Retrospective Clinical Evaluation for the Development of Reference Chemical Lists

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SUMMARY

- A major advantage of human cell and tissue culture models is the ability to improve the accuracy of translation of results from the research bench to real-world scenarios. However, limitations can emerge during validation if gathering prospective clinical data is not possible, especially for hazardous chemicals. Therefore, practical approaches to develop and maintain the most clinically relevant data for comparison are needed.
- To this end, information from case studies can be evaluated retrospectively to identify and characterize the hazards associated with chemical use in real-world conditions. Herein we describe such an approach for the identification of respiratory sensitizers, in which we utilize the EPA-developed Abstract Sifter literature review tool and standardized search terms to maximize the retrieval of publications relevant to respiratory chemical allergy or asthma in humans.
- The Abstract Sifter was populated with chemicals retrieved from the EPA literature database by querying with MeSH terms related to respiratory sensitization (e.g., Asthma, Bronchial Hyperreactivity, and Respiratory Hypersensitivity). The literature for these candidate chemicals was further queried, sifted, tagged, and evaluated to identify publications relevant to respiratory chemical allergy or asthma in humans.
- This approach successfully identified twenty-eight compounds as respiratory sensitizers based on well-defined clinical diagnostic criteria. This output will be used along with other available data to establish a reference list of respiratory sensitizers, irritants, and non-sensitizers, to update existing risk assessment approaches and evaluate the accuracy of new approaches for this key endpoint.
- Comparison of the protein binding mechanisms of our identified "in litero" respiratory sensitizers suggests acylation is a prevalent protein binding mechanism, in contrast to Michael addition and Schiff base formation common to skin sensitizers.
- Overall, this approach provides an exemplary method to evaluate and apply human clinical data as part of the weight-of-evidence towards establishing reference chemical lists.

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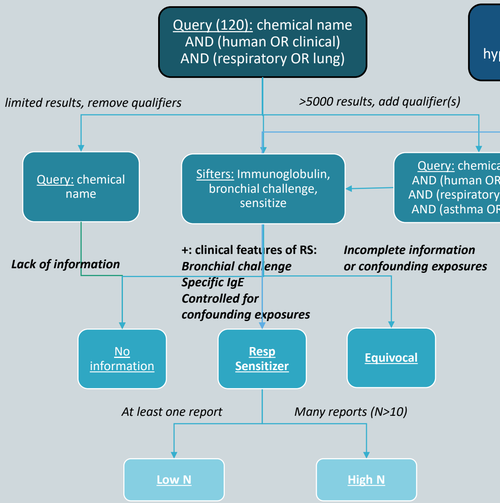
OBJECTIVE

Establish a high-confidence reference set of low molecular weight respiratory sensitizers based on clinically verified case reports of occupational asthma.

IN LITERO APPROACH

PubMed search with Abstract Sifter



Clinical Evaluation Criteria

Central Query:
Has this compound been shown to cause respiratory sensitization in clinical literature?

NO INFORMATION: There is no information to evaluate the compound's sensitizing potential

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
- There is conflicting evidence of immune-mediated responses and/or confounding exposures

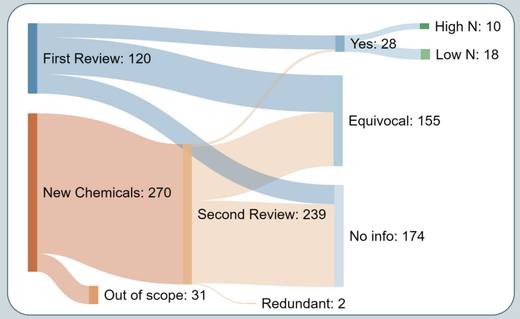
YES: There is significant clinical evidence that the compound has caused respiratory sensitization in at least one case, as defined by either:

- Patient history of exposure with positive specific bronchial challenge, combined with evidence of specific IgE and/or IgG immune-mediated response
- Patient history of exposure with positive nonspecific bronchial challenge, combined with evidence of IgE and/or IgG immune-mediated response, when paired with appropriate negative controls to eliminate confounding exposures

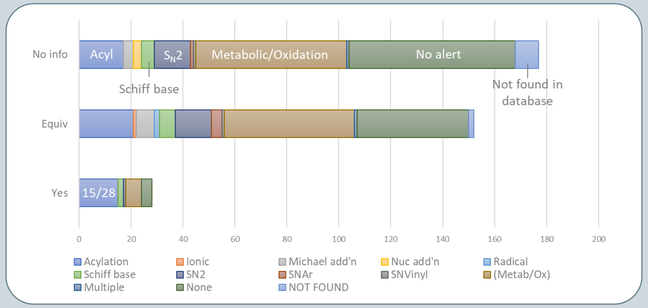
Compound	Occupational Asthma Diagnosis	Specific IgE/IgG	Confounders	Resp Sens?
2,4-Dichloro-5-chlorsulfonyl-benzoic acid	(+) history for asthma and rhinitis, (+) specific bronchoprovocation	(+) skin prick test	none	YES (Low N)
Furfuryl alcohol	(+) history for asthma and rhinitis following catalyst exposure	(-) skin prick test, (-) sIgE, sIgG	sulfuric acid and butyl alcohol	EQUIVOCAL
Hexachlorophene	(+) history for asthma, (+) nonspecific bronchial reactivity	(-) skin prick test	none	EQUIVOCAL
Phthalic anhydride	(+) history for asthma and rhinitis, (+) specific bronchial challenge	(+) skin prick tests, (+) sIgE	controlled	YES (High N)

Clinical evidence was tabulated for review. Abstract Sifter was utilized to collect and prioritize relevant literature reports for evaluation. The collected literature was systematically evaluated for clinical evidence that indicated allergic asthma caused by low-molecular weight chemical exposure.

RESULTS



Sankey diagram depicting classification of clinical literature evidence for 359 potential low-molecular weight respiratory sensitizers. Twenty-four of the original 120 compounds were found to be have convincing clinical evidence of causing true respiratory sensitization without, or with well-controlled, confounding factors. A review of 270 materials (identified using MeSH terms relevant to chemical respiratory allergy) identified four additional sensitizers.



Distribution of protein binding mechanisms . 15/28 of the identified respiratory sensitizers are predicted to bind proteins by acylation. Although nine distinct protein binding mechanisms were represented in our search, only acylation, bimolecular nucleophilic substitution, and Schiff base formation were predicted for clinically-evidenced respiratory sensitizers. Six sensitizers had no protein binding alerts as parent molecules but predicted skin metabolism or auto-oxidation products had alerts, suggesting a pro- or pre-hapten mechanism. Four sensitizers showed no protein binding alerts, two of which included metal complexes.

REFERENCES

1. Sullivan K, Enoch S, Ezendam J, Sewald K, Roggen E, and Cochrane, S. Applied In Vitro Toxicology. Sep 2017.213-226.
2. Baker N, Knudsen T and Williams A. Abstract Sifter: a comprehensive front-end system to PubMed [version 1; peer review: 2 approved]. F1000 Research 2017, 6(Chem Inf Sci):2164