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

1. 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 et al., 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., 2016). 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., 2016).

To address these challenges and identify current research needs regarding chemical-related asthma, the University of Cincinnati hosted a multipart webinar series from February 25th to October 21st, 2016 in conjunction with the American Cleaning Institute (ACI) to discuss the current state of science regarding chemical-

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Abbreviations

AAAAI	American Academy of Allergy Asthma & Immunology
ACGIH	American Conference of Governmental Industrial Hygienists
ACI	American Cleaning Institute
ATSDR	Agency for Toxic Substances and Disease Registry
CDC	Centers for Disease Control and Prevention
ECVAM	European Centre for the Validation of Alternative Methods
HMW	High Molecular Weight
IgE	Immunoglobulin E
LICEDS	Low-intensity chronic exposure dysfunction syndrome
LLNA	Local lymph node assay
LMW	low molecular weight
MOA	Mode of Action
MRL	Minimal Risk Level
mRNA	messenger ribonucleic acid
NAS	National Academy of Sciences
NO	Nitric oxide
NRC	National Research Council
OEL	Occupational Exposure Limit
PEFR	Peak expiratory flow rate
RADS	Reactive Airways Dysfunction Syndrome
SAR	Structural Activity Relationship
SDS	Safety Data Sheets
SPT	Skin Prick Test
TLV©	Threshold Limit Value
US EPA	United States Environmental Protection Agency

induced asthma. Key issues and research opportunities were described in the context of five presentations. These presentations are available online[1]. 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.

2. 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.

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., 2012a,b).

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,[2] 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

[1] http://www.med.uc.edu/eh/centers/rsc/education/webinars/asthma.

[2] An endotype is a subtype of disease or condition. Endotypes of asthma, for example, would include allergic and non-allergic asthma.