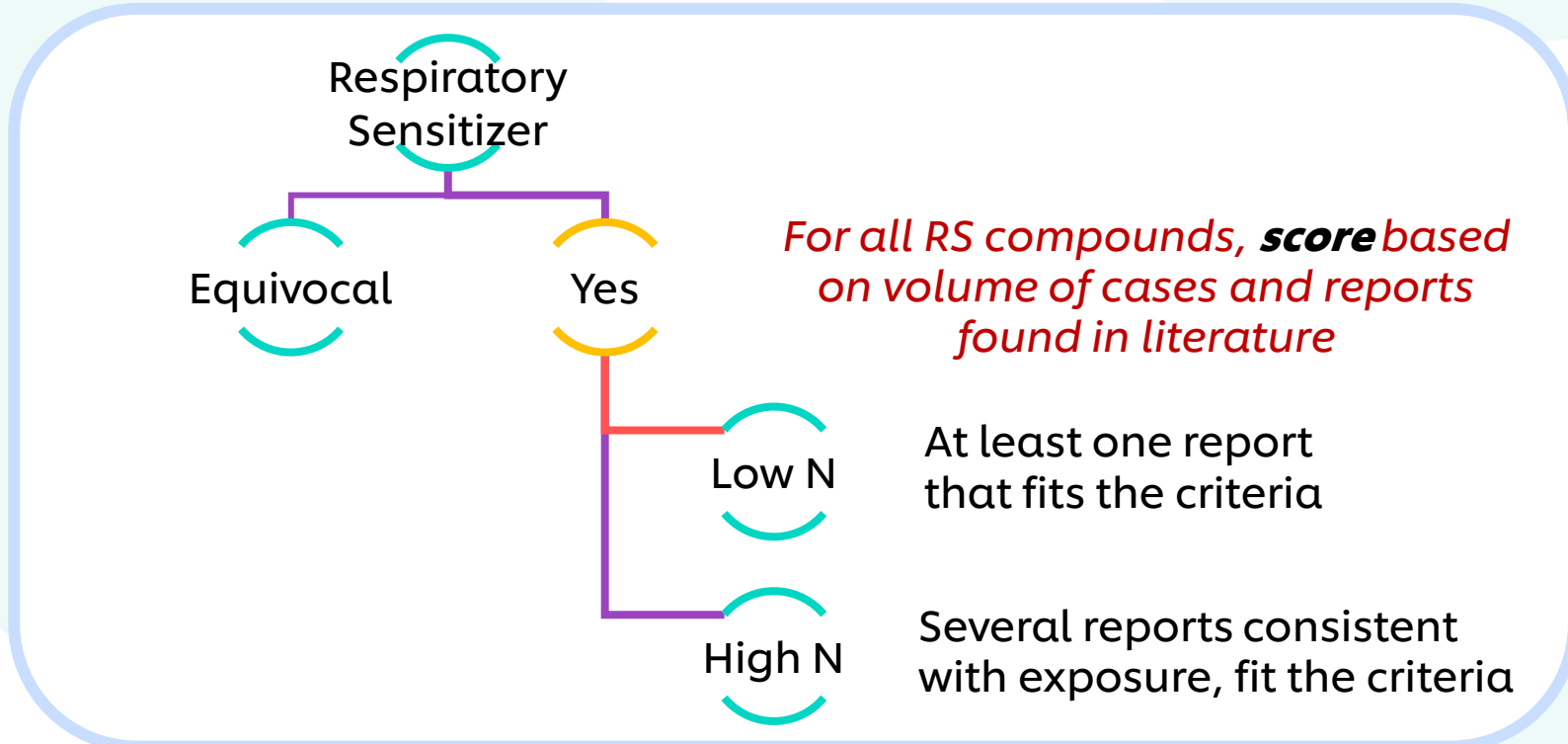
Criteria for Classification

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**

Literature Search & Classification

PHASE III



PHASE IV

Peer review of all classed compounds

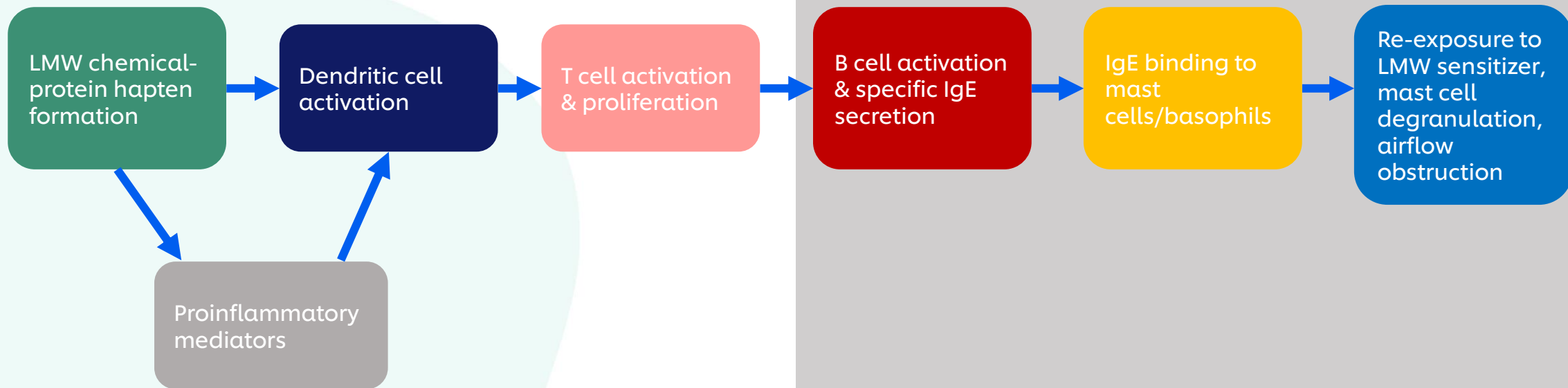
PHASE V

Additional compound review

Using Medical Subject Heading (MeSH) terms of 'Yes' compounds, queried for disease terms, viz. Asthma, Bronchial Hyperreactivity, or Respiratory Hypersensitivity & identified another 270 chemicals

Align classifications with *in silico*, *in chemico*, *in vitro* and other existing *in vivo* datasets

Classing of the Reference List Chemicals: Examples



Glutaraldehyde

	Presence of specific IgE	SPT positive	≥ 20% decrease in FEV ₁
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Piperazine

	Presence of specific IgE		≥ 20% decrease in FEV ₁
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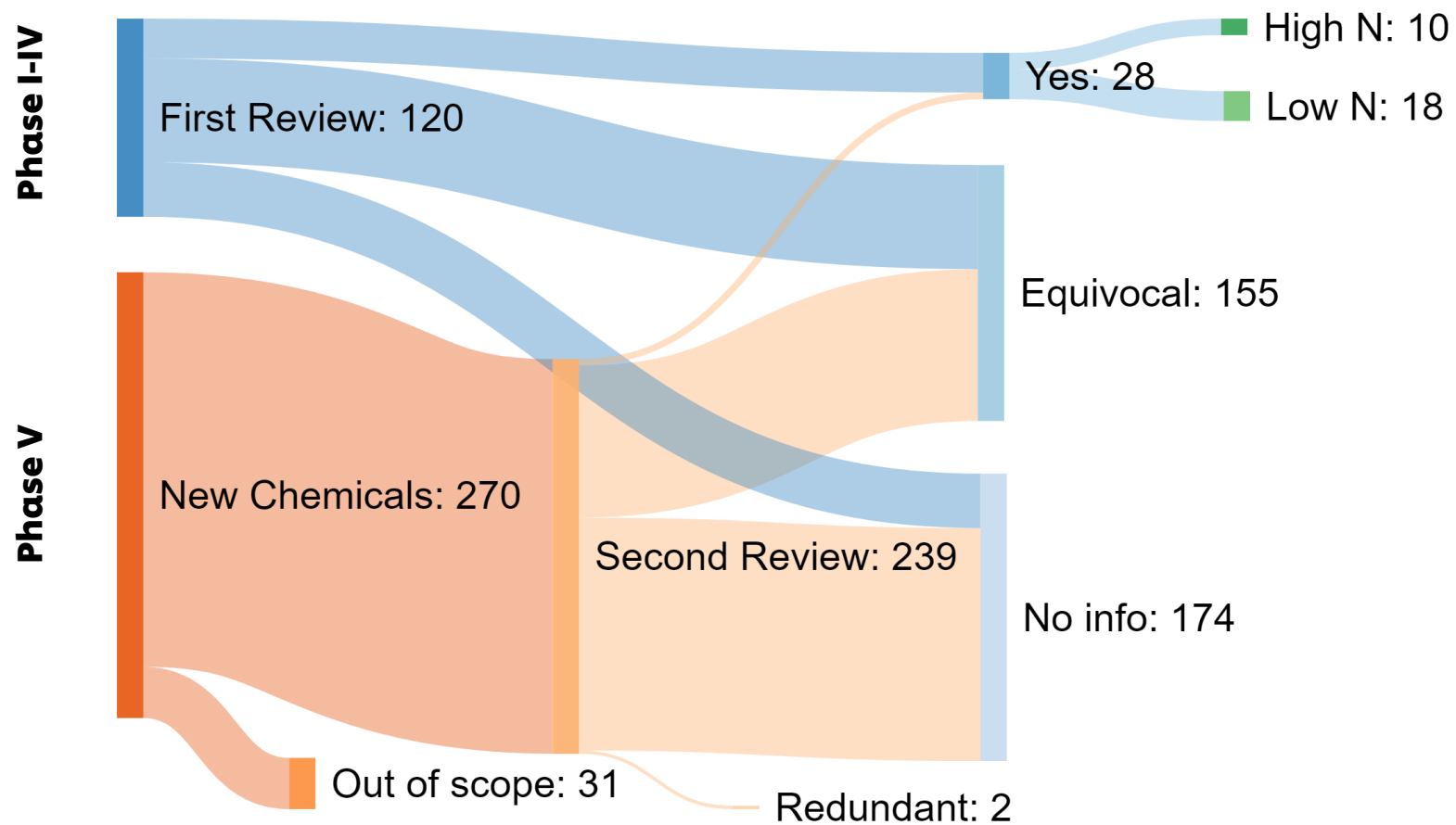
Glycyl compound

		SPT negative	≥ 20% decrease in FEV ₁
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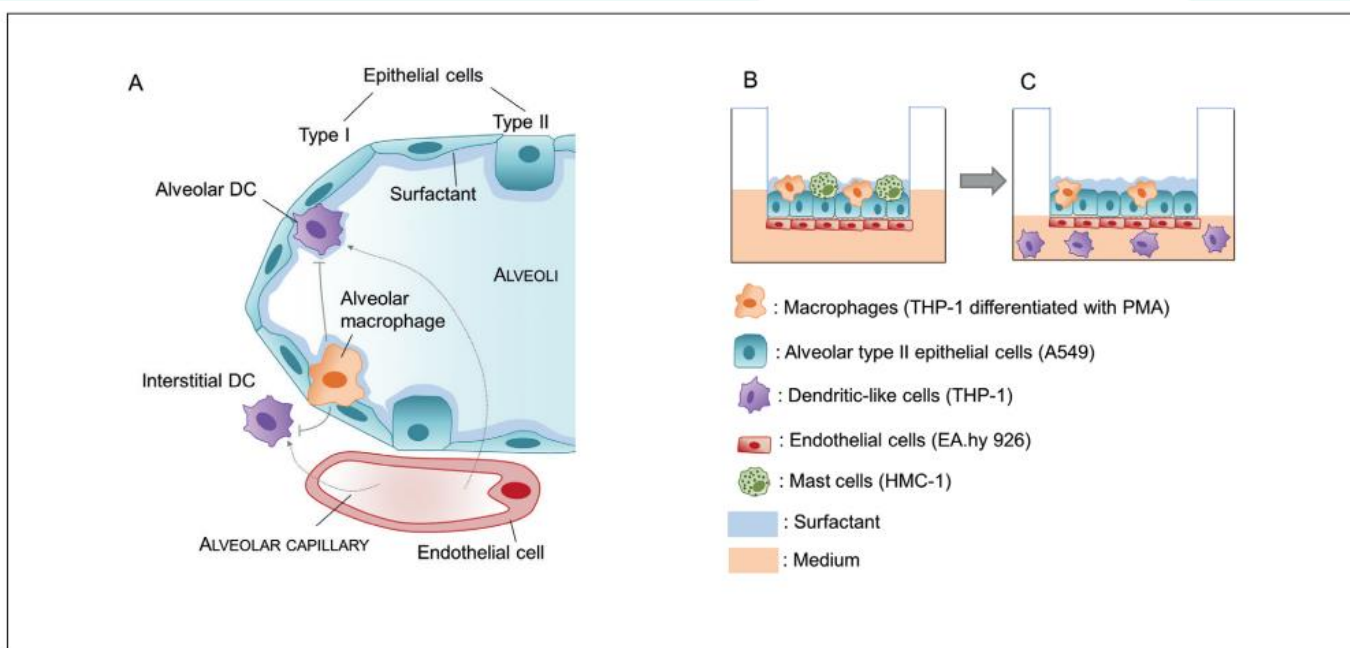
SPT- Skin Prick Test; FEV₁- Forced Expiratory Volume, in one second

Classing of the Reference List Chemicals: Metrics



Next Steps, Opportunities, Outlook

- Testing in lung relevant cell types, specific markers, benchmarking outcomes of respiratory sensitizers in existing OECD assays towards developing an IATA



(Chary et al., 2019)

- Opportunities for toxicologists and clinicians to work together to maximize the learnings from clinical experience, make available certain types of data, build in some standardization in clinical data collection, and consider further unexplored or underutilized clinical evidence
- An exposure-based outlook for assessing the risk of respiratory sensitization

**Lysine reactivity;
Th1 vs. Th2 markers ...**

AOP	In Vitro Assay	OECD Test Guidelines
KE1	Direct Peptide Reactivity Assay (DPRA)	TG442C
KE2	KeratiSense™, LuSense	TG442D
KE3	H-CLAT, U-SENS™, IL-8 Luc	TG442E

Collaborations



Unilever

Stella Cochrane



Kristie Sullivan
Jessica Ponder



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Madhuri Singal



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ITEM

Katherina Sewald



CORTEVA™
agriscience

Raja Settivari



Erwin Roggen



Unilever

THANK YOU