Integrating hazard characterization approaches for evaluating the potential of consumer products to cause asthma

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Abstract

Concerns have been raised regarding the potential for consumer products, including cleaning products to cause or exacerbate asthma or asthma-like responses. Although many forms of asthma are inflammation-based, some low-molecular-weight chemicals have been shown to trigger immunoglobin E (IgE) independent occupational asthma. Single exposures to high concentrations of chemical irritants are also known to elicit an asthma-like response: reactive airways dysfunction syndrome (RADS). RADS can occur within hours of the initial exposure and may continue, as non-specific bronchial hyper-responsiveness, for extended durations. Exposure to irritants may be a trigger for respiratory symptoms in individuals with pre-existing asthma. Current methods cannot adequately assess the potential for consumer product ingredients to trigger asthma or asthma-like responses; epidemiological studies can only measure possible effects associated with a multitude of chemicals and products, and no single animal model can reliably replicate the complexity of an asthma-like response in humans. In order to characterize asthma and respiratory related hazards associated with consumer products, a decision system is needed that incorporates existing guidance, frameworks, and models. To develop such a tool, we compiled and evaluated *in vivo*, *in vitro*, and *in silico* methods that may provide data, or insight, to predict potential asthma or asthma-like responses (e.g., respiratory sensitization) and noted strengths and weaknesses associated with each method. We collaborated with asthma research experts to refine our findings and approach. Despite the wealth of information on asthma, current guidelines, bioassays, and computer models cannot definitively identify whether a particular ingredient, or chemical, causes or exacerbates asthma or asthma-like responses. However, possible predictors of allergy-induced asthma, such as sensitization of the respiratory tract, are useful to assess the likelihood that a particular chemical, ingredient, or product may be associated with asthma induction.

Methods

Hazard Characterization Framework Evaluation:

- Consider asthma or sensitization of the respiratory tract
- Include multiple lines of evidence for evaluating the potential to cause or exacerbate asthma
- Provide a decision method for identifying chemicals that may increase the risk of asthma

The following resources were excluded from this evaluation because they only provided a list of suspect chemicals or substances:

- National Library of Medicine's Hazmap database
- NJ Department of Health and Senior Services listings
- NJ and NY State Departments of Health listings
- Collaborative on Health and the Environment listings
- Michigan State University listings

Organizations included in this assessment:

- The Association of Occupational and Environmental Clinics (AOEC)
- U.S. EPA Design for Environment
- Toxicology Excellence for Risk Assessment (TERA)
- World Health Organization (WHO)/ International Programme on Chemical Safety (IPCS)
- ICF International (Selgrade et al. 2012)
- UN Globally Harmonized System of Classification and Labeling of Chemicals

Weight of Evidence Considerations:

We used published literature to identify available assays and models that could be used to contribute to weight of evidence decisions regarding the relationship between exposure to a chemical and asthma. This evaluation focuses on assays for possible mechanisms of sensitization, not irritation. In general, the intent was to focus on assays that evaluate respiratory sensitization directly, given that sensitization of the respiratory tract may be more related to new onset asthma than irritation. However, many of the hazard characterization frameworks being applied also consider evidence for sensitization following topical exposures. Thus, the most frequently cited dermal sensitization assays were also considered.

Results

Summary of the Pros and Cons from Frameworks for Determining Relationships of a Chemical Exposure with Asthma

Organization	Pros	Cons
AOEC	. Uses a weight of evidence approach to determine the cause(s) of asthma induction (i.e., one positive response is not enough to determine causality) . Focuses on new-onset cases of asthma	. Mostly limited to occupational exposures . Does not consider animal data in its approach . Not tox-based; designed to assist physician diagnosis
EPA Design for Environment	. Gathers information from multiple other organizations	. Dependent on assessments from other organizations . No documentation for their own approach for assessing sensitization
TERA	. Considers multiple lines of evidence . The framework is based on assessing asthma, not just asthma-related surrogates . Attempts to identify the cause of new-onset asthma . Uses dermal sensitization and irritation data in the absence of respiratory information allows for assessment of a wider array of exposures . Allows investigators to make characterizations based on multiple levels of certainty	. Uses dermal sensitization and irritation data may lead to false associations, but is ultimately a conservative approach . Does not consider the relevance of exposure scenarios
WHO/IPCS	. Clearly defines an approach for determining potential respiratory and dermal sensitization and allergy, including prioritization of data types and tests . Allows the user to define their level of confidence in determining causality of immunotoxic exposures.	. Does not provide a framework for assessing asthma, just the surrogate responses related to sensitization
Selgrade et al. (2012)	. Clearly defines an approach for determining potential dermal sensitization, including prioritization of data types and tests . Clearly defines the strength of evidence for human data . Use of animal data, structural activity relationships and other evidence (e.g., in vitro data) for a weight of evidence	. Does not provide a framework for assessing asthma, just the surrogates, although this evidence can be used to build a weight of evidence argument
UN GHS	. Has minimum recommendations for epidemiological data quality . Clearly defines an approach for determining potential respiratory sensitization, including prioritization of data types and tests	. Does not provide a framework for assessing asthma, just the surrogates such as sensitization.

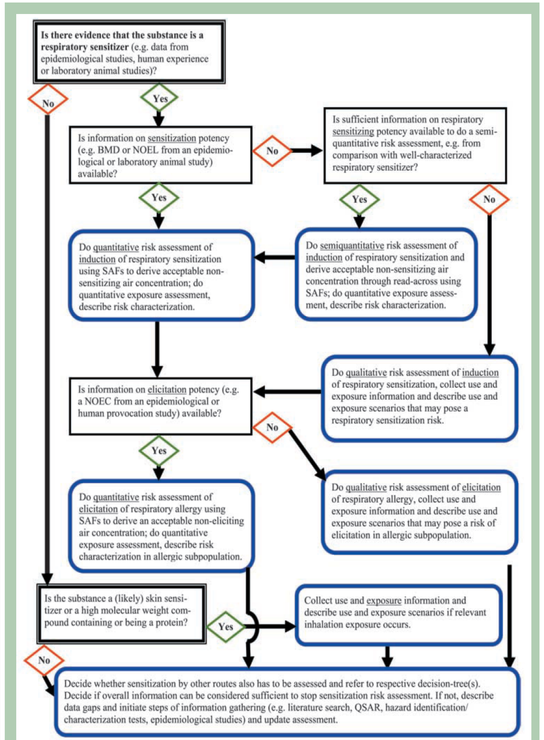

Figure 6.2B: Decision-tree for the assessment of sensitization and allergic response: respiratory sensitization.

IPCS decision-tree for assessing respiratory sensitization and allergic response (IPCS 2012): an example of a clearly defined, systematic approach that could be used as a model for developing a framework to assess asthma hazard.

Peer Consultation Webinar

The utility of each framework and model was discussed amongst a panel of five asthma and respiratory allergy experts (Drs. William Beckett, Pamela Dalton, Ian Kimber, and MaryJane Selgrade), representing expertise in pulmonology, chemosensory irritation, immunosensitization, and risk assessment.

The panelists were asked to comment on the following questions during the meeting:

Evaluate assays and lines of evidence

- Identify any additional models or assays not previously captured and corrections to table.
- Evaluate the assays and reach conclusions regarding their strengths and weaknesses for predicting potential for causing asthma or eliciting asthma responses.
- For dermal assays, how predictive are these of a respiratory response?
- To what degree has bioassay predictivity been validated? What is the status of validation for these assays?
- Discuss and make recommendations regarding how the available assays can be used within a decision framework that addresses the evaluation of relationships between asthma and consumer products.

Evaluate possibility of developing a Hazard Characterization Decision Tool for improved safety assessments for asthma and relationships with exposure to consumer products.

- Discuss whether a decision tool can be developed. Are there elements from existing frameworks or WOE approaches that can be used or built upon? What necessary elements are missing? What other barriers are there to developing a decision tool?
- If a decision tool can be developed, describe the scope of a hazard characterization decision tool, including 1) endpoints to be included - sensitization and irritation?, 2) routes or exposure to be included - dermal with respiratory? 3) other scope elements?

Identify and rank research or data needs to fill gaps in knowledge and analysis

- Identify data and research gaps, and additional efforts that may be needed, in order to develop a risk characterization decision tool.

Discussion

Is there a single recommended framework that can be adopted directly?

No, there are multiple aspects from multiple frameworks that could be used to create a modified approach. Elements that we think would be critical for a refined framework include:

- Clear description of the scope and purpose of the tool
- Capturing the nuances of mechanism of action (i.e., allergic versus non-allergic induction)
- Relationships to exposure considerations
- Hierarchy of data, based on types of tests, that will better allow a well-documented WOE decision process

A WOE approach is needed and no single assay (in animals) is definitive because:

- No single biomarker that is specific to asthma or consistently found in conjunction with asthma
- Multiple MOAs likely exist and the lines of evidence need to incorporate MOA
- There is uncertainty about key immunological events in the sensitization of the respiratory tract
- The role of non-allergic asthma (e.g., RADS) variants is controversial

To what degree have bioassays been validated for assessing relationships with asthma?

No test is 100% accurate, there will always be false positives and negatives. For example, some gold standards for dermal and respiratory irritation or sensitization (e.g., LLNA and GPMT) are only approximately 90% accurate.

A thoughtful and reasoned approach for interpreting tests and combining evidence from multiple assays.

Assay development is active. Some assays that need additional validation include:

- Fractured Nitrous Oxide
- Ovalbumin challenge model
- BAL fluid and peptide release
- Neurokinins of inflammatory release
- 3D SAR
- Precision-cut lung slices to look at contractility of the airways

Data Gaps and Next Steps

A goal of this effort is to clarify the landscape of approaches for assessing asthma risk from consumer product exposures. This is intended to be a risk assessment tool, or a model for predicting hazard. The next step is to expand up on the work of previous frameworks and test an enhanced framework with multiple case studies.

***in vivo, in vitro,* and *in silico* models that were selected for review.**
Human Models
Spirometry (with or without challenge agent) and Bronchial Provocation Testing
Non-specific bronchial provocation testing (methacholine, histamine)
Laboratory specific quantitative inhalation challenge with a suspected cause of occupational asthma
Human Repeat Insult Patch Test (HRIPT)
Human maximization test (HMT)
Repeated Open Application Test (ROAT) (or prospective use test (PUT), or Open patch test)
Skin Prick Test
Serological assays
Guinea Pig models
Guinea pig intratracheal test, GPIT
Karol guinea pig whole body plethysmography
Guinea pig respiratory parameter test: injection model
Guinea pig maximization test, GPMT
Buehler Guinea Pig Test
Open epicutaneous test (OET)
Mouse models
Standard murine lymph node assay (LLNA)
Respiratory LLNA
LLNA: DA
LLNA: BrdU-ELISA[[Enzyme-Linked Immunosorbent Assay]
Reduced LLNA (rLLNA)
Mouse Ear Swelling Test (MEST)
Mouse IgE test
Mouse Intranasal Test (MINT)
Mouse Intratracheal Test
Mouse respiratory cytokine profiling or fingerprinting
Eosinophil Peroxidase (EPO) Assay
BALB/c Mouse
Rat models
Brown Norway (BN) rat
In vitro models
Human alveolar epithelial cell line
Human bronchial epithelial cell line
Human dendritic cell-like cell lines
Murine dendritic cell line
Co-cultures
Three-dimensional (3D) models
In chemico models
The Direct peptide reactivity assay (DPRA)
The GSH reactivity database
In silico models
Structure-activity relationships (SARs)
Quantitative structure-activity relationships (QSARs)

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