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Workshop Report

Integrating asthma hazard characterization methods for consumer products

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ABSTRACT

Despite extensive study, definitive conclusions regarding the relationship between asthma and consumer products remain elusive. Uncertainties reflect the multi-faceted nature of asthma (i.e., contributions of immunologic and non-immunologic mechanisms). Many substances used in consumer products are associated with occupational asthma or asthma-like syndromes. However, risk assessment methods do not adequately predict the potential for consumer product exposures to trigger asthma and related syndromes under lower-level end-user conditions. A decision tree system is required to characterize asthma and respiratory-related hazards associated with consumer products. A system can be built to incorporate the best features of existing guidance, frameworks, and models using a weight-of-evidence (WoE) approach. With this goal in mind, we have evaluated chemical hazard characterization methods for asthma and asthma-like responses. Despite the wealth of information available, current hazard characterization methods do not definitively identify whether a particular ingredient will cause or exacerbate asthma, asthma-like responses, or sensitization of the respiratory tract at lower levels associated with consumer product use. Effective use of hierarchical lines of evidence relies on consideration of the relevance and potency of assays, organization of assays by mode of action, and better assay validation. It is anticipated that the analysis of existing methods will support the development of a refined WoE approach.

1. Introduction

Approximately 23 million persons in the United States of America, including children, are currently affected by asthma (American Lung Association, 2010). Due, in part, to the increasing prevalence of this disease, the possible relationship between asthma and exposure to consumer products is gaining public attention and increasingly becoming a research priority. Several reviews have implied that the use of cleaning products in residential and commercial applications may potentially induce or trigger asthma (Jaakkola and Jaakkola, 2006; Nielsen et al., 2007; Quirce and Barranco, 2010; Zock, 2005; Zock et al., 2010; Rosenman et al., 2003). One response to this concern has been the publication of lists of substances that are known to, or are suspected of, causing asthma (NIH, 2012; AOEC, 2008).

The efforts to better understand and prevent asthma-inducing chemical exposures benefit public health due to the significant impact these exposures have on the large number of affected patients and potentially susceptible consumers. Asthma is generally defined as a chronic inflammatory disease of the lung (NHLBI, 2007), in which the airways narrow due to a combination of smooth muscle contraction, inflammatory responses, mucosal edema, and mucus in the lumen of the bronchi and bronchioles (Lemanske and Busse, 2010; NHLBI, 2007). It commonly presents with intermittent and reversible symptoms of cough, wheeze, dyspnea (shortness of breath), and/or chest tightness (AOEC, 2008) and with wheezing heard on chest exam, and reversible airflow obstruction found on pulmonary function tests. Asthma is a clinical diagnosis but, due to variation in symptom presentation and an absence of asthma-specific tests or biomarkers, it is often difficult to evaluate the link between specific exposures and

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asthma. Instead, it is commonly necessary to rely on studies that evaluate relationships between exposure and asthma-like symptoms (e.g., cough, wheeze, and dyspnea), although such studies are generally subject to a number of limitations.

Asthma is a complex disease with multiple potential mechanisms of toxicity for both induction and aggravation of pre-existing asthma (see Fig. 1). Asthma is associated with pulmonary inflammation, and the mechanism of action (MOA) often, but not always, involves adaptive immunity. This mechanism is generally associated with high- (HMW) or low-molecular-weight (LMW) chemicals that trigger immune responses that are associated with the appearance of IgE and IgE antibodies in the plasma. Occupational asthma to chemicals is sometimes associated with a specific IgE antibody. There has been some debate about the requirement for IgE antibody in the pathogenesis of occupational asthma to chemicals. However, it has been hypothesized that the association between occupational asthma and IgE antibody is somewhat closer than has been claimed previously (Kimber and Dearman, 2002). Nevertheless, with some chemicals, and in particular with the diisocyanates, it has often proven difficult to find IgE antibody in the serum of symptomatic patients and it might be that other immunological processes are relevant (Mapp et al., 1994, 2005; Walker et al., 1992). This potential pathway is unknown, and there is still uncertainty whether sensitization (i.e., hyperresponsiveness) of the respiratory tract can be achieved properly in the absence of IgE. Moreover, it is important ro recognize that some chemicals are associated with asthma responses in the absence of an immunological response. Thus, for instance, a single exposure to high concentrations of chemical irritants (e.g., hydrogen chloride) can cause an asthma-like condition called reactive airways dysfunction syndrome (RADS), which is non-immunologically mediated. RADS symptoms occur within hours of the initial exposure and may continue as non-specific bronchial hyper-responsiveness for extended durations (Bernstein, 1993). More recently, the hypothesis that low level, longer-term exposure to irritants may also induce asthma or an asthma-like syndrome called low-intensity chronic exposure dysfunction syndrome (LICEDS) is gaining acceptance (Baur et al., 2012). This complex mixture of biological mechanisms makes the prediction and characterization of causal relationships between exposure and asthma very challenging.

Thus, there is a need for further evaluation of environmental exposures, especially those linked to household environments and indoor air quality, and their possible association with asthma (ACI, 2012). To tackle this challenge in a systematic way, many organizations and agencies (e.g., European Union, World Health Organization, Association of Occupational and Environmental Clinics) have developed decision tools for assessing relationships between a specific chemical (or process) and asthma or asthma-like symptoms (e.g., sensitization of the respiratory tract). None of these methods is harmonized; each compiles and integrates diverse lines of evidence from human health effects investigations or toxicology studies in different ways. Moreover, the intended uses and data analysis criteria that support the numerous available hazard classification schemes vary widely, possibly due to a lack of accurate and specific diagnostic and prognostic tools for asthma. Currently, there are no fully validated animal, *in vitro*, or *in silico* models that have received widespread acceptance for identifying whether a specific chemical can cause asthma and/or sensitization of the respiratory tract.

From a risk and product safety assessment perspective, a methodology to predict likely causation of asthma would be highly useful, specifically a hazard characterization tool that is well-developed and communicated. Determining risks of asthma is difficult since exposure scenarios for consumer products vary greatly and dose–response estimation is complex due to uncertainties about the underlying biology. Nonetheless, a hazard characterization framework can be used to provide an informed approach for risk management and for protecting against and limiting exposure to chemicals thought to cause asthma. A significant challenge for developing a hazard characterization framework is creating a highly integrated approach that considers both immunologic and non-immunologic mechanisms of the induction of asthma, and can accommodate the various types of studies and alternative lines of evidence that might be available for such diverse toxicity mechanisms.

In this manuscript, we review and critically evaluate multiple hazard characterization frameworks and consider how *in vivo*, *in vitro*, and *in silico* models can be used for characterizing asthma hazards. The goal of this work is to identify the aspects of currently available systems that are most effective for evaluating asthma hazards, and/or effects that are related to the induction of asthma (including, importantly, sensitization of the respiratory tract), with the intent of building a novel, WoE-based hazard characterization tool for determining asthma-specific risk.

2. Methods

We identified multiple hazard characterization frameworks and guidelines that provide methods for evaluating and determining

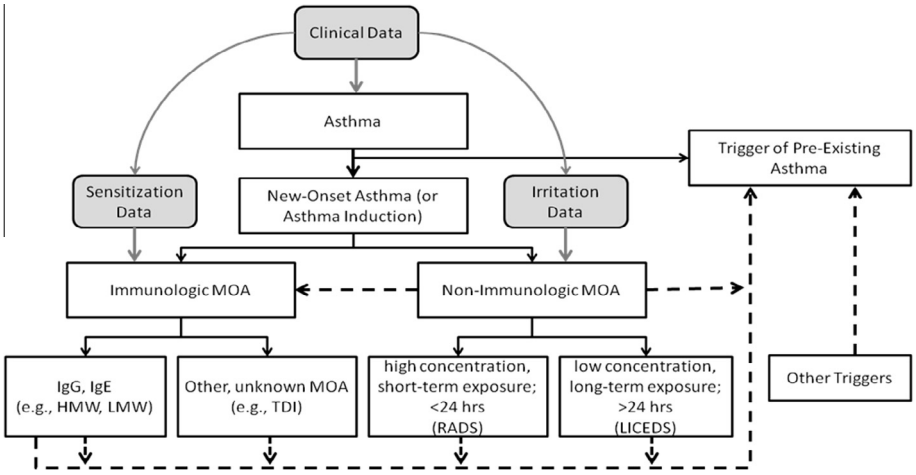

Fig. 1. Asthma is a complex disease with multiple modes of action (MOA) that may or may not act independently of each other. Dashed arrows indicate probable, but unknown relationships. Clinical data are important for the diagnosis of asthma, but can also be used to gather sensitization and irritation information. Sensitization data are primarily useful for determining the potential of a chemical to cause an immunologic reaction. Irritation data can be used to predict whether a non-immunologic MOA for asthma induction is plausible. Adapted from Bernstein et al. (2006).