Characterizing Potential Chemical Asthma Hazards: A Weight of Evidence Method and Case Study for Acetic Acid

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Vincent. M.J.[1], Parker. A.[1], Gadagbui. B.[1], Krishan. M.[2], Maier. A.[2]

1. Toxicology Excellence for Risk Assessment
2300 Montana Avenue, Suite 409
Cincinnati, Ohio 45211
t. 513-542- RISK (7475) X23
f. 513-542-7487
www.TERA.org
Email: Vincent@tera.org

2. University of Cincinnati, 3223 Eden Ave, Cincinnati, OH 45267

Abstract

The relationship between asthma and consumer products is uncertain, but many substances used in consumer products are associated with occupational asthma or asthma-like syndromes. Due to multiple factors, including multiple possible etiologies (e.g., IgE-mediated asthma and RADS) and the absence of reliable asthma-specific animal models, it is difficult to adequately characterize the asthma hazard for each of these individual substances. A weight of evidence (WoE) approach using diverse lines of evidence, including evidence of asthma and respiratory and dermal sensitization and irritation information in both humans and animals, allows for qualitative categorization of the potential for asthma induction. Although dermal sensitization is not completely predictive of respiratory sensitization, it can provide valuable information for data-poor chemicals. The proposed WoE method organizes these data lines through a systematic, hierarchical framework. Acetic acid is used as a case study to test this framework. Overall, this methodology integrates human and animal data to establish a causal inference. The goal of this work is to provide a method for prioritizing chemicals as a first step for quantitative and scenario-based safety assessments.

Introduction

The prevalence of asthma in the United States, and worldwide, is continually increasing. Approximately 8% of all persons (18.9 million) and 9.5% of children (7.1 million) in the U.S. have been diagnosed with asthma (CDC, 2013). Asthma is a chronic inflammatory disease of the lung in which the airways narrow due to a combination of smooth muscle spasms, inflammatory responses, mucosal edema, and mucus in the lumen of the bronchi and bronchioles (Djukanovic et al., 1996; Haley et al., 1998; Hogg, 1997; Howarth, 1998; Vignola et al., 1998). It commonly presents with symptoms of cough, wheeze, dyspnea, or chest tightness (AOEC, 2008). Although most forms of asthma are inflammation-based, some low-molecular-weight (LMW) chemicals (e.g., toluene diisocyanate) may cause immunoglobin E (IgE) independent occupational asthma (Mapp et al., 1994; Walker et al., 1992). In addition, single exposures to high concentrations of chemical irritants (e.g., hydrogen chloride) can cause an asthma-like condition called reactive airways dysfunction syndrome (RADS) with symptoms occurring within hours of the initial exposure and non-specific bronchial hyper-responsiveness persisting for extended durations (Bernstein, 1993). In addition, exposure to such irritants may be a trigger for respiratory symptoms in individuals with pre-existing asthma.

The use of cleaning products in residential and commercial applications is implicated as a potential inducer of asthma or as a trigger for respiratory symptoms in asthmatics, which may contribute to the observed increase in morbidity. Numerous epidemiological studies have linked the use of cleaning products or work in cleaning occupations to an increased prevalence of physician-diagnosed asthma (Andersson et al., 2003; Arif et al., 2009; Arif et al., 2003; Mirabelli et al., 2007; Zock et al., 2007) and of asthma-like symptoms (Arif et al., 2009; Arif et al., 2003; Bernstein et al., 2009; Fatima-Macaira et al., 2007; Medina-Ramon et al., 2003; Medina-Ramon et al., 2006; Medina-Ramon et al., 2005; Nielsen and Bach, 1999; Zock et al., 2002). Despite these findings, current evidence is not sufficient to determine a clear relationship between specific cleaning product exposures and the development of asthma. In epidemiology studies, asthma-like symptoms can be associated with various other respiratory disorders (e.g., bronchitis) or common household exposures (e.g., pet allergens, molds) and ambient pollutants (e.g., ozone, nitrogen oxides, formaldehyde). Bronchoprovocation can be used to identify the insulting chemical in the clinical setting, but absent such studies linking specific chemical exposures to individual occurrences of asthma is very challenging.

In general, toxicology studies are useful to assess the causal role of individual ingredients in the development of adverse effects since the exposures are defined. Although there are multiple animal models for asthma, none can reliably replicate the complexity of the human disease in a single model (Bice et al., 2000; Kucharewicz et al., 2008; Zosky and Sly, 2007). An ideal model would need to examine IgE-mediated antigen sensitivity and the resulting bronchoconstriction, airway resistance, chronic airway inflammation with eosinophilia and Th2 cytokines, late-phase bronchoconstriction, persistent airway obstruction, nonspecific hyper-responsiveness, excessive

mucus accumulation, decreased mucociliary clearance, mesenchymal tissue remodeling, and smooth-muscle hyperplasia (Bice et al., 2000). Multiple species-specific complications limit the utility of most currently-available animal models for asthma (insert citations from highlighted part).

Assessing potential asthma hazards for proposed product ingredients or evaluating claims of casual relationships with recent exposures requires integration of multiple lines of evidence. Methods are not harmonized for integrating such disparate information sources when answering hazard and risk assessment questions (Good 1991, Linkov 2009). However, a weight-of-evidence (WoE) approach is preferred for synthesizing heterogeneous information in a structured manner to support scientific judgments and is fundamental to hazard characterization (NRC 2009; IPCS 2001). Several WoE frameworks have been developed for asthma or sensitization of the respiratory tract (AOEC 2008; GHS, 2007; Selgrade et al. (2012; WHO/ICPS, 2012). Each of these hazard characterization frameworks provides value for its intended purpose, but the methods also have significant limitations in evaluating the WoE for asthma (Maier et al. 2014). The AOEC (2008) framework focuses on identifying new-onset cases of asthma, but is limited to occupational exposures and does not consider toxicological data in its approach. The WHO/IPCS (2012), GHS (2007), and Selgrade et al. (2012) frameworks provide criteria for indentifying respiratory sensitizers but do not address asthma specifically.

In light of the limitations of current hazard characterization frameworks, we have developed a WoE approach to characterize, on a qualitative basis, the potential for specific cleaning product ingredients to either induce asthma or trigger asthma-like responses through sensitization or irritation-induced mechanisms. The procedure uses diverse lines of evidence, specifically human evidence of asthma and human and animal evidence of sensitization and irritation to establish a weight-of-evidence descriptor. In the absence of adequate respiratory information, skin irritation or sensitization data are used as a surrogate for predicting the severity of respiratory irritation or sensitization. The methodology is applied to a case study on acetic acid to test its robustness, accuracy, and repeatability.

Proposed Weight of Evidence Methodology

The steps in the overall WoE process are shown in Figure 1. Because no validated animal models for asthma currently exist, evidence of respiratory sensitization or irritation in animals are evaluated as a potential precursor or inducer of asthma. The analysis includes assumptions about the degree one can infer likely respiratory tract responses from assays that involve exposures by routes other than inhalation. However, since data following inhalation are often not available, the method accommodates the use of data from other routes. The use of surrogate health endpoints for asthma and data for routes other than inhalation are reflected in the data hierarchies applied in the WoE process.
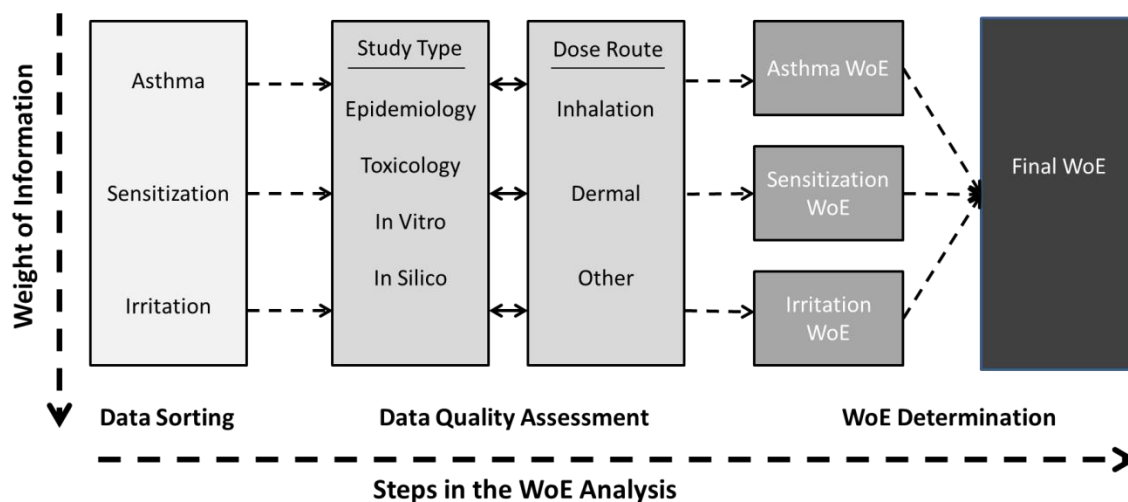
Figure 1. Weight of Evidence (WoE) Analysis Process for Potential Chemical Asthma Hazards. The process incorporates multiple lines of evidence. The data are sorted by endpoint to align with endpoint specific WoE descriptors that are combined to inform the overall asthma hazard characterization. Data are arrayed showing higher weight (i.e., greater value to the determination of asthma potential) moving from the top to bottom of each column.

Respiratory sensitization is categorized as either present or absent in the WoE analysis. To assess respiratory sensitization potential, multiple lines of evidence are used. Epidemiology studies, case reports and controlled exposure studies in volunteers are preferred. However, for most chemicals, human effects data on respiratory sensitization are not available. To provide a meaningful hazard prioritization, the WoE also includes findings from standard sensitization protocols, including those conducted via the dermal route. This approach was taken because there are no fully validated, predictive tests available to identify with a high degree of specificity whether or not a chemical is a respiratory allergen in humans (Anderson et al., 2011; Kimber et al., 2011). Lack of such tests is due to the complexity of the immune system, species differences in respiratory tract and immune system physiology and anatomy, and experimental challenges involved in conducting inhalation exposure experiments compared to dermal application studies (Arts et al., 2006; Pauluhn et al., 1999).

The ability of a chemical to trigger asthma-like responses is assumed to correlate with the degree of irritation it induces. Because there are inherent uncertainties in extrapolating from irritant potential to asthmagenic potential, data on irritation are placed in only one of two broad categories to avoid the suggestion of an unwarranted level of precision in the WoE procedure. Respiratory irritation potential is categorized as (1) none or mild and (2) moderate or severe. The degree of irritation induced by a chemical used for the WoE generally reflects the response to the neat material, although concentration dependent responses are noted when such data are

available. This approach of lumping irritation into two categories reflects the intended use of the method to identify chemicals likely to have the potential to cause or elicit asthma responses and prioritize them for more in-depth analysis or data collection.

Data from standard irritation protocols (skin, ocular, and in vitro methodologies) are used to predict respiratory irritation potential in the absence of adequate respiratory effects information. Although eye, skin, and respiratory responses do not always correlate well (Levy and Wegman 1988), peripheral sensory irritants act locally in the skin, eye, and respiratory tract mucosae by stimulating nerve receptors which produce local sensations of irritation (Ballantyne, 1999). Moreover, Rennen et al. (2002) determined that skin and eye irritants frequently also caused local respiratory irritation. Correlations between standard eye irritancy tests and potential for respiratory tract irritancy showed a quantitative relationship between Draize eye scores (eye irritation) and respiratory tract irritant effect levels (TERA, 2009). Furthermore, for some types of irritants, the underlying mechanism is likely to be relevant across routes. Such mechanisms include direct tissue reactivity for corrosive substances (e.g., hydrochloric acid) or activation of transient receptor potential (TRP) ion channels present in various epithelial tissues (e.g., capsaicin) (Caterina et al., 1997).

For each endpoint (asthma, respiratory sensitization, respiratory irritation) a likelihood descriptor is assigned based on the WoE (see Table 1). Individual studies are evaluated for both reliability and relevance according to the principles laid out by Klimisch et al. (1997) for evaluation of toxicology studies. A modified, but comparable, approach was developed for epidemiology study evaluation based on assessment of study design quality and internal and external validity, consistent with other epidemiology evaluation methods (Money et al. 2013). The integration of the individual studies and lines of evidence reflect the general preference for human studies versus animal studies and inhalation studies versus studies involving exposure via other routes. However, these general preferences are balanced with other considerations related to study quality. The endpoint descriptors reflect the robustness of the database identified for each endpoint based on the weight of evidence from the available data.

Table 1. Categories for describing the likelihood that a chemical causes asthma, respiratory sensitization, or irritation.			
	Asthma	**Respiratory Sensitization**	**Respiratory Tract Irritation**
Likely	There is sufficient evidence of a significant positive asthmatic effect following exposure to this chemical. This	There is sufficient evidence of a significant positive sensitization effect in humans by the inhalation route. This	This chemical is likely to be a moderate or severe respiratory irritant. This descriptor is used for chemicals with a high

	descriptor reflects data sets with strong evidence to induce asthma or asthma-like responses in humans and/or in animal models in conjunction with, at minimum, weak evidence of asthma in humans.	descriptor also reflects data sets with one or more standard assays (including those via dermal application) or data sets showing high sensitization potential or data sets where a preponderance (i.e., a clear majority) of studies show sensitization potential supported by limited human effects information.	irritancy or corrosive potential based on inhalation data or very strong indirect evidence from skin or ocular irritancy information with a mode of action that is likely to be relevant across routes.
Suggestive	There is convincing, but not sufficient evidence of a significant positive asthmatic effect. This descriptor reflects data sets with reports of marginal effects and/or situations where overall data are of limited quality or provide mixed or inconsistent evidence for an effect.	There is evidence of a positive effect, but it is not strong. This descriptor reflects data sets with reports of marginal effects and situations where overall data are of limited quality, or provide mixed or inconsistent evidence for an effect. Generally no reliable evidence following inhalation is available or positive inhalation studies are contradicted by high quality sensitization assays.	This chemical has evidence that suggests it may be a moderate to severe respiratory irritant, but a mild irritancy potential is also probable under some conditions consistent with chemical use.
Unlikely	There is sufficient evidence of a significant negative asthmatic effect following exposure to this chemical. This descriptor reflects data sets with strong evidence that the chemical does not induce asthma or	There is sufficient evidence of a negative effect. This descriptor reflects data sets with multiple standard bioassays showing negative results or a data set where a preponderance (i.e., a clear majority) of studies shows no significant effect supported	This chemical is unlikely to be a moderate to severe respiratory irritant. It is shown to have only a mild or no irritancy potential following inhalation or based on a robust data set from skin or eye irritation studies at concentrations consistent with chemical use.

	asthma-like responses in humans and/or strong evidence that the chemical does not induce asthma or asthma-like responses in animals in conjunction with an absence of asthma in humans.	by negative findings in human effects studies.	
Inadequate	This descriptor reflects data sets that are too limited to evaluate the endpoint directly	This descriptor reflects data sets that are too limited to evaluate the endpoint.	This descriptor reflects data sets that are too limited to evaluate the end point.

After determining the appropriate category for each of the individual endpoints (asthma, sensitization, and irritation), the individual descriptors are used to assign a descriptor for the overall WoE for asthma (see Table 2). Evidence of respiratory sensitization and irritation in humans is weighed more heavily than in animals when deciding the overall WoE for each chemical. Evidence of respiratory effects (sensitization and irritation) is also weighed more heavily than evidence of dermal effects. Although dermal irritation and sensitization data are potential surrogates in the absence of respiratory irritation and sensitization data, the two endpoints are not completely correlated, which adds additional uncertainty to the evaluation.

Table 2. A decision matrix for determining the overall weight of evidence for asthmagenic potential based on the weight of evidence for each individual endpoint, specifically asthma, moderate to severe respiratory irritation, and respiratory sensitization.

Asthma	Respiratory Irritation	Respiratory Sensitization	Overall WoE
Likely	All Categories*	All Categories	Likely
Suggestive	Likely	Likely	Likely
Suggestive	All Categories	Suggestive	Suggestive
Suggestive	All Categories	Inadequate	Suggestive
Suggestive	All Categories	Unlikely	Suggestive
Inadequate	Likely	Likely	Likely
Inadequate	Suggestive	Likely	Suggestive
Inadequate	Inadequate	Likely	Suggestive
Inadequate	Unlikely	Likely	Suggestive

Asthma	Respiratory Irritation	Respiratory Sensitization	Overall WoE
Inadequate	Likely	Suggestive	Suggestive
Inadequate	Suggestive	Suggestive	Suggestive
Inadequate	Inadequate	Suggestive	Suggestive
Inadequate	Unlikely	Suggestive	Inadequate
Inadequate	Likely	Inadequate	Inadequate
Inadequate	Suggestive	Inadequate	Inadequate
Inadequate	Inadequate	Inadequate	Inadequate
Inadequate	Unlikely	Inadequate	Inadequate
Inadequate	Likely	Unlikely	Inadequate
Inadequate	Suggestive	Unlikely	Inadequate
Inadequate	Inadequate	Unlikely	Inadequate
Inadequate	Unlikely	Unlikely	Unlikely
Unlikely	All Categories	All Categories	Unlikely

*"All Categories" indicates that the same ultimate weight of evidence descriptor (i.e., likely, suggestive, inadequate, or unlikely) will be assigned regardless of the descriptor in this endpoint."

Definitions of Overall WoE Descriptors:

(2) "Likely" indicates robust evidence the chemical causes asthma in humans, or limited human evidence for inhalation exposures coupled with robust evidence that the chemical is both a respiratory sensitizer and severe respiratory irritant (since these are potential asthma triggers).

(3) "Suggestive" indicates evidence that suggests the chemical induces asthma or triggers asthma-like responses in humans, but it is not conclusive, or there is evidence of respiratory sensitization and moderate-to-severe respiratory irritation in the absence of human asthma data.

(4) "Unlikely" indicates there is strong evidence of lack of asthma potential in humans, or strong evidence of absence of respiratory sensitization and weak or no irritation potential.

(5) "Inadequate" indicates that available data are not sufficient to affirm whether or not the chemical can cause asthma. This reflects poor or non-existent data that this chemical is related to asthma responses, or there is mixed or inconclusive evidence of respiratory sensitization and severe irritation, or there is a lack of information on asthma and respiratory sensitization. "Inadequate" is a common descriptor in the asthma category due to the absence of validated animal or in vitro models for this endpoint and does not infer the absence of required safety testing.

Methods-Based Case Study: Acetic acid

Evidence of Asthma

Multiple studies were identified, in both humans and animals, which indicated a likely potential for acetic acid to cause or exacerbate asthma.

One epidemiological study reported an association between RADS incidence and exposure intensity following accidental exposures to acetic acid (Kern, 1991). Additionally, an occupational study among 117 female pickling and mustard-producing workers indicated that exposure to vinegar vapors (40% acetic acid) was correlated with occupational asthma, hypothetically irritant-induced asthma or RADS (Zuskin et al., 1993, 1997). Multiple case studies (Rajan and Davies, 1989; Kivity et al., 1994) also indicate that exposure to high concentrations of acetic acid (i.e., occupational or accidental exposure) can cause asthma or asthma-like symptoms. Controlled exposure studies in volunteers have also been conducted. Shusterman et al. (2003) measured nasal airways resistance (NAR) following 15 minute exposures to 15 ppm acetic acid and reported an increase in physiologic reactivity to acetic acid in subjects with seasonal allergic rhinitis. Enstgard et al. (2006) measured subjective ratings of nasal irritation and smell in addition to quantitative pulmonary function measurements, nasal swelling, NAR, and plasma inflammatory markers; exposure to 10 ppm acetic acid caused mild nasal irritation but no symptoms related to an asthma-like response. Overall, exposure to high concentrations of acetic acid, particularly those observed in occupational settings, induce irritation and possibly asthma or an asthma-like response. Whether similar responses would also occur at lower concentrations is unclear based on the extant data.

Animal studies also confirm the potential for acetic acid to cause upper respiratory tract (URT) effects consistent with irritation and subsequent symptoms that are common with asthma-like responses. Studies in rats, mice, and guinea pigs all indicated a change in lung or URT flow resistance immediately following exposure (Ariel et al., 1998; Morris et al., 2003; Amdur, 1961). The observed breathing patterns and obstructive responses were enhanced in mice with allergic airway disease, indicating that sensory nerves and irritation likely play an important role in exposure response (Morris et al. 2003).

The overall WoE indicates that acetic acid is likely to induce asthma responses in humans. The data are not adequate to determine whether these responses reflect that acetic acid induces asthma directly or whether acetic acid elicits responses via irritant mechanism that trigger a response in individuals with asthma due to other causes.

Evidence of Respiratory Irritation Potential

Acetic acid causes respiratory, skin and eye irritation in humans and animals (DeCeaurriz et al. 1981; Gagnaire et al. 2002; Ghiringhelli and Difabio 1957; Nixon et al. 1975; Roudabush et al.

1965; Grant 1986; US EPA 1992a, 1992b, 1992c; Maurer and Parker 2000). Concentrations as low as 10 ppm did not cause URT discomfort or irritation (Savina and Ansimov 1988). However, exposure of unacclimatized individuals to acetic acid vapors caused slight eye irritation at concentrations up to 10 ppm, tolerable irritation at 25 ppm, and intolerable nose, throat, and eye irritation at 50 ppm (AIHA 1972; Proctor 1988). Acetic acid can quickly cause serious burns and is corrosive to the skin at high concentrations (Rajan and Davies 1989; Kuniyuki and Oonishi 1997).

Overall, studies in humans (Shusterman et al. 2003; Ernstgard et al. 2006) suggest that the asthmagenic effects of acetic acid are due to its irritancy in the respiratory tract and that individuals suffering from allergic rhinitis may be considered a sensitive population. Animal studies that identified RD_{50} values (163 and 227 ppm) suggest that acetic acid is likely to cause at least moderate respiratory irritation (DeCeaurriz et al. 1981; Gagnaire et al. 2002). Therefore, the overall weight of evidence indicates that acetic acid is likely to cause moderate to severe respiratory irritation in humans.

Evidence of Respiratory Sensitization Potential
No human or animal studies evaluating the potential for acetic acid to cause respiratory sensitization were identified. Kivity et al. (1994) suggested that glacial acetic acid can be considered a sensitizer based on the late airway response leading to chronic inflammation and severe bronchial asthma in a patient. Several material safety data sheets (MSDS) available on-line have indicated that skin sensitization with acetic acid has been reported, but is rare. However, no studies confirming this observation were located. Therefore, the weight of evidence is inadequate to determine the potential for acetic acid to cause respiratory sensitization in humans.

Summary
Data available from epidemiological studies and case reports indicate that short-term accidental and long-term acetic acid exposures can result in RADS, asthma-like symptoms, or changes in ventilatory capacity in humans (Rajan and Davies 1989; Kivity et al. 1994; Zuskin et al. 1993, 1997; Shusterman et al. 2003; Ernstgard et al. 2006). In addition, animal studies have confirmed an increase in airway resistance (Morris et al. 2003; Amdur 1961) after inhalation exposure to acetic acid; however, animal models for asthma have not been adequately evaluated and accepted. Sufficient data were identified that indicate that acetic acid is a moderate respiratory irritant in animals (DeCeaurriz et al. 1981; Gagnaire et al. 2002). No adequate human, animal, or *in vitro* studies evaluated the potential for acetic acid to cause respiratory sensitization in humans. Based on evidence that acetic acid is likely to induce asthma and respiratory irritation but inadequate evidence regarding respiratory sensitization, the overall weight of evidence suggests that acetic acid is likely to have asthma hazard potential (defined as the potential to induce asthma or asthma-like responses) in humans.

Discussion

The goal of this hazard characterization tool is the assessment of chemicals with potential for inducing or triggering asthma based on a WoE approach. This methodology builds on the strengths, and addresses the limitation, of existing hazard characterization tools for asthma and related endpoints (Maier et al., 2014). A particular challenge for asthma hazard characterization is the integration of human and animal data to establish a causal inference (Adami et al. 2011, Li et al 2012). The methodology is aimed at prioritizing chemicals as a first step for quantitative and scenario-based safety assessments.

Our case study results are largely similar to recommendations from other agencies, particularly those with proposed frameworks (e.g., EU GHS and AOEC). The European Union (EU 2011) assigned a classification that indicates acetic acid has corrosive or irritating effects on the respiratory system depending on the concentration. This is in agreement with our designation that acetic acid is "likely" a respiratory irritant. The AOEC (2011) has assigned an "Asthmagen" notation for acetic acid based on its potential for respiratory sensitization and irritation (e.g., RADS). Using our approach, the evidence for sensitization was not considered adequate, but evidence for asthma responses and irritation yield an overall characterization of "likely". Although this case study presented results in-line with assessment from other agencies, likelihood designations may not align for other chemicals due to the focus on asthma as the endpoint of interest. Two key elements of the approach that extend the ability to make hazard characterization decisions with combinations of disparate data types are the use of surrogate endpoints for predicting asthma (i.e., sensitization and irritation) and the application of dermal hazard data in the absence of route-specific inhalation data.

Overall, most animal asthma models cannot be considered to have an allergic response, cannot reproduce the chronic nature of the disease (Bice et al., 2000; Fulkerson et al., 2005), and require the use of anesthesia, which decreases autonomic reflexes, to observe nonspecific airway hyperreactivity (Hessel et al., 1995b). In guinea pigs and rabbits, lung eosinophilia are prominent in the absence of sensitization and do not correlate to hyper-responsiveness (Banner et al., 1996; Chapman and Morley, 1996; Minshall et al., 1996; Rothenberg et al., 1995). Rats are poor bronchoconstrictors, so estimated effect levels (e.g., NOAEL and LOAEL values) may be high compared to other species (Bice et al., 2000). Currently, mice are commonly used for asthma studies because of the wide knowledge of their genetics and immune responses, but it is difficult to accurately measure airway reactivity or hyperreactivity due to their small size (Bice et al., 2000; Karol, 1994). Rats and mice also have little late-phase pulmonary obstruction (De Bie et al., 2000; Hessel et al., 1995a; Zosky et al., 2006) and appear to build-up a tolerance to repeat exposures, resulting in decreased airway response and inflammation over time (Bice et al., 2000; Kumar and Foster, 2002; Ostroukhova et al., 2004; Zosky and Sly, 2007).

There are significant caveats in drawing conclusions from sensitization assay results extrapolated across exposure routes. Anderson et al. (2011) pointed out that although select strong sensitizers have been shown to result in sensitization of the respiratory tract, this does not hold true for all LMW chemical sensitizers or high molecular weight (HMW) protein allergens that cannot pass through the skin. While extrapolation of data from validated skin sensitization studies may be considered possible indicators of respiratory sensitization, current studies also provide evidence that different immunological mechanisms are responsible for contact dermal versus respiratory sensitization. Respiratory allergens generally induce increases in the Th2 cytokines, IL-4, IL-5, IL-10, and IL-13, while contact allergens have been associated with increases in the Th1 cytokines, INF-γ and TNF (Plitnick et al., 2003; Dearman et al., 1996). While advancements in the murine local lymph node assay (LLNA) are providing evidence of different cytokine profiles between dermal and respiratory responses, currently, "the discordance between dermal cytokine profiles and respiratory responses suggest that dermal responses do not necessarily predict respiratory responses" (Farraj et al., 2007). However, Anderson et al. (2011) noted that a negative result in the LLNA typically excludes a LMW chemical as a respiratory sensitizer.

Despite the limitations of cross-route extrapolation, in the absence of route-specific data, data derived from exposure via other routes can still be informative for hazard prioritization purposes. Cross-route consistency in response has been demonstrated in several studies (Christensen et al., 1994; Pajno et al., 2003). Other tests of sensitization (e.g., LLNA and increased serum IgE levels) are in some cases predictive of airway hypersensitivity caused by LMW chemicals (Arts et al., 1998; Arts et al., 2006). Another argument for use of sensitization assays that are not route specific is that some LMW allergens have been demonstrated to produce allergic sensitization and diseases of the respiratory tract independent of route of exposure in both humans and animals, reflecting the systemic nature of the sensitization response (Arts and Kuper 2007; Anderson et al. 2011; Arts et al. 2008).

For most chemicals, there are no studies investigating asthma directly. This necessitates the use of surrogate endpoints for conducting a meaningful hazard characterization for most of the chemicals in commerce. Since allergy-based asthma is well-documented (Kimber and Dearman, 2002), studies that evaluate sensitization of the respiratory tract are often considered directly indicative of asthma potential. The relationship between irritation and asthma causation is less clear, but exacerbation of pre-existing asthma can be caused by URT irritation. In addition, asthma-like syndromes (e.g., RADS) are also clearly linked to irritation responses (Bernstein 1993).

There are a number of considerations in evaluating irritation responses in the context of asthma induction or exacerbation. The likelihood of a chemical to be a respiratory irritant was determined by evaluating both the severity of the reaction and the concentration of exposure at

which the reaction was observed. Many chemicals in cleaning products are expected to have some level of irritant potential, so the emphasis on irritant potency was used in our WoE procedure to prioritize chemicals that were identified as moderate or severe irritants, assuming that such levels of irritation are more likely to induce or trigger RADS and/or asthma or asthma-like responses than only mild irritation. However, published research testing this hypothesis was not identified. Thus, the approach taken for this proposed method is likely to err on the side of being health protective. One limitation of this method is that, for many chemicals, irritancy is directly related to the concentration used. Thus, application of the method requires documentation of exposure concentration, when available. In general, the irritancy descriptors reflect the potency of concentrated solutions and will often result in health protective conclusions.

Qualitative WoE approaches have a long history in risk assessment practice (US EPA 1986 a, b, c; 2005). These approaches provide structure and flexibility, but are sometimes lacking in transparency and considered too subjective. Alternatively, quantitative methods use statistical models or structured decision for weighting, ranking, indexing and integrating multiple lines of evidence. However, the use of statistical and mathematical models require significant amount of data, which is a limiting factor. To address these strengths and limitations in various WoE methods (Linkov et al., 2009) we developed a method that bridges the gap between qualitative and quantitative methods. The proposed hazard characterization approach integrates characteristics from logic and scoring-based methods. This approach incorporates a categorical hierarchical decision process, consistent with logic-based methods. Although mathematical scores are not used (i.e., such as multiple criteria decision analysis), WoE judgments are ordinal and combined in a pre-determined way. This effort is also consistent with recent significant efforts to enhance WoE application using systematic approaches that integrate data through both qualitative and quantitative methods (Rhomberg et al. 2013; Weed 2005; Guzelian et al. 2005).

Further work is needed to test the approach in terms of maximizing consistency in ratings through clear descriptions of the various categories and worked examples. In addition, demonstrating the integration of the scoring tools for epidemiology along with toxicology studies would also inform the degree to which the scoring systems align and optimize decision-making for complex data sets. One of the special needs for asthma is related to the integration of human and animal data to establish a causal inference and recent work has focused integration of such study designs for assessing health effects literature (Adami et al. 2011, Li et al 2012). Improved availability of epidemiology and animal data on sensitization and irritation could help in refining this approach using MCDA tools as described by Linkov et al. (2009).

A potential extension of the results would be to build from this analysis and select scenarios for quantitative assessments using the agents with the highest hazard potential as case studies. This approach could include a safety characterization based on evaluation of dose-response and

exposure estimates from assessments and exposure reconstruction studies for specific products or chemical ingredients (e.g., Fedoruk et al., 2005; Vincent et al., 2014). A tiered evaluation approach based on the proposed hazard assessment framework would greatly enhance the overall ability to make decisions regarding the asthma hazard potential of cleaning products to support new product ingredient reviews and assure consumer safety.

Acknowledgements

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