Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

Workshop Report

Integrating asthma hazard characterization methods for consumer products

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A. Maier [a,*], M.J. Vincent [b], B. Gadagbui [b], J. Patterson [b], W. Beckett [c], P. Dalton [d], I. Kimber [e], M.J.K. Selgrade [f]

[a] University of Cincinnati, 3223 Eden Avenue, Cincinnati, OH 45267, United States
[b] Toxicology Excellence for Risk Assessment, 2300 Montana Avenue, Suite 409, Cincinnati, OH 45211, United States
[c] Mount Auburn Hospital and Harvard Medical School, 330 Mount Auburn St., Cambridge, MA 02138, United States
[d] Monell Chemical Senses Center, 3500 Market St., Philadelphia, PA 19104, United States
[e] University of Manchester, Faculty of Life Sciences, Manchester M13 9PT, UK
[f] ICF International, 2222 East NC-54 Hwy, Durham, NC 27713, United States

ARTICLE INFO

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.

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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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* Corresponding author. Fax: +1 513 542 7487.
  E-mail address: maierma@ucmail.uc.edu (A. Maier).

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
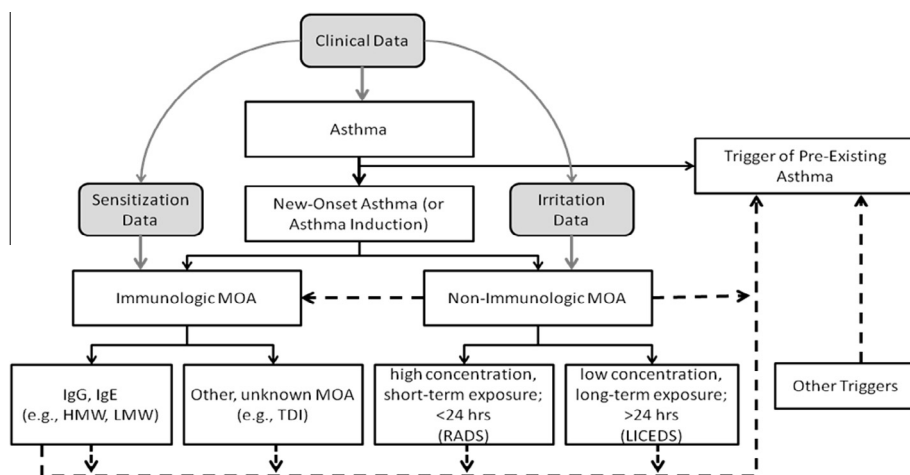

Fig. 1. Asthma is a complex disease with multiple modes of action (MOA) that may or may not act independently of each other. Dashed arrows indicate probable, but unknown relationships. Clinical data are important for the diagnosis of asthma, but can also be used to gather sensitization and irritation 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).

the potential of a chemical or product to elicit asthma, asthma-like symptoms, and/or respiratory sensitization. Our identification drew heavily from the NIH-sponsored report on asthma (NHLBI, 2007). Frameworks or guideline documents were excluded if they did not: (1) consider asthma or sensitization of the respiratory tract, (2) include multiple lines of evidence for evaluating the potential to cause or exacerbate asthma, and/or (3) provide a decision method for identifying chemicals that may increase the risk of asthma. By including only frameworks with a documented decision process or rationale, we have chosen not to include resources from agencies or organizations that provide only a list of suspect chemicals or substances. Many of these excluded resources were originally considered for this project because they were cited in the NIH-sponsored report on asthma and chemicals in consumer products (NHLBI, 2007). The included frameworks were evaluated by a panel of experts using a peer consultation approach.

3. Results

3.1. Defining asthma, and other related terms

The definition of asthma varies among organizations dealing with public health and asthma-related research (Table 1). Although there are different definitions for asthma, those proposed by each organization reflect their intended context and purpose as used by that organization (see Fig. 2). Thus, a single consensus definition is not needed because what is most important is to clarify how one defines asthma in the specific use context for each organization. However, for risk and safety assessment tool development, defining a common language to describe, recognize, and assess particular health effects would drastically reduce confusion and allow for accurate and appropriate evaluation of hazard.

In addition to the lack of harmonization around the definition of asthma, there are multiple other key terms related to asthma that have many different implications and can cause confusion among the scientific, medical, and lay communities (see Table 2). For the purposes of this manuscript, it is important to note that sensitization of the respiratory tract is not equivalent to asthma, although it shares some symptoms and is likely related to asthma; asthma may be one result of allergic sensitization of the respiratory tract, but sensitization of the respiratory tract does not necessarily result in asthma (i.e., about 40% of individuals with allergic rhinitis also have asthma, and about 94% of patients with allergic asthma have allergic rhinitis; Bergeron and Hamid, 2005). Overall, it is recommended that precise language be used and terms be clearly defined for each application, while noting the value of flexibility of needs for communicating to different audiences.

3.2. Hazard characterization frameworks for evaluating asthma

A concise summary of findings from the analysis of frameworks for evaluating asthma or asthma-like symptoms (e.g., sensitization of the respiratory tract) is shown in Table 3; this highlights features of the frameworks that are used for characterizing hazard. Table 4 summarizes the endpoints that are evaluated within each framework. Each framework is described in more detail in the following sections.

3.3. AOEC (Association of Occupational and Environmental Clinics)

The AOEC Exposure Code List is a list of chemicals with potential to cause and/or exacerbate asthma; it is intended to identify substances that may cause *de novo* cases of asthma, not just response elicitation, based on both the sensitizing and non-sensitizing, or irritant (e.g., RADS), causes of asthma (Hunting and McDonald, 1995). Of the large number of substances identified, only approximately 60 substances were reviewed using the specific criteria established by AOEC (2008). The AOEC method uses a WoE approach to determine possible causality; one positive response is not sufficient to associate a product or chemical with asthma. However, it is limited by its focus on occupational exposures. Many of the chemicals included in its analyses and lists are also used within the home and/or by the general public. Due to differences in exposure scenarios, workers may exhibit asthmatic responses in relationship to occupational exposures of chemicals that may not be relevant exposures for consumers. Moreover, the approach does not take animal toxicology data into consideration; instead, the AOEC approach was intended for patient diagnosis and relies on human effects information. The absence of animal data use limits the number of substances that can meet the AOEC criteria since most chemicals lack clinical or epidemiology studies.

3.4. TERA (Toxicology Excellence for Risk Assessment) (2014)

This framework considers three endpoints: asthma, respiratory tract irritation, and sensitization of the respiratory tract. Each endpoint is assigned a category based on the likelihood that a chemical causes that effect, which in turn is based on the WoE available. The purpose of these categories is to prioritize chemicals by their likelihood to potentially cause and/or exacerbate asthma recognizing the possibility that multiple toxic mechanisms might be relevant. Data from standard, non-respiratory irritation protocols (e.g., skin, ocular, and *in vitro*) are also evaluated. Respiratory sensitization is categorized as either present or absent in this WoE approach because there is no current consensus method for determining relative sensitizing potency. This approach also includes a data hierarchy that accounts for test species, exposure route, study quality, and endpoint relevance.

Depending on the outcome of the WoE evaluations for each individual endpoint, a decision matrix is used to categorize the likelihood that a chemical will cause and/or exacerbate asthma.

3.5. World health organization/international programme on chemical safety

The WHO/IPCS approach provides guidelines for assessing immune suppression, immunostimulation, sensitization and allergic response, and autoimmunity and autoimmune disease. This guidance recommends use of a WoE approach for determining respiratory and skin sensitization and allergy risk (shown in Figures. 6.2 A and B of IPCS, 2012); this approach requires the presence of a dose–response relationship and biological plausibility to determine causality. The framework is not, however, specific to asthma. Human data are weighted more heavily than data from animal studies, with clinical studies having a greater weight than observational studies (e.g., cohort, case-control, and cross-sectional studies); case-reports are considered supporting evidence.

3.6. Selgrade et al. (2012)

Selgrade et al. (2012) developed guidance for determining the sensitizing potential of chemicals based on EC Regulation No. 1272/2008 Classification, Labeling, and Packaging of Substances; REACH guidance from the European Chemicals Agency; and the United Nations Globally Harmonized System (GHS). Separate decision trees evaluate potential skin and respiratory sensitizers and for individual exposures and mixtures (Figs. 1, 2 and 4, in Selgrade et al., 2012). The guidance is specific for sensitization, and does not address asthma that is not associated with immune or allergic responses. Only key human studies can be used to

Table 1
Definitions of asthma gathered from multiple organizations.

Group	Definition	Website
The Association of Occupational & Environmental Clinics (AOEC, 2008)	Asthma is a condition of variable airflow obstruction, commonly presenting with symptoms of cough, wheeze, dyspnea, or chest tightness. In most cases wheezing is heard in the chest during active episodes, but wheezing may resolve completely between episodes. Asthma is a clinical diagnosis since there is no single test, biomarker, or gene specific for asthma	http://www.aoec.org
American Thoracic Society (ATS, 2010)	Asthma is a common but complex disease of the pulmonary airways (trachea, bronchi, and bronchioles) that is characterized by difficulties getting air in and out of the lungs (variable airflow obstruction), environmental triggers causing breathlessness (airway hyperresponsiveness), and cellular inflammation	http://www.thoracic.org/education/breathing-in-america/resources/chapter-3-asthma.pdf
British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) (2009)	The diagnosis of asthma is a clinical one; there is no standardized definition of the type, severity, or frequency of symptoms, nor of the findings on investigation. The absence of a gold standard definition means that it is not possible to make clear evidence based recommendations on how to make a diagnosis of asthma. Central to all definitions is the presence of symptoms (more than one of wheeze, breathlessness, chest tightness, cough) and of variable airflow obstruction. More recent descriptions of asthma in children and in adults have included airway hyper-responsiveness and airway inflammation as components of the disease. How these features relate to each other, how they are best measured, and how they contribute to the clinical manifestations of asthma, remains unclear. Although there are many shared features in the diagnosis of asthma in children and in adults, there are also important differences. The differential diagnosis, the natural history of wheezing illnesses, the ability to perform certain investigations and their diagnostic value, are all influenced by age. Asthma in children causes recurrent respiratory symptoms of: wheezing, cough, difficulty breathing, and chest tightness. Clinical features in adults that influence the probability that episodic respiratory symptoms are due to asthma include: (1) More than one of the following symptoms: wheeze, breathlessness, chest tightness and cough, particularly if: symptoms worse at night and in the early morning; symptoms in response to exercise, allergen exposure and cold air; and symptoms after taking aspirin or beta blockers; (2) History of atopic disorder; (3) Family history of asthma and/or atopic disorder; (4) Widespread wheeze heard on auscultation of the chest; (5) Otherwise unexplained low FEV_1 or PEF (historical or serial readings); and (6) f Otherwise unexplained peripheral blood eosinophilia	http://www.brit-thoracic.org.uk/Portals/0/Guidelines/AsthmaGuidelines/sign101%20revised%20June%2009.pdf
US Centers for Disease Control and Prevention	Asthma is a chronic disease that affects the airways in the lungs. During an asthma attack, airways become inflamed, making it hard to breathe. Asthma attacks can be mild, moderate, or serious — and even life threatening	http://www.cdc.gov/asthma/impacts_nation/AsthmaFactSheet.pdf
US Environmental Protection Agency (2010)	Asthma is a chronic inflammatory disorder of the airways, designated as ICD9-CM-493 in the International Classification of Diseases (ICD-9). Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and the chronic nature of the disease. Airflow limitation and the narrowing of airways can be manifested as acute bronchoconstriction, airway edema, mucus plug formation, and remodeling of the airway walls. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Asthma patients are usually categorized as having mild persistent, mild intermittent, moderate persistent, or severe persistent asthma, based on symptoms and the results of diagnostic tests	http://www.epa.gov/opptintr/coi/pubs/iv_2.pdf
European Union (EU) (2013)	The EU defines asthma as an allergic reaction to substances commonly breathed in through the air, such as animal dander, pollen, or dust mite and cockroach waste products. The catch-all name for these substances, allergens, refers to anything that provokes an allergic reaction. Some people have a genetic predisposition to react to certain allergens. When these people breathe in the allergen, the immune system goes into high gear as if fighting off a harmful parasite. The system produces a molecule called immunoglobulin E (IgE), one of a class of defensive molecules termed antibodies. The IgE antibody is central to the allergic reaction. For example, it causes mast cells, a type of specialized defensive cell, to release chemical "weapons" into the airways. The airways then become inflamed and constricted, leading to coughing, wheezing, and difficulty breathing – an asthma attack (definition provided by the US National Institute of Allergy and Infectious Diseases)	http://ec.europa.eu/health/major_chronic_diseases/diseases/asthma/index_en.htm
Mayo Clinic Staff (2012)	Asthma is a condition in which your airways narrow and swell and produce extra mucus. This can make breathing difficult and trigger coughing, wheezing and shortness of breath. For some people, asthma is a minor nuisance. For others, it can be a major problem that interferes with daily activities and may lead to a life-threatening asthma attack. Asthma can't be cured, but its symptoms can be controlled. Because asthma often changes over time, it's important that you work with your doctor to track your signs and symptoms and adjust treatment as needed	http://www.mayoclinic.com/health/asthma/DS00021

Table 1 (continued)

Group	Definition	Website
National Library of Medicine (2013)	Asthma is a disorder that causes the airways of the lungs to swell and narrow, leading to wheezing, shortness of breath, chest tightness, and coughing. Asthma is caused by inflammation in the airways. When an asthma attack occurs, the muscles surrounding the airways become tight and the lining of the air passages swells. This reduces the amount of air that can pass by. In sensitive people, asthma symptoms can be triggered by breathing in allergy-causing substances (called allergens or triggers)	http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001196/
Selgrade et al. (2006)	"Dealing with asthma means many different things to different people. To the patient, it means episodic wheezing, coughing, and/or shortness of breath. To the parent, it may mean sleepless nights or missed workdays because of the presence of symptoms in their child. To the clinician, asthma is a complex condition that presents as multiple different phenotypes that can vary with age, gender, and race. Moreover, the frequency and severity of asthma "attacks" may have both inter- and intrapatient variability and can be triggered by diverse stimuli including aeroallergen exposure, viral infections, exercise, irritant exposure, certain medications (e.g., aspirin), and gastroesophageal reflux. To the pathologist, asthma is characterized by airway inflammation and mucus hypersecretion. To the physiologist, airflow obstruction and airway hyperresponsiveness are most relevant"	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1440790/pdf/ehp0114-000615.pdf
National Heart Lung and Blood Institute (2007)	Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment	http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf
World Health Organization (2013)	Asthma attacks all age groups but often starts in childhood. It is a disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. In an individual, they may occur from hour to hour and day to day. This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. In an attack, the lining of the passages swell causing the airways to narrow and reducing the flow of air in and out of the lungs	http://www.who.int/respiratory/asthma/definition/en/

classify a substance as a respiratory sensitizer without building a WoE argument. The guidance describes how to determine whether human data are of sufficient quality to support classification as a sensitizer. If good quality human data are not available, weaker human data, data from animal studies, and structure activity relationships may all be used to build a WoE assessment.

3.6. Globally harmonized system

GHS is used and incorporated into the hazard characterization approaches of many international organizations and regulatory agencies. This system provides a clear approach for determining both respiratory sensitization and irritation, relying heavily on a WoE approach. Data types are clearly prioritized and there are requirements for meeting a minimum standard for determining causality. Immunological mechanisms do not have to be evident in order to assign a respiratory sensitizer classification. However, this approach does not assess asthma, specifically, and instead allows investigators to make an assumption on the potential of a substance to cause and/or exacerbate asthma based on respiratory sensitization and irritation alone.

3.7. Critical review of the multiple frameworks on asthma hazard characterization

A summary of the advantages and disadvantages from each framework is shown in Table 5. There is no single, currently-existing framework that can be directly adopted or readily modified for effectively characterizing the asthma hazard of substances with an unknown potential for causing asthma. Rather, different features of multiple frameworks could be combined to create an improved approach with additional refinement.

4. Discussion

We analyzed the landscape of methods used to assess and communicate potential hazards related to asthma responses and chemical exposures. The analysis centered on a critical examination of existing hazard characterization methods. Although none of the methods cover all aspects of asthma response, highlighting elements of existing methods clarifies the intent of the individual methods and enables informed safety assessment decisions. One clear finding from our analysis is that a highly-predictive model for asthma hazard characterization needs to be nimble to account for the complexities of the asthma response. Key features of a robust approach for evaluating asthma safety include: a clear description of the scope and purpose of the assessment, consideration of exposure (extent, duration, and pertinent routes) and relevance to consumer product scenarios, a nuanced approach to the mode of action testing for asthma induction and elicitation (e.g., allergic versus non-allergic asthma), and a well-documented WoE process to organize data in a hierarchical manner (Fig. 3).

Two key elements of this overall framework that are particularly complex for hazard characterization of asthma are defining the mode of action (MOA) (because of the biological complexity of asthma) and developing a rigorous WoE approach (because of limitations in data, assays, and predictive models).

The complication of an MOA-centered approach is of special importance for asthma, as no single assay can identify with certainty the potential of a chemical to induce asthma or verify the original cause of asthma once it has developed. Even if we limit a hazard characterization method to a specific MOA (e.g., sensitization of the respiratory tract), it is difficult to identify the defining characteristics of the chemicals that cause symptoms related to asthma. To the degree that the MOA hypothesis can be narrowed, the overall WoE can reflect this prior knowledge, and give greater
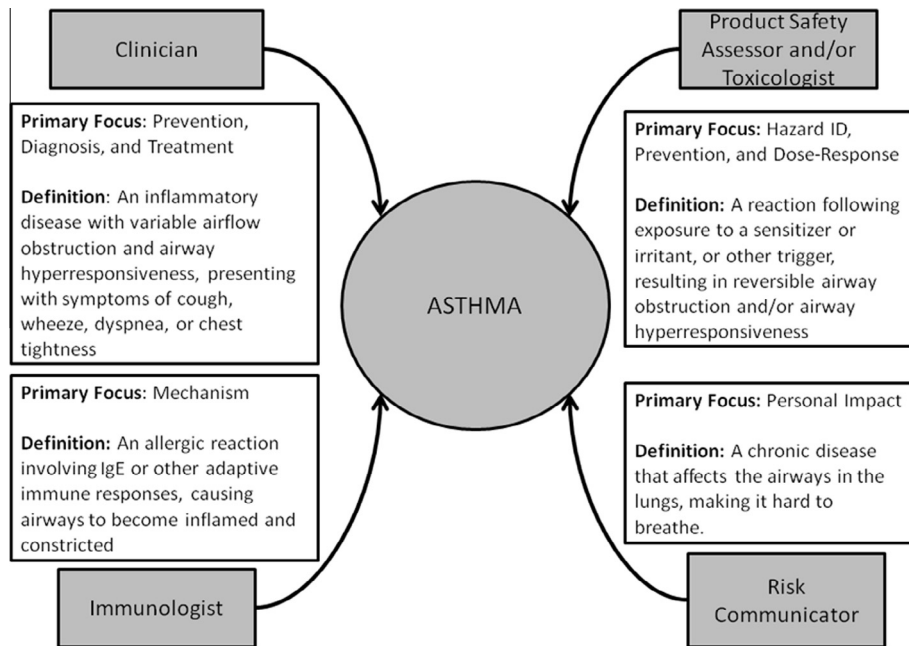
Fig. 2. The definition of asthma varies across disciplines of public health. Although each of these definitions is accurate within a narrow context, they can cause confusion as they are not comprehensive to all stakeholders and do not describe the full range of characteristics that define "asthma". It is important to clearly define what is meant by the term "asthma", as well as other key terms, when developing a hazard characterization tool.

Table 2
A list of terms related to asthma that are not clearly or consistently defined and may lead to confusion in the evaluation and hazard identification of exposures that may cause asthma.

Term	Reasons why a harmonized and/or clarified definition is needed
Irritant-induced asthma (IIA)	This term is often used to describe non-sensitizing causes of asthma (e.g., RADS). However, there may be multiple modes of action for non-immunologically based asthma. An alternative definition might be the development of asthma via mechanisms other than allergic sensitization
Reactive airways dysfunction syndrome (RADS)	This term does not fit the classic definition of asthma, which includes chronic inflammation. It is instead an irritant-induced syndrome caused by a single heavy irritant inhalation exposure. Additionally, RADS may not result in chronic disease and lung remodeling
Asthma induction	This term is often used to identify the initial sensitizing phase of asthma but can be misconstrued to represent the trigger, or induction, of an asthma attack
Asthma elicitation	This term often is used to describe the events that lead to the onset of asthma symptoms in a person with pre-existing asthma
Asthma trigger	This term is non-specific, but implies exacerbation of pre-existing disease following exposure to another stressor (that may not be chemical in nature)
Asthmagen	This term is overly vague and cannot capture whether an exposure causes new-onset asthma or triggers an asthmatic response in a person with pre-existing asthma. When used, the reader should closely consider the context
Respiratory sensitizer	The term respiratory sensitizer is ambiguous and implies that a substance is only acting via the respiratory tract. Some dermal exposures may also lead to sensitization of the respiratory tract
Asthmagenic potential	This term indicates the potential to induce asthma by any mechanism, but this is not very informative. As with the term "asthmagen", it is not clear whether this refers to the potential for inducing asthma or triggering pre-existing disease

Table 3
Assessment of common features from weight-of-evidence frameworks for evaluating asthma.

	WoE approach?[a]	Varying levels of certainty about causality?[b]	Hierarchy of evidence[c]	All lines of evidence[d]	Hazard for asthma induction[e]	Hazard for asthma elicitation[f]	Mixtures considered[g]
AOEC (2008)	Yes	No	Yes	No	Yes	No	No
TERA (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No
WHO/IPCS (IPCS 2012)	Yes	Yes	Yes	Yes	Yes	Yes	No
Selgrade et al. 2012	Yes	No	Yes	Yes	No	No	Yes
EU HSE/GHS (2007)	Yes	Yes	Yes	Yes	Yes	No	Yes

[a] Does the framework use a WoE approach?
[b] Does the framework allow the investigator to assign a level of certainty to their toxicological conclusions about causality, based on pre-determined categories?
[c] Does the framework clearly state how to prioritize evidence (e.g., should human evidence be weighed more heavily than animal)?
[d] Does the framework include all lines of evidence (i.e., in vivo, in vitro, in silico) in its approach?
[e] Does the framework provide guidance for identifying exposures that may induce asthma?
[f] Does the framework provide guidance for identifying exposures that may elicit an asthmatic response?
[g] Does the framework provide guidance for evaluating mixtures and/or multiple exposures?

Table 4
A comparison of the designations that can be assigned following use of weight-of-evidence frameworks from multiple organizations.

	New-Onset Asthma[a]	Asthma Exacerbation[b]	Asthma (Unspec.)[c]	Skin Sensitization[d]	Respiratory Sensitization[e]	Irritation[f]
AOEC (2008)	Yes	No	–	No	Yes	Yes
TERA (2014)	No	No	Yes	Yes	Yes	Yes
WHO/IPCS (IPCS 2012)	Yes	Yes	Yes	Yes	Yes	No
Selgrade et al. 2012	No	No	No	Yes	Yes	No
EU HSE/GHS (2007)	Yes	No	–	Yes	Yes	Yes

[a] Does the framework provide guidance for determining if an exposure causes new-onset asthma?
[b] Does the framework provide guidance for determining if an exposure exacerbates pre-existing asthma?
[c] Does the framework provide guidance for determining if an exposure is related to asthma, but does not differentiate between induction and exacerbation?
[d] Does the framework provide guidance for determining if an exposure causes skin sensitization?
[e] Does the framework provide guidance for determining if an exposure causes respiratory sensitization?
[f] Does the framework provide guidance for determining if an exposure causes irritation (skin or respiratory)?

Table 5
Summary of the Advantages and Disadvantages of Frameworks for Determining Relationships of a Chemical Exposure with Asthma.

Organization	Advantages	Disadvantages
AOEC (2008)	• Uses a WoE 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
TERA (2014)	• 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 skin sensitization and irritation data in the absence of respiratory information which allows for assessment of a wider array of exposures • Allows investigators to make characterizations based on multiple levels of certainty	• Use of dermal sensitization and irritation data may lead to false associations, but is ultimately a conservative approach • Does not include structural-activity information
WHO/IPCS (IPCS 2012)	• Clearly defines an approach for determining 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 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 WoE	• Does not provide a framework for assessing asthma, just the surrogates
EU HSE/GHS (2007)	• Has minimum recommendations for epidemiological data quality • Clearly defines an approach for determining respiratory sensitization, including prioritization of data types and tests	• Does not provide a framework for assessing asthma, just the surrogates such as sensitization

importance to lines of evidence concordant with the most likely MOA. However, heterogeneity of the many biological mechanisms (Fig. 1) increases the difficulty of identifying key events in the MOA and limits validation of a single predictive test or test battery for asthma. The end result is a heavy reliance on the WoE approach using diverse data inputs for hazard characterization.

The application of WoE approaches to consumer product exposures and asthma is often heavily subjective, may not be transparent (i.e., decision rules are not clear), and may yield very different results depending on the organization and/or individual doing the assessment. To address these limitations, more formalized and systematic approaches for determining WoE (e.g., hypothesis-based weight of evidence methods) are gaining popularity for communicating uncertainties or gaps in the available data and organizing and evaluating information (Linkov et al., 2009; Rhomberg et al., 2013).

One particular complication in applying the WoE approach for asthma hazard characterization is the need to make decisions when faced with uncertainty regarding the predictive power of the types of evidence (assays) that are most commonly available. The use of dermal sensitization assays is one complication for predicting the potential for sensitization of the respiratory tract. Although some skin sensitizers have been shown to also cause respiratory sensitization (Arts et al., 2008) and the induction phase of allergy is generally similar for both types of allergic response (Arts and Kuper, 2007), this is not true for all low molecular weight sensitizers or high molecular weight sensitizers or allergens that cannot pass through the skin (Andersson et al., 2011). Identification of irritant

potential for prediction of asthma faces similar data challenges as for sensitization. These include evaluating multiple complex mechanisms, extrapolation across routes and test species, and interpreting human response data (Doty et al., 2004; Dalton, 2001). Due to these complications, significant assay development for evaluation of relationships between chemical exposures and asthma is ongoing using metrics such as genomics (Vandebriel and van Loveren, 2010), fractional nitric oxide in exhaled breath (Dweik et al., 2011; Barath et al., 2013; Donohue and Jain, 2013), ovalbumin challenge models (Caceres et al., 2009), and bronchoalveolar lavage (BAL) fluid evaluation and peptide release, as well as neurokinins of inflammatory release, and contractility of the airways in precision cut lung slices (Sanderson, 2011; Switalla et al., 2010).

A systematic process to decide which of the various laboratory animal models/assays to use in supporting conclusions about asthma hazard characterization systems should be employed. Some key considerations in rating the utility of an assay include: (1) recognition by a consensus body as predictive of asthma; (2) empirical validation of the model/assay; (3) direct or indirect measure of respiratory sensitization or irritation; (4) evaluation of responses in the model or assay that are specific to asthma, respiration sensitization, or irritation; (5) inclusion of multiple measures (to test internal consistency); and (6) direct assessment of functional responses or their precursors. Developing a weighted score applied to each assay, in the context of asthma, can standardize a WoE approach and make documentation more transparent. Instead of scoring individual tests, it may be more useful to
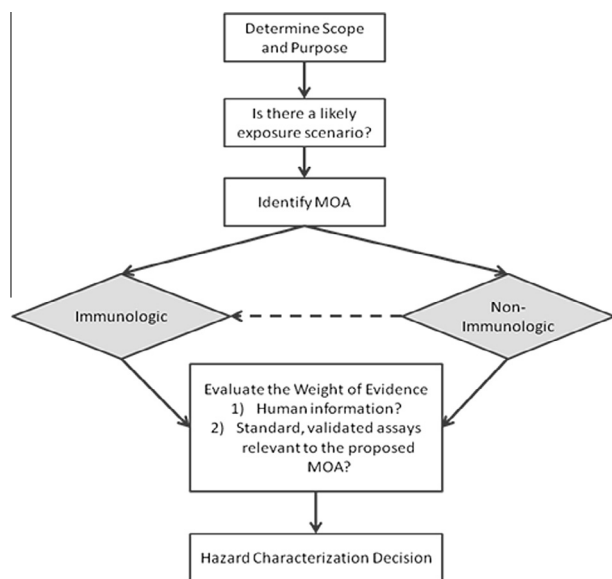
Fig. 3. A brief overview of hazard characterization for asthma and chemical exposures, which considers the relevance of the exposure scenario, toxicity mode of action (MOA), and weight of evidence (WoE).

sort the assays into different groups by the type of information they provide, and then weigh how the results by assay category provide information in the broader context of asthma.

Although the WoE approaches employed for decisions regarding asthma have not yet been harmonized, opportunities for better alignment of WoE techniques include increased use of MOA and quantitative tools for evidence-based decision making. For example:

- Current systems often rely on "lines of evidence" defined by a hierarchical approach with inferred relevance to human responses organized by assay system type (*in vivo* is better than *in vitro*, which is better than *in silico*). Each assay should be considered relative to its predictivity. However, many of these assays do not have specificity or sensitivity information specific to asthma, so predictivity may be impossible to ascertain.
- Organization of families of assays along mode of action lines may be more informative than other categorization systems. Such an approach recognizes that conclusions about the primary cause of a clinical response will likely reflect an integration of multiple assays that test different aspects of the same MOA pathway. Use of mode of action principles also aids in defining the scope of the asthma assessment (e.g., immunologic versus non-immunological; new-onset versus response elicitation).
- Current systems often rely on qualitative considerations to support a conclusion. Such decision-making would be strengthened with access to assay validation data (e.g., predictivity measures and data on sensitivity and selectivity) and decision support systems that begin to provide rules that allow for reproducible WoE decisions. Even with such systems, clear documentation of the rationale for decisions would be required.

5. Conclusion

The analysis of hazard characterization methods in this manuscript provides a guide for the assessment of potential asthma hazards associated with exposures to chemicals present in consumer products. Placing existing methods in the context of their intended uses and documenting their inherent strengths and limitations

provides the input to support decision-making and decreases the potential for misinterpretation of the outputs of existing hazard classification schemes. The analysis also serves as a base for the development of new user-specific hazard and risk characterization approaches that integrate elements of various existing systems to meet the needs of specific safety assessment applications. This work is intended as one step in the ongoing goal to develop improved methods for proactive assessment strategies for consumer exposure scenarios.

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