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## Chemical-induced asthma and the role of clinical, toxicological, exposure and epidemiological research in regulatory and hazard characterization approaches

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### Abstract

Uncertainties in understanding all potential modes-of-action for asthma induction and elicitation hinders design of hazard characterization and risk assessment methods that adequately screen and protect against hazardous chemical exposures. To address this challenge and identify current research needs, the University of Cincinnati and the American Cleaning Institute hosted a webinar series to discuss the current state-of-science regarding chemical-induced asthma. The general consensus is that the available database, comprised of data collected from routine clinical and validated toxicological tests, is inadequate for predicting or determining causal relationships between exposures and asthma induction for most allergens. More research is needed to understand the mechanism of asthma induction and elicitation in the context of specific chemical exposures and exposure patterns, and the impact of population variability and patient phenotypes. Validated tools to predict respiratory sensitization and to translate irritancy assays to asthma potency are needed, in addition to diagnostic biomarkers that assess and differentiate allergy versus irritant-based asthmatic responses. Diagnostic methods that encompass the diverse etiologies of asthmatic responses and incorporate robust exposure measurements capable of capturing different temporal patterns of complex chemical mixtures are needed. In the absence of ideal tools, risk assessors apply hazard-based safety assessment methods, in conjunction with

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active risk management, to limit potential asthma concerns, proactively identify new concerns, and ensure deployment of approaches to mitigate asthma-related risks.

### Keywords

asthma; hazard characterization; respiratory sensitization; consumer products; risk management

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### Introduction

The increasing prevalence of asthma in the United States, and worldwide, is a growing burden on health care costs and quality of life (CDC, 2015). Numerous epidemiological studies and reviews have suggested a link between the use of cleaning products in residential and commercial settings to an increase in risk of physician-diagnosed asthma (Jaakkola and Jaakkola, 2006; Nielsen et al., 2007; Quirce and Barranco, 2010; Zock, 2005; Zock et al., 2010; Rosenman, 2003), however a causal link between exposure and response is unclear, in part due to poor characterization of the complex mixtures to which cleaners are exposed (Vincent et al., 2017). The multiple phenotypes and causes of disease and response elicitation hamper the ability to design hazard characterization and risk assessment methods that adequately screen and protect against chemical exposures (Maier et al., 2014, 2015; Vincent et al., 2017).

To address these challenges and identify current research needs regarding chemical-related asthma, the University of Cincinnati hosted a multipart webinar series from February 25<sup>th</sup> to October 21<sup>st</sup>, 2016 in conjunction with the American Cleaning Institute (ACI) to discuss the current state of science regarding chemical-induced asthma. Key issues and research opportunities were described in the context of five presentations. These presentations are available online<sup>1</sup>. The results of the effort are summarized to guide development of safety and risk assessment approaches and address uncertainties and data gaps in asthma-related disease as it pertains to chemical product exposures.

### Clinical Perspectives in Evaluating Chemical-Induced Asthma

Asthma pathophysiology is heterogeneous, but can be generally divided into smooth muscle dysfunction (characterized by bronchoconstriction, bronchial hyperreactivity, hypertrophy or hyperplasia, and inflammatory mediator release) and airway inflammation (characterized by inflammatory cell infiltration/activation, mucosal edema, cellular proliferation, epithelial damage, and basement membrane thickening) pathways (Bousquet et al., 2000). All of these pathophysiological changes ultimately result in asthma symptoms. Asthma-related inflammation can also be considered as an acute response often followed by a chronic response where immediate bronchoconstriction, swelling, increased secretions and cough can lead to a chronic inflammation phase associated with cell recruitment, epithelial damage, airway remodeling with cellular proliferation, and extracellular matrix changes that can eventually lead to fixed airway obstruction if not treated.

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<sup>1</sup><http://www.med.uc.edu/eh/centers/rsc/education/webinars/asthma>

In addition to pathophysiologic differences in asthma response, the molecular underpinnings of the disease are also variable. Mechanisms related to sensitization arise when allergens trigger immunoglobulin E (IgE)-mediated pathways which lead to airway inflammation. T cells, in addition to other effector cells (e.g., mast cells, eosinophils, dendritic cells), play an important role by producing an array of cytokines that contribute to acute symptoms and perpetuate chronic inflammation. Irritant-induced asthma (i.e., reactive airways dysfunction syndrome), however, involves a different, less-understood mechanistic pathway. Irritants cause disruption of the airway epithelium and activate different regulating molecules and cytokines that can also trigger the migration of effector cells into the lungs leading to release of cytokines and mediators. There may be cross talk between allergic and non-allergic mechanistic pathways as many patients with asthma are affected by allergic and non-allergic triggers. In fact, a recent study that reclassified chronic rhinitis patients with a physician diagnosis of allergic, mixed (allergic and non-allergic triggers) or non-allergic rhinitis using an irritant index scale found that a significant percentage of patients previously diagnosed with allergic rhinitis actually had mixed rhinitis. Furthermore, these mixed rhinitis patients with a high irritant index score had a greater prevalence of physician diagnosed asthma suggesting that chemical irritants in conjunction with allergen triggers compared to allergen triggers alone may contribute to disease severity (Bernstein et al., 2012).

Mixed mechanistic pathways can complicate the assessment of chemical exposure causality. Although there are multiple biomarkers such as peripheral or sputum eosinophils, exhaled nitric oxide, total IgE levels and urinary leukotrienes that can be measured to characterize different asthma endotypes<sup>2</sup>, their application as specific predictive indicators of chemical induced asthma requires further understanding of the mechanistic pathways for this condition. An irritant index questionnaire, similar to the one used to assess non-allergic triggers in chronic rhinitis patients, previously was used to demonstrate that increased irritant index scores correlated with increased bronchial airway hyperresponsiveness (Brooks et al., 1990). Although this clinical tool may be useful for assessing irritant-induced asthma qualitatively and quantitatively, this instrument depends on patient recall and exposure opportunity which introduces bias into the responses and thus has some inherent limitations for assessing chemical exposures and related health effects especially as they pertain to asthma. Another potential biomarker is periostin, which is a ligand for various integrins, important for cell adhesion and migration of epithelial cells. Finally, the nasal tissue, which is much more easily accessible than obtaining induced sputum, bronchial alveolar lavage, or lung tissue biopsies, could be used as a surrogate for identifying biomarkers that could predict inflammatory responses in the lower respiratory tract, specifically by looking at mRNA transcriptomes and translational proteins in response to chemical triggers.

In the absence of a reliably diagnostic biomarker, a variety of traditional approaches are more commonly used to diagnose and assess patients with asthma. Risk factors for asthma include atopy, family history, passive/active smoke exposure, early childhood bronchiolitis, eczema, childhood persistent wheeze, and a number of environmental determinants. Factors such as frequent use of antibiotics and breast feeding may also protect against or promote

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<sup>2</sup>An endotype is a subtype of disease or condition. Endotypes of asthma, for example, would include allergic and non-allergic asthma.

the progression to asthma, based on their effects on the gastrointestinal microbiome. However, there is much we still do not understand regarding asthma risk factors and the variable and heterogeneous nature of this disease.

In diagnosing asthma, the clinician needs to consider the course of the disease (management history), what a typical episode involves, previous treatments, environmental and social settings, family history, allergy history, occupational history, patterns of symptoms (e.g., episodic vs. persistent, nocturnal, seasonal), and the types of triggers. Obtaining an occupational history is extremely important since up to approximately 15% of asthma cases may be caused by workplace exposures (AAAAI, 2017). Occupational exposures associated with asthma are characterized as inciters (i.e., irritants with moderate to high levels of exposure that exacerbate asthma) or inducers (i.e., sensitizing allergens or irritants that cause new-onset asthma). In contrast to occupational asthma induced by a sensitizing agent, there is generally no latency period associated with irritant-induced occupational asthma (e.g., Reactive Airways Dysfunction Syndrome, or RADS). After discovering a suspected occupational cause of asthma through patient history, it is important to request Safety Data Sheets (SDS) to identify and/or confirm suspected exposures. A survey by Bernstein and Shusterman (2010) indicated that a third of physicians who treated patients with disinfectant-related asthma symptoms had difficulty obtaining chemical information (e.g., product ingredients, concentrations, etc.) from the workplace or manufacturer, and half could not identify the chemical class of the products in question.

Diagnostic tools, such as the skin prick test (SPT), intracutaneous testing, and specific IgE immunoassays can confirm sensitization but whether the agent(s) is responsible for causing symptoms needs to be correlated with exposure history and, when possible, confirmed by specific provocation. However, most chemicals related to causing or aggravating asthma are irritants and cannot be tested for causality using immunologic assessments. There are a number of key tools used in asthma evaluation, specifically spirometry and peak expiratory flow rate (PEFR) monitoring, but these tools have limitations. Sometimes patients do not show signs of reversibility and physicians must use non-specific provocation tests such as methacholine challenge to demonstrate airway hyperresponsiveness, a key feature of asthma related to smooth muscle dysfunction. Exhaled nitric oxide (NO), a non-specific measurement of inflammation, is another complementary, non-invasive test that is correlated with asthma control (Meyts et al., 2003). Although this tool may be a reliable predictor of poor asthma control based on symptoms,  $\beta$ -agonist use, and spirometry, physicians must interpret this test cautiously since inflammation does not always coincide or correlate with smooth muscle dysfunction.

The absence of chemical specificity of many existing diagnostic approaches has led to efforts to use controlled exposure chamber methods. Environmental exposure chambers can be used to expose patients to allergic and non-allergic asthma triggers (e.g., cold air; Bernstein et al., 2012). Responses are generally heterogeneous but these challenges can confirm what is learned from the patient's history (Pfaar et al., 2017). In addition to research purposes, controlled challenges with specific suspected causative agents may also be considered in cases where there is diagnostic uncertainty due to a poor patient history, confounding factors, diagnostic disputes and for legal purposes.

Despite the current availability of diagnostic tools, there is still a need for more research to better understand different asthma phenotypes/endotypes and pathomechanisms, specifically incorporating provocation studies to assess end organ reaction to environmental irritants in conjunction with *ex vivo* and *in vivo* cellular responses. If researchers can elucidate unique “endotypes” for asthma, biomarkers can be identified that will help better assess a patient’s potential for developing asthma in response to a spectrum of causal factors including chemical irritants.

#### Key Research Recommendations

- Understand mechanisms of asthma related to specific exposures including chemicals
- Define patient phenotypes based on existing clinical tools
- Integrate specific asthma phenotypes with pathomechanisms to define a unique asthma “endotype”
- Identify biomarkers that assess and differentiate irritant versus allergy-based asthma responses
- Access and apply advanced diagnostic approaches, including controlled challenges

### The Role of Toxicology in Asthma Hazard Assessment

Asthma can be caused by both allergic and non-allergic mechanisms. There are two phases to allergies: an induction (or silent) phase and an elicitation phase involving manifestation of disease. Repeated exposures to proteins or chemicals with inherent respiratory sensitizing properties cause formation of antigens, induce the production of specific IgE, and prime tissue mast cells and basophils (induction) which results in clinical symptoms after continued or subsequent exposure (elicitation). Cross-over is limited between Type 1 (IgE mediated) responses (i.e., immediate allergic responses), which are more closely associated with respiratory allergy responses (e.g., sneezing, wheezing, and anaphylaxis) and Type 4 (T-cell mediated) responses (i.e., delayed allergic responses) that are more closely associated with skin allergy responses (e.g., skin rashes and eczema). An argument has been made that, even for small molecules, IgE is the prevailing biological mechanism, although the presence or absence of antigen-specific IgE does not, alone, constitute causality or a lack thereof (Kimber et al., 2014). However, the detection of hapten-specific IgE for chemicals, as compared to protein allergens, may be much more difficult due to technical detection limitations, antibody distribution, and inability of clinical skin prick testing to recreate responses to past exposures.

Various predictive assays are used in the research context (e.g., guinea pig antigenicity test, guinea pig intratracheal instillation test, mouse intranasal test, structure activity relationships (SARs), mouse IgE tests, local lymph node assay (LLNA) and cytokine profiling, etc.) but remain unvalidated for use to detect respiratory sensitizers and are neither widely accepted nor used for hazard assessment purposes. Challenges remain in calibrating responses in *in*

*in vivo* animal assays to human *in vivo* responses, in particular a lack of ability to predict potency. Additionally, quantitative SAR and mechanistic chemistry approaches have been explored (Dik et al., 2014), but such tools are limited for testing unknown or diverse chemicals that fall outside the training sets of substances. Biomarkers of asthma-like effects could also be monitored, specifically with chemicals that mimic haptens and form a complete allergen with endogenous proteins (e.g., trimellitic anhydride), and would provide longitudinal exposure information. In short, there are many useful tests or biomarkers for predicting and measuring asthma-related responses, but none can be used to identify or predict asthmatic responses, especially across the broad spectrum of asthmatic phenotypes.

Although currently available assays (e.g., SPT and LLNA) have limited utility in asthma risk assessment, there are a number of assays and tests in development that may be useful for predicting asthma (e.g., respiratory LLNA, SAR). However, development of a repeatable, validated, practical assay for asthma prediction is nascent and still substantially far from completion. Researchers have a robust, predictive, and accurate assay for predicting skin sensitization, the LLNA, but only because of the large body of clinical data used to validate the assay and its predictions. There is no equivalently robust dataset for development of respiratory sensitization assays, due to a combination of a lack of human data and avoidance of using animal models (e.g., Tox 21; NAS, 2017). There are *in silico* methods that permit consideration of the chemistry of particular compounds that are known to cause asthma (e.g., isocyanates) where we can make judgements by categorical classes based on chemical structure (e.g., Cramer classes; Cramer et al., 1978) in the absence of a sophisticated model. However, for respiratory sensitizers, current SAR models are not able to predict approximately 2/3 of the chemicals known to cause asthma, and inevitably new substance prediction is likely to be even less accurate (Dik et al., 2014). To move forward in assay development, we need a stronger understanding of the underlying biology and mode of action for both allergic and non-allergic asthma.

There are relationships between dermal sensitization *in vivo* tests and respiratory sensitization that can be used to inform risk assessments. To date, all known respiratory sensitizers are also dermal sensitizers, while the converse is not true; only a small minority (<1%) of dermal sensitizers are also respiratory sensitizers (Basketter and Kimber, 2016; Dearman et al., 2013). As a result, if one tests a compound using the validated *in vivo* skin assays and the result is negative, it is very unlikely the compound will be a respiratory sensitizer. However, if the same dermal tests yields a positive response, then the respiratory sensitization potential is uncertain and needs additional examination. Chemicals that cause allergic responses in skin and lung can be identified by cytokine fingerprinting (typically by examining the differential expression of IL4 vs IFN $\gamma$ ), which may help separate Th1 and Th2 cytokine mechanisms that are potentially indicative of skin versus respiratory involvement respectively (Dearman et al., 2003; De Jong et al., 2009; Kimber et al., 2007; Dearman et al., 2013). Skin, but not respiratory, sensitizers caused IL18 release from NCTC2544 cells (Corsini et al., 2009), but the method still awaits more formal validation. Genomic profiling approaches for identifying respiratory sensitizers are also in development (Dik et al., 2015).

It is clear that some largely unknown, non-allergic mechanisms can generate bronchial hyperreactivity. There is well known evidence that high concentration exposures to bronchial and pulmonary irritants can produce RADS. Other non-allergic mechanisms can also provoke an asthmatic reaction in persons with hyperreactive airways. For example, fragrance factory workers do not have an increased risk of occupational asthma, and persons with fragrance allergies, manifested as allergic contact dermatitis, almost never have respiratory effects even following airborne skin contact; nonetheless, fragrances have been shown to provoke asthmatic reactions (Basketter and Kimber, 2015). Translating current *in vivo*, *in vitro*, or *in silico* irritancy assays to asthma potency in a quantitative way has not been validated. An additional challenge is gaining an understanding of the basis for such asthma responses with low dose chronic exposures to irritants that are non-allergens (e.g., LICEDS, low-intensity chronic exposure dysfunction syndrome). In absence of detailed knowledge of the mode of action (MOA), one might consider that, from a risk and safety assessment perspective, a pragmatic management approach would be to avoid substantial irritant responses to reduce concerns about asthma responses.

In summary, respiratory allergy is a well characterized toxicology endpoint, and benchmark approaches are used to overcome a lack of reliable, validated predictive tests. Non-allergic asthma, however, has little information, no predictive tests, and no acceptable risk assessment methods for overcoming these data gaps. There may be ways to achieve useful, defensible safety assessment decisions to protect against non-allergic sensitization and asthma, but additional research is needed. Careful consideration must be given to whether current benchmarks are sufficiently protective, especially in the context of non-allergic asthma.

#### Key Research Recommendations

- Identify the multiple mechanisms, allergic and non-allergic, that cause asthma and develop molecular screening approaches to differentiate among these mechanisms
- Develop a validated predictive assay specific to respiratory sensitization
- Translate current *in vivo*, *in vitro*, or *in silico* irritancy assays to asthma potency in a validated, quantitative method

### Assessing Exposure Contributions to Asthma Prevalence

Exposure science is the study of an organism's contact with physical, chemical, biological and other agents in the environment. Exposure assessments are important – in part - because they provide the underpinnings for many of the health protective limits and risk management strategies set by public health and environmental regulatory agencies. Environmental epidemiological research examines links between exposures and human health outcomes, while risk assessments use the results of this type of research (along with that from toxicological and other studies) to develop characterizations of risk associated with specific exposures. Human health risk assessment uses hazard information, dose-response assessment and exposure assessment to determine a risk characterization, or probability of

an adverse health outcome occurring in an exposed population. These fields require robust assessments of exposure. The extent of exposure can be determined using an aggregate approach or cumulative approach. Aggregate exposure assessments evaluate exposures to a single chemical across multiple routes and pathways. Cumulative exposure evaluates exposure to multiple chemicals from multiple routes. Cleaning-related exposures are complex (Maier et al., 2015) and not well-characterized by exposure measurements of single chemicals or single products. Single products may include multiple chemicals, and multiple products are used over the course of cleaning durations. Moreover, impacts of non-chemical stressors (e.g., biological aerosols) may also modify asthmatic responses (Ross et al., 2000; Bush et al., 2006; Dick et al., 2014). An additional limitation relates to the extremely minimal amount of data available on specific cleaning agent exposures, especially in the context of asthma outcomes (Vandenplas et al., 2013).

Further issues associated with attempting to measure or model human exposures to cleaning agents and associated respiratory outcomes relate to the different populations of interest. For example, occupational exposure assessment may need to include worker use of protective equipment and regular long-term exposures in contrast with the more sporadic exposures assumed for non-occupational users. Exposure assessments must also consider differences in behavior, surface area, breathing rates, mouthing activities, etc. between children and adults. Other important exposure considerations are frequency of use (e.g., once, daily, weekly, repeated or continuous), type of application (e.g., wipes, sprays, waxes, liquids, particulates, or vapors), and the route of exposure (e.g., inhalation, dermal, or oral).

The three main approaches for quantitatively estimating exposure are direct measurements, indirect measurements, and use of exposure reconstruction with biomonitoring (U.S. EPA, 2011, 2016). Direct (point of contact) measurements evaluate exposures in real time as they occur. This provides an exposure profile that yields information regarding temporal variability and peak exposures (e.g., Bello et al., 2010). Indirect estimation quantifies exposure by measuring or estimating the amount and frequency or duration of contact with a substance (U.S. EPA, 2011, 2016). This can be done using actual measurements, models or questionnaire data and combining this information with what is known about human activity to estimate exposure, as has been done with U.S. EPA's superfund risk assessment guidance (U.S. EPA, 2004, 2009). Exposure reconstruction/biomonitoring approaches use internal body measurements to estimate dose. Advantages of this approach are that aggregate and cumulative exposures are accounted for and uptake and accumulation are considered. The limitations include cost and burden on study participants. A further issue is that collection of human matrices is often conducted a single time in a study, making it unclear whether the measurement is capturing a peak or other representation of exposure. Another difficulty with interpreting exposure reconstruction methods is that the data are not source- or pathway-specific (U.S. EPA, 2011, 2016).

There are still too many gaps in understanding real-time exposure and, without continuous, real-time exposure monitoring, clinicians and researchers cannot truly understand the causal exposures needed to elicit respiratory effects. Although the technology is in place, direct, cumulative exposure measurements for quantitative, informative exposure estimation are costly and difficult to fund and implement. Researchers, therefore, frequently rely on clues



from epidemiological data and clinical information that may provide only a binary yes/no exposure characterization which is not translatable to dose. Improvements in, and increased use of sensor technology can advance our characterization of exposures. Ideally there could be individualized real-time exposure assessments in the future that can better capture exposure variability across a population and improve our understanding of individual exposure patterns and risks. Some of this technology is envisioned in the concept of the exposome (NRC, 2012).

As tools and methods for capturing improved exposure data are developed, care must be taken to ensure that high quality data are generated. For example, with the increased in use of biomonitoring as a measurement gold standard, researchers assumed the method would capture the totality of exposure across routes. We now know, however, that biomarker data are much more complicated in interpretation (i.e., some data need adjustment for additional factors such as urinary dilution) and susceptible to contamination from unexpected sources (i.e., leaching of plastic from storage containers into the samples; Blount et al., 2010). It is important that we validate the data we are collecting, and understand the quality of the data and its strengths and limitations (LaKind et al., 2014).

Exposure information is critical for dose-response assessment, yet it is difficult to obtain the kind of data needed on cleaning products due to resource and time restraints. Although it may be impossible to get funding for a perfect study, we have multiple tools available that ensure exposure data represent actual exposures at relevant times. High quality exposure information will aid in interpreting associations reported in epidemiological research and to support risk assessment for cleaning-related activities and products.

#### Key Research Recommendations

- Gather information on specific cleaning agent exposures, especially in the context of asthma outcomes, to aid development of a robust exposure assessment
- Address population variability which prevents generalization of measured or modeled human exposures
- Identify methods for reducing the prohibitive costs and volunteer participation needs for obtaining robust exposure data that incorporates temporality

### Setting Exposure Limits for Chemical Allergens

Chemical allergens are typically categorized by their molecular weight (i.e., high molecular weight (HMW) versus low molecular weight (LMW) allergens). HMW allergens (e.g., animal and plant proteins, latex, enzymes) are directly recognized by the immune system. LMW allergens (e.g., diisocyanates, organic anhydrides, some metals) are highly reactive and electrophilic, but are so small that they must bind with an endogenous protein to be recognized by the immune system. In 2016, approximately 6–7 hundred compounds have Threshold Limit Values (TLVs<sup>©</sup>) established by the American Conference of Governmental Industrial Hygienists (ACGIH<sup>©</sup>), despite the observation that many additional chemicals

can induce allergic sensitization. Many others are based on upper respiratory tract irritation, but the degree to which asthma responses were explicitly considered is unclear. The portfolio of health-based limits suggests significant uncertainty in relying on OELs for risk assessment and management of occupational asthma.

An understanding of basic biological mechanisms is needed so that risk assessors can appropriately select critical health endpoints for risk assessment. Ideally risk assessors could prevent sensitization, which would subsequently prevent elicitation. However, a portion of the population is already sensitized and it would be theoretically more health protective to prevent the elicitation of allergic responses in these individuals. Endpoints under consideration as the basis of risk assessment efforts and potentially capable of identifying persons who are in the process of being sensitized include: 1) lymphocyte proliferative responses, 2) changes in cytokine expression, 3) IgE antibodies, and 4) chemical challenges (e.g., patch test) (Cochrane et al., 2015). Because the biological response is complex (sensitization vs elicitation) and potency is difficult to estimate in a dose-response context, setting quantitative OELs has been limited primarily to chemicals with significant epidemiological data.

Exposure patterns are also important to consider for risk assessment, specifically temporal patterns. Exposure data are scarce for chemical allergens so it is unclear whether longer-term, short-term (peak) exposures, or both are the driver for sensitization. This information informs whether ceiling or TWA exposure limits should be used. For example, enzyme research was previously used to indicate that peak exposures were responsible for induction of sensitization (Basketter et al., 2012), which corresponds with our understanding of non-linear (threshold) dose-responses. However, current research indicates that reality is much more complicated; in an enzyme factory, the prevalence of workers with specific IgE levels indicating sensitization is approximately 10%, but only 1% or lower exhibit symptoms (Basketter et al., 2015), which suggests that a higher concentration is possibly needed to elicit a response rather than induce sensitization. There are clearly some aspects of the exposure-response relationship that we are failing to understand, however, key experiments cannot be conducted, due to a lack of reliable assays and ethical considerations. Even real-time exposure monitoring is not useful for answering this question unless biomarkers are also measured in real-time, otherwise response is not truly understood in the context of the exposure.

The impact of aggregate exposures (i.e., single exposures from multiple routes) also needs to be considered. For chemical allergens, there is a potential crossover between inhalation and dermal exposures, with the possibility that asthma may be induced by dermal exposure with elicitation occurring following a much lower inhalation dose. If dermal exposure potential is not considered, the application of derived exposure limits may not be sufficiently protective. Our inability to characterize the exposure-response relationship for both sensitization and allergic responses, including asthma, coupled with a poor understanding of cross-route mechanisms are the primary barriers to asthma risk assessment. In theory, if we could overcome these barriers we would be capable of assessing the risk for airway sensitization and immune-mediated asthma that also take other routes of exposures (e.g., dermal) into consideration.

Until a respiratory equivalent to the dermal LLNA or other accepted assays is developed and validated, quantitative risk assessments used to develop exposure recommendations applicable to occupational and non-occupational settings for chemical allergens are likely to be limited. The current barriers are 1) identifying respiratory allergens, 2) finding well-validated bioassays that provide dose-response information for multiple classes of chemicals, 3) differentiating between immune-mediated versus non-allergic asthma, 4) understanding short- and long-term and well as peak and background exposures, and 5) understanding the relative contributions of dermal and respiratory exposures on asthma response. The current science is not adequate to provide such data for most chemicals.

For chemical allergens with OELs, the exposure recommendations tend to be based on extensive human exposure data sets and are often based on sensitive subpopulations. In the absence of such quantitative health-based limits, qualitative hazard designations and risk management tools for exposure control are often used. Several sources of information provide useful guidance. The Globally Harmonized System for Labeling and Classification of Chemicals (GHS) provides qualitative sensitization designations for both respiratory and dermal sensitizers (UN, 2011). The National Institute for Occupational Safety and Health (NIOSH) and ACGIH also use similar designations to warn against the potential of dermal sensitization (NIOSH, 2009; ACGIH, 2016). Hazard-based systems can be included in hazard banding tools used to categorize available data into risk categories that drive control strategy selection (Arnone et al., 2015; Scheffers et al., 2016).

For risk assessment purposes, in the absence of chemical-specific dose-response information, a benchmarking based approach can be used to assess the need for tighter exposure control. Such approaches have been used successfully to manage respiratory sensitization in industries that handle enzymes (Basketter et al., 2015). Similar approaches might be applicable to chemical asthmagens such as diisocyanates and acid anhydrides. Use of these benchmarks should be done with caution, and a margin of error should be applied. If exposure levels are close to estimated exposure limits for occupational respiratory allergens, then further evaluation is needed. These approaches, when coupled with a comprehensive risk management approach (e.g., medical monitoring and surveillance, substitutions, engineered processes, etc.), can be used to mitigate risk when the available data is too limited or uncertain for a quantitative risk assessment.

#### Key Research Recommendations

- Understand the underlying biology of sensitization and the pathways that cause induction and elicitation of responses to support quantitative dose-response prediction
- Determine the impact of temporal and route-dependent exposure patterns on asthma induction and response elicitation
- Refine and communicate risk management tools based on hazard related information

## Conclusions on Asthma-Specific Risk and Characterization

This brief review paper has described key challenges and research opportunities that will enable us to continue to enhance processes for assessing potential risk related to asthma and handling of consumer product chemicals.

A number of ways to assess chemical exposures and asthma and related endpoints (i.e., sensitization, irritation, and inflammation potentials) were described. Routine clinical and validated toxicological tests as well as exposure assessment approaches are not currently sufficiently robust for predicting or determining causal dose-response relationships between exposures and asthma induction. There are multiple barriers to assigning causality and understanding risk in clinical or risk assessment settings, specifically a lack of diagnostic tools or tests that can encompass the multiple diverse etiologies of asthmatic responses and a lack of robust exposure measurements that capture exposure patterns over time.

The limitations in our understanding of asthma etiology and biological mechanisms, together with a lack of validated predictive assays for assessing asthma induction or elicitation, require the use of alternative hazard-based safety assessment methods to address chemical-induced asthma risks when making decisions proactively. A toolkit has been proposed for safety assessment to provide a health-protective screening method that utilizes weight-of-evidence principles for identifying chemicals that may increase asthma risk (Maier et al., 2015; Vincent et al., 2016). This systematic approach used in conjunction with an active risk management program provides a mechanism to limit potential asthma concerns, identify any concerns that arise, and ensures deployment of an approach to mitigate asthma-related risks.

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## Abbreviations

<b>AAAAI</b>	American Academy of Allergy Asthma & Immunology
<b>ACGIH</b>	American Conference of Governmental Industrial Hygienists
<b>ACI</b>	American Cleaning Institute
<b>ATSDR</b>	Agency for Toxic Substances and Disease Registry
<b>CDC</b>	Centers for Disease Control and Prevention
<b>ECVAM</b>	European Centre for the Validation of Alternative Methods
<b>HMW</b>	High Molecular Weight
<b>IgE</b>	Immunoglobulin E

<b>LICEDS</b>	Low-intensity chronic exposure dysfunction syndrome
<b>LLNA</b>	Local lymph node assay
<b>LMW</b>	low molecular weight
<b>MOA</b>	Mode of Action
<b>MRL</b>	Minimal Risk Level
<b>mRNA</b>	messenger ribonucleic acid
<b>NAS</b>	National Academy of Sciences
<b>NO</b>	Nitric oxide
<b>NRC</b>	National Research Council
<b>OEL</b>	Occupational Exposure Limit
<b>PEFR</b>	Peak expiratory flow rate
<b>RADS</b>	Reactive Airways Dysfunction Syndrome
<b>SAR</b>	Structural Activity Relationship
<b>SDS</b>	Safety Data Sheets
<b>SPT</b>	Skin Prick Test
<b>TLV<sup>©</sup></b>	Threshold Limit Value
<b>US EPA</b>	United States Environmental Protection Agency

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