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Setting Occupational Exposure Limits for Chemical Allergens—Understanding the Challenges

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Chemical allergens represent a significant health burden in the workplace. Exposures to such chemicals can cause the onset of a diverse group of adverse health effects triggered by immune-mediated responses. Common responses associated with workplace exposures to low molecular weight (LMW) chemical allergens range from allergic contact dermatitis to life-threatening cases of asthma. Establishing occupational exposure limits (OELs) for chemical allergens presents numerous difficulties for occupational hygiene professionals. Few OELs have been developed for LMW allergens because of the unique biological mechanisms that govern the immune-mediated responses. The purpose of this article is to explore the primary challenges confronting the establishment of OELs for LMW allergens. Specific topics include: (1) understanding the biology of LMW chemical allergies as it applies to setting OELs; (2) selecting the appropriate immune-mediated response (i.e., sensitization versus elicitation); (3) characterizing the dose (concentration)-response relationship of immune-mediated responses; (4) determining the impact of temporal exposure patterns (i.e., cumulative versus acute exposures); and (5) understanding the role of individual susceptibility and exposure route. Additional information is presented on the importance of using alternative exposure recommendations and risk management practices, including medical surveillance, to aid in protecting workers from exposures to LMW allergens when OELs cannot be established.

Keywords allergens, asthma, chemicals, exposure, occupational, sensitization

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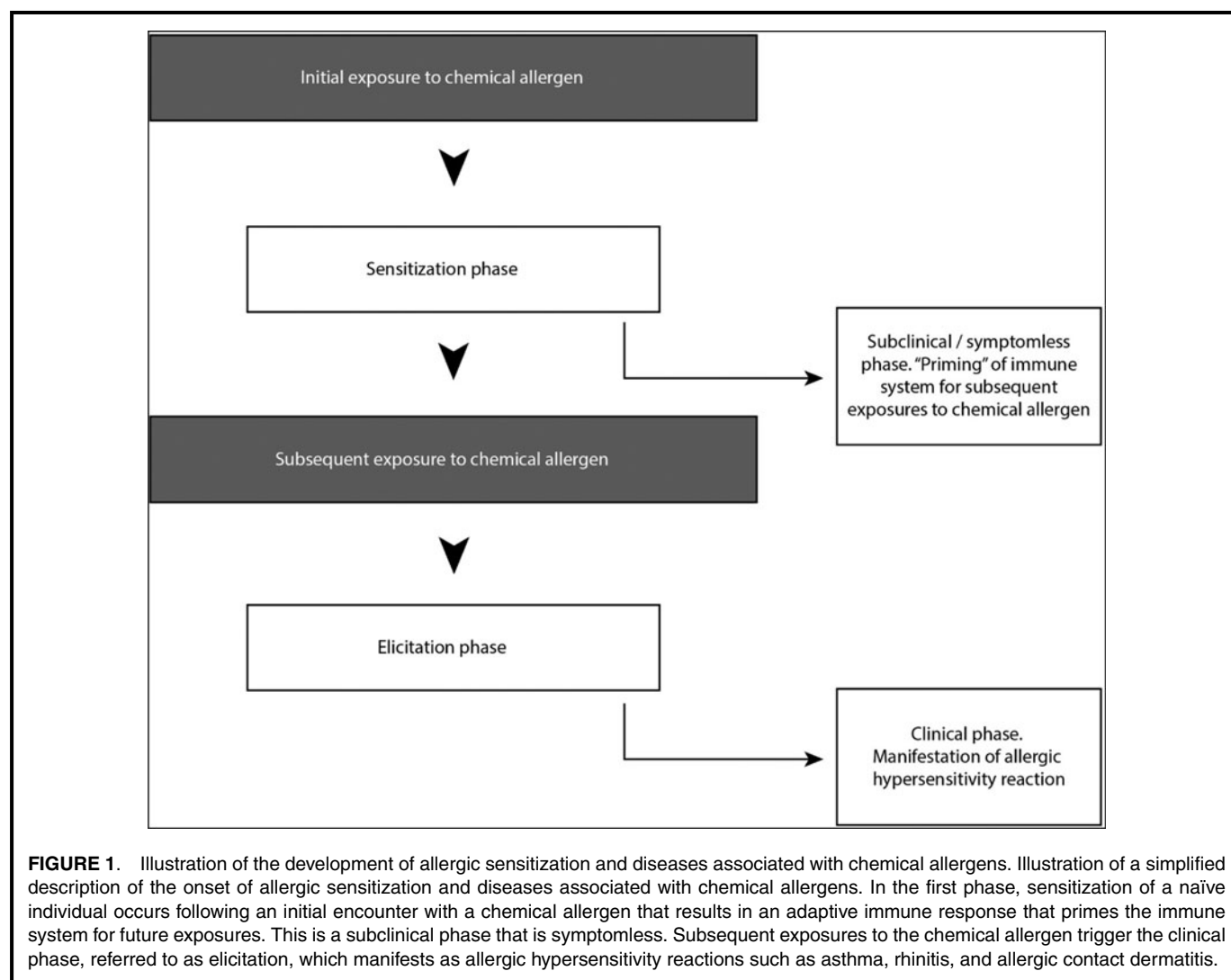
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INTRODUCTION

The term “chemical allergy” describes immune-mediated adverse health effects, including allergic sensitization and diseases, caused by exposures to chemicals.^(1, 2) These adverse health effects manifest as a diverse group of disorders caused by an inappropriate immune-mediated response in susceptible individuals following exposure to a foreign substance, or allergen, which is often not otherwise toxic at the concentrations that trigger the allergic response.⁽³⁾ The immune-mediated responses linked to chemical allergens are complex and vary based on multiple factors including the nature of the allergen, exposure scenario (e.g., route, duration, frequency and magnitude) and individual susceptibility.

Figure 1 illustrates a two-phase model frequently used to characterize the immune response to chemical allergens. The first phase, sensitization (also referred to as induction), follows initial encounters with an allergen that results in an adaptive immune response that primes the immune system for future exposures. The second phase, elicitation, occurs when the sensitized individual receives subsequent exposures to the



allergen that triggers an enhanced immune-mediated response recognized clinically as an allergic reaction.⁽¹⁾

Chemical allergies are among the most common immunological manifestation in humans and represent a significant occupational health hazard.⁽⁴⁾ Hundreds of chemical allergens have the potential to cause allergic contact dermatitis (ACD), which accounts for 10–15% of all occupational diseases.^(5–8) Allergic respiratory diseases are associated with high levels of worker morbidity.⁽⁹⁾ Some chemical allergens are known to be associated with immune-mediated responses of the respiratory tract.^(10–12) One common response is asthma, which is a complex syndrome with varying definitions and underlying etiologies.⁽¹³⁾ An estimated 9–15% of all cases of adult asthma are associated with occupational factors.⁽¹⁴⁾ Both immunological⁽¹⁴⁾ and irritant mechanisms^(15–18) appear to be etiological factors for occupational asthma cases. Other estimates indicate that occupational exposures account for 10–25% of the population attributable risk for adult asthma; equivalent to an incidence of new-onset occupational asthma of 250–300 cases per million annually.^(19–23)

Allergens are commonly delineated into two categories based on their mass and the specific immune-mechanisms. Low molecular weight (LMW) allergens typically have a mass less than 5000 Daltons and comprise the majority of the chemical allergens described in this article. These chemicals are typically highly reactive and electrophilic, or are metabolized to reactive forms (prohaptens). Many LMW allergens function as haptens, or incomplete allergens, that can bind to a protein to form a hapten-protein complex that has sufficient mass for recognition by the immune system.⁽²⁴⁾ Other mechanisms involving direct interaction with components of the immune system may facilitate the immune response for metals.^(25, 26) Examples of LMW allergens that are recognized occupational hazards include diisocyanates, organic anhydrides and certain metals, such as beryllium and nickel. In contrast, HMW allergens have a mass that exceeds 5000 Daltons allowing for their direct recognition by the immune system. Green and Beezhold identified more than 250 HMW allergens in various work settings ranging from seafood processing to detergent manufacturing.⁽²⁷⁾

TABLE I. ACGIH Threshold Limit Values (TLVs) Based on Immune-mediated Health Endpoints^A

Chemical	CAS #	ACGIH
Beryllium and compounds	7440-41-7	TLV-TWA = 0.00005 mg/m ³ (as Beryllium, inhalable particulate matter); RSEN, DSEN
Flour dust	Not identified	TLV-TWA = 0.5 mg/m ³ (IVF); RSEN
Hexahydrophthalic anhydride	85-42-7; 13149-00-3; 14166-21-3	TLV-C = 0.005 mg/m ³ (IVF); RSEN
Hexamethylene diisocyanate	822-06-0	TLV-TWA = 0.005 ppm
Isophorone diisocyanate	4098-71-9	TLV-TWA = 0.005 ppm
Maleic anhydride	108-31-6	0.01 mg/m ³ (IVF); RSEN, DSEN
Methylene bisphenyl isocyanate	101-68-8	TLV-TWA = 0.005 ppm
Methylene bis(4,cyclohexylisocyanate)	5124-30-1	TLV-TWA = 0.005 ppm
Natural rubber latex	9006-04-6	TLV-TWA = 0.0001 mg/m ³ (IVF); RSEN, DSEN, Skin
Piperazine	110-85-0	0.03 ppm (IVF); RSEN, DSEN
Toluene diisocyanate (TDI) (mixture of 2,4-TDI and 2,6-TDI)	584-84-9 91-08-7	TLV-TWA = 0.005 ppm; TLV-STEL = 0.02 ppm; RSEN
Trimellitic anhydride	552-30-7	TLV-TWA = 0.0005 mg/m ³ (IVF); TLV-STEL = 0.002 mg/m ³ ; RSEN, DSEN, Skin

^ABased on ACGIH⁽¹⁰¹⁾

ACGIH = American Conference of Governmental Industrial Hygienists; C = ceiling limit; CAS # = chemical abstract service number; DSEN = dermal sensitization notation; (IVF) = inhalable fraction and vapor; mg/m³ = milligrams per cubic meter; ppm = parts per million; RSEN = respiratory sensitization notation; skin = skin notation; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time weighted average

Controlling occupational exposures to chemical allergens is critical for ensuring the health and well-being of workers. An important tool used to assess workplace exposures and ensure the effectiveness of risk management strategies is an occupational exposure limit (OEL). There is a long history of application of quantitative risk assessment approaches used to develop OELs for non-immune mediated health effects, including portal of entry irritation (i.e., irritation of the upper respiratory tract), non-cancer systemic effects (i.e., neurotoxicity, reproductive, and developmental effects) and cancer.⁽²⁸⁻³³⁾ Although OEL derivation approaches are fairly well established, they are often less suitable for establishing OELs capable of protecting workers from chemical allergies.

Table I provides a list of OELs that have been developed for chemicals allergens. These OELs are primarily based on limited human effects and exposure data. The data are capable of supporting OEL derivation, but significant uncertainties remain in the construction of a dose- or concentration-response relationship between the chemical and onset of allergic sensitization in worker populations. Most chemical allergens have insufficient data to establish a concentration-response relationship preventing the derivation of an OEL based on allergic sensitization or diseases as the critical endpoint. The absence of data also negatively impacts other critical considerations such as the selection of the appropriate immune-mediated response and the characterization of temporal exposure pat-

terns, individual susceptibility, and multiple exposure routes on the development of allergies. For example, diisocyanates represent a group of chemicals highly used in commerce and are recognized respiratory allergens. Despite this profile, there are many open scientific questions that inhibit the full assessment of occupational risk.⁽³⁴⁾

The purpose of this article is to highlight the key scientific challenges associated with the establishment of OELs for chemical allergens. Additional information is presented on the use of alternative exposure recommendations and risk management practices to aid in protecting workers from the health risks associated with chemical allergens when OELs cannot be derived. Because of the inherent differences between LMW and HMW allergen response, limited information is presented on HMW allergens. The primary focus of this article is on understanding the process and challenges in establishing OELs for LMW allergens. This focus includes a discussion of the fundamental biological principles for characterizing data on sensitization and diseases associated with LMW allergens.

Key points covered in this article include:

- highlighting the biological concepts associated with the onset of chemical allergies as it related to OEL setting;
- characterization of the process and challenges associated with setting OELs for chemical allergens; and

- exploring alternative exposure recommendations and risk management practices for addressing exposures to chemical allergens when OELs cannot be derived.

UNDERSTANDING THE BIOLOGY OF CHEMICAL ALLERGENS

An appreciation of the basic biological concepts of chemical allergy provides a platform for understanding how occupational risk assessments can more fully account for allergy. Chemical allergy can take a variety of forms. In the context of occupational disease, it is skin sensitization resulting in ACD, and sensitization of the respiratory tract associated with asthma and rhinitis that are of greatest significance. In all instances, chemical allergy, in common with other forms of allergic disease, develops in two phases. The first phase, sensitization, occurs when the naïve individual is exposed to the chemical. During this phase allergen specific effector and memory cells develop, proliferate, and migrate throughout the body, but with greater homing to the initial site of exposure. This phase is clinically silent. Following subsequent exposure, an immune response can be provoked that results in inflammation and the signs and symptoms of allergic disease. All forms of allergy, including chemical allergy, are dependent upon the induction of an immune response, and this distinguishes allergy from other adverse health effects, that may be associated with similar symptoms, but manifestations are the same in both immunologically sensitized and non-sensitized individuals.

Key aspects of immune-mediated responses associated with LMW allergens are summarized below to introduce occupational hygiene professionals to the terms and science encountered in reviewing the literature cited in OEL documents and in evaluating the basis for sensitization notations. More in-depth descriptions of the concepts presented in this section are available in the published literature.^(4, 35-42)

Sensitization vs. Elicitation

As indicated above, sensitization describes a state of enhanced responsiveness to a chemical allergen due to immunological priming. The development of sensitization is initiated following recognition of the inducing chemical allergen by the immune system. In this process professional antigen presenting cells (APC) play a pivotal role. Such APC reside at the site of exposure, recognize, process, present, and transport allergen to regional lymph nodes where an adaptive immune response is initiated. The recognition, handling, and transport of antigen in this way involves a number of interacting cellular and molecular immunological mechanisms that together are required for the activation and directed movement of APC towards lymph nodes. In addition, the allergen (haptenated protein) can be carried through lymphatic vesicles to lymph nodes and the blood to the spleen where they are processed by APC and presented to T-cells. Molecular mediators of immunity—cytokines and chemokines—play important roles in orchestrating such events.

One critical event during the acquisition of sensitization is for the creation of a stable association between the chemical allergen and host protein. LMW allergens are too small to be recognized as foreign by the immune system. To acquire immunogenic potential, LMW allergens form what are known as hapten-protein conjugates, which initiate the immune response. Consequently, LMW allergens must be electrophilic, or must be transformed into an electrophilic species following exposure.

A central event in immune sensitization is the presentation of antigen by DC to antigen-responsive T lymphocytes. Antigen activation of responsive T lymphocytes causes clonal expansion and differentiation into various functional subpopulations of cells, some of which will migrate back to the site of exposure. At this point, the individual is sensitized and capable of mounting a clinically relevant hypersensitivity response to the same, or cross-reactive chemical allergen upon re-exposure. The immunological basis for sensitization can take a variety of immunological forms that are described below.

Forms of Chemical Allergy

As indicated above, the two forms of chemical allergy that are of greatest importance in the context of occupational health are skin sensitization resulting in allergic eczema and contact urticaria,⁽⁴³⁾ in addition to sensitization of the respiratory tract associated with asthma and rhinitis. Both are caused by exposure of susceptible subjects to a LMW allergen, but the form that sensitization takes and the characteristics of subsequent allergic reactions will take different pathways.

Contact allergens are associated with cell-mediated immune responses and delayed type hypersensitivity reactions. In the acquisition of skin sensitization and the elicitation of contact hypersensitivity reactions, allergen-specific T lymphocytes play the major role. More specifically, the key T lymphocytes that mediate these effects are CD4⁺ Th1/Th17 cells and CD8⁺ Tc1/Tc17 cells. Conventionally it has been recognized that the key T lymphocytes that mediate these effects are CD4⁺ Th1 cells and CD8⁺ cells. However, other subsets of CD4⁺ (Th17, Th9, Tregs and Th22) and CD8⁺ (Tc1 and Tc17) are beginning to be elucidated.⁽⁴⁴⁾ Recently, it has been recognized that the innate immune system may also be intricately involved by inducing innate effector mechanisms and signaling pathways providing the needed early inflammatory immune response for the activation of acquired immunity.⁽⁴⁵⁾

It is of some interest that while the majority of LMW allergens are associated primarily with skin sensitization and ACD, other allergens preferentially cause allergic sensitization of the respiratory tract resulting in asthma and rhinitis. It appears that the ability of LMW chemicals to elicit different forms of allergic disease is a function of the type and quality of immune response that they preferentially induce. Thus, whereas contact allergens favor the development of primarily Th1-type responses, chemical respiratory allergens are associated instead with preferential Th2-type immune responses. These Th2 cells are believed to play a pivotal role in the

development of respiratory sensitization. Such cells also promote the induction of immunoglobulin E (IgE) antibody responses that have been implicated in various allergic diseases such as hay fever and food allergy. Although IgE antibodies are found in patients with chemical respiratory allergy, this is not always the case and there remains some uncertainty about the role played by IgE antibodies in some occupational asthmas. Innate immunity is also thought to play key roles in the development of respiratory allergy and asthma, although little to no work has been conducted looking at the role in LMW allergic respiratory diseases. Specifically invariant natural killer T cells and innate lymphoid cells (ILCs) have been implicated in asthma and allergic disease.^(46,47) ILCs have been shown to produce a variety of cytokines associated with Th2 and other CD4+ cellular subsets as well as interact with other innate and adaptive immune cells involved in asthma. MicroRNAs (small, non-coding regulatory RNA) have also recently been suggested to play a role in asthma pathogenesis.⁽⁴⁸⁾

CHALLENGES INVOLVED IN THE DEVELOPMENT OF OCCUPATIONAL EXPOSURE LIMITS FOR CHEMICAL ALLERGENS

The biology of immune-mediated responses presents significant challenges in applying the traditional OEL derivation process to chemicals. The primary challenges that make the derivation of OELs for LMW allergens difficult include:

1. selection of an appropriate immune-mediated response to serve as the basis of the OEL (e.g., sensitization versus elicitation);
2. characterization of the concentration-response relationship (e.g., absence of human effects and exposure data and validated animal test protocols for sensitization of the respiratory tract);
3. effects of temporal exposure patterns on response (e.g., complex or unknown relationships between cumulative or peak exposures and sensitization);
4. level of sensitization and severity of elicited response (e.g., severity response is variable based on individual susceptibility and degree of sensitization);
5. role of exposure route in chemical allergies (e.g., relationship between dermal contact and sensitization of the respiratory tract is poorly understood); and
6. characterizing workplace exposures in a biologically meaningful way.

Selection of the Appropriate Immune-Mediated Response

A major consideration during the development of OELs is the identification of the appropriate health endpoint as the basis of the risk assessment. For LMW allergens, the critical question focuses on whether the OEL should protect from induction of sensitization in naïve individuals or from elicitation of a hypersensitivity response in persons who are already sensitized. OELs based on preventing sensitization are

expected to protect naïve individuals from becoming sensitized to the chemical allergen. For sensitized individuals, elicitation of clinical symptoms may occur at or below an OEL derived to prevent induction of sensitization in naïve individuals. For example, elicitation of an asthmatic response has been reported in some sensitized workers following toluene diisocyanate (TDI) inhalation challenge at the ACGIH threshold limit value Time Weighted Average (TLV-TWA) of 5 parts per billion (ppb).⁽⁴⁹⁾ Similarly, O'Brien et al. reported challenge elicitation of TDI-induced asthma in a subgroup of highly sensitized workers at ≤ 1 ppb.⁽⁵⁰⁾ Based on these occupational studies, it is generally accepted that both early diagnosis and concurrent removal from exposure result in a better outcome for the sensitized worker. Vandenplas concluded that reduction of exposure may lead to improvement or resolution of symptoms in some workers;⁽⁵¹⁾ however, continued exposures to respiratory chemical allergens usually results in worsening of symptoms and poorer prognosis.⁽⁵²⁾ These observations indicate that predicting a safe exposure level for sensitized individuals is difficult due to high variability in individual susceptibility. For this reason, prevention of sensitization in naïve individuals, rather than elicitation in already sensitized persons, appears to be a more suitable and health protective health endpoint to serve as the basis of an OEL.

Characterization of the Concentration-Response Relationship for Sensitization

A critical component of the risk assessment process is the establishment of the concentration-response relationship that describes the anticipated magnitude of response (i.e., adverse health outcome) associated with a particular amount of exposure. This relationship is used to identify the point of departure (i.e., extrapolation starting point) for deriving the OEL.⁽³³⁾ Unlike non-allergenic chemicals which generally exhibit a no adverse effect level, individual susceptibility to sensitizers makes deriving such a threshold much more difficult. Hence, full characterization of the concentration-response relationship for sensitization is optimal for setting OELs for LMW allergens.

Most LMW allergens do not have sufficient human effects or exposure data to establish a concentration-response relationship for sensitization and thereby necessitate the use of alternative data sources. Unfortunately, no animal test protocols are available that have been validated (i.e., demonstrated to be consistent and reliable) and can identify with a high degree of specificity that will distinguish chemical allergens that preferentially produce respiratory allergic disease vs. ACD, or accurately predict its potency to produce respiratory sensitization.^(4,24,53-56) The absence of well-accepted animal models for such an important endpoint reflects several considerations including 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 skin application studies.^(24,57,58)

Another option for characterizing the concentration-response relationships for respiratory chemical allergens could be the use of biomarkers of immune sensitization or recognition such as specific IgE antibodies. Detection of specific antibodies (e.g., IgE or IgG) is commonly employed for the assessment of HMW and some LMW allergens and screening of exposed workers.⁽³⁰⁾ Although scientific consensus on the use of sensitization biomarkers has not been established for LMW allergens, the use of such biomarkers in constructing a concentration-response relationship holds promise if key conditions are addressed. More precisely, this approach would require: (1) the detection of circulating antibodies (i.e., IgE) specific for the allergen of interest; (2) the detection the specific antibodies prior to the development of clinical disease; and (3) the quantification of the specific antibodies at levels at the sensitization threshold.

Establishing a concentration-response relationship for LMW chemicals directly for respiratory allergies is difficult because of the absence of inhalation studies and lack of validate animal models. Thus, risk assessment decisions are frequently based on the sensitization potential of chemicals as determined via dermal screening and animal test protocols. Animal models to identify contact allergens have been developed and validated. Modification of the standard murine local lymph node assay has been reported where specific cell surface markers and cytokine profiling are used to segregate Th1 and Th2 skewing chemical allergens.⁽⁵⁹⁾ These tests vary in design, but typically involve the application of the test agent to the skin of a test animal (or human if clinical patch test is being done). Table II presents descriptions of common human and animal dermal sensitization assays, which are validated and capable of confirming sensitization and potentially predicting potency. The findings of these assays are commonly reported in OEL documentation. For this reason, it is crucial for occupational hygiene professionals to develop a basic understanding of the assays to ensure the correct interpretation of the test results and their application in protecting workers from chemical allergens.

Effects of Temporal Exposure Patterns on Response

The relationship between the temporal patterns of exposure and the resulting effective dose associated with the induction of allergic sensitization is an important consideration in the development of OELs. The effective dose, if identifiable, could serve as the point of departure on which an OEL can be based or aid in the construction of the concentration-response relationship. Determining the effective dose associated with allergic sensitization is difficult due to the large variability in temporal exposure patterns. For example, workplace exposures can generically be characterized as repeated (i.e., cumulative) exposures or short-term, peak (i.e., acute) exposures. Both temporal patterns may contribute to the development of respiratory allergic diseases, but there is a lack of information on whether one temporal exposure pattern is of greater relevance to the onset of allergic sensitization and diseases.⁽⁵²⁾

Cumulative dose is the amount of chemical in the body or target organ system, integrated over repeated exposure events. Available evidence indicates that cumulative dose is an important predictor of response. Several diisocyanate studies where exposure was estimated as cumulative exposure rates have reported associations between exposure and hypersensitivity disease.^(60, 61) The role of cumulative or repeated exposures may relate to accumulation of the dose and biological response (e.g., build-up of antibodies). In addition, the dose of TDI can be increased by increasing exposure time, with dose \times time-response relationships.⁽⁶²⁾ Malo et al. (1999) studied the pattern of respiratory response (decline in forced expiratory volume in one second (FEV1)) following inhalation challenges to diisocyanates. Several dose-response patterns were observed, with the most common being a linear drop in FEV1 with cumulative dose (exposure challenges from 1–2 hr per day over 3+ days), although a quadratic response relationship were observed in several subjects.⁽⁶²⁾ The authors speculated that the response patterns observed may be due to an accumulation of isocyanate haptenated protein in the body over the test period and changes in immune response components. In contrast, insufficient data are available to determine the role of acute exposures on the induction of respiratory sensitization.

For most chemical respiratory allergens, the profile, biology, and impact of temporal exposure patterns is poorly understood.^(24,52) These uncertainties make it difficult to select the best time duration to serve as the basis of an OEL. More precisely, these limitations complicate the evaluation of the appropriate short-term exposure limit (STEL) for an LMW allergen when compared to an 8-hr TWA-OEL. The STEL is a 15-min TWA exposure that should not be exceeded within a single 8-hr day. Banks et al. demonstrated that a 15-min exposure at the 8-hr TWA-OEL (at that time the OEL was 20 ppb) to TDI was sufficient to elicit an asthmatic attack in a sensitized worker.⁽⁶³⁾ What remains unknown is the role of such exposures on induction of sensitization in naïve individuals. In comparison, available data support a potential relationship between cumulative dose and immune response. Cumulative dose not only would account for repeated inhalation exposures, but also encounters with short-term, peak exposures to LMW allergens. Until the sufficient data are available to characterize the temporal exposure patterns and the associated biological responses, it appears that OELs based on cumulative dose associated with repeated inhalation exposures may be more achievable for protecting workers from the induction of allergic sensitization than the STEL.

Level of Sensitization and Severity of Elicited Response

The immune-mediated processes that result in naïve individuals developing sensitization do not stop once elicitation of an allergic disease has occurred. Subsequent exposures can result in increased sensitization to the allergens and elicitation of a more severe immune response. The exposure required to elicit a hypersensitivity response in a sensitized individual (threshold) will depend on the sensitization status.

Theoretically, the threshold to induce or elicit the hypersensitivity response is related to the amount of haptenated protein, but this is complicated by the (dose \times time) relationship as haptenated proteins have varying elimination rates from the body. Several diisocyanates studies where exposure was extrapolated as cumulative exposure rates have reported associations between exposure and hypersensitivity disease.⁽⁶¹⁾ In addition, the immunological processes that produce sensitization do not stop once a clinical response is elicited by subsequent exposure. While subsequent allergen exposure can boost immune sensitization, the sensitization (and inversely, the elicitation) dose-response curve can be bimodal. The exposure dose required to elicit a hypersensitivity response in a sensitized individual (threshold) will depend on the sensitization status. Thus, a high concentration exposure would be required to elicit a response in a minimally sensitized worker (or one who has become tolerant), and inversely a low concentration exposure may elicit a hypersensitivity response in a highly sensitized worker. This phenomenon is consistent with the finding from studies of exposure to diisocyanates and organic acid anhydrides.^(64,65)

Role of Exposure Route in Chemical Allergies

In occupational settings, inhalation and dermal contact are the primary routes of exposure. LMW allergens have been demonstrated to produce allergic sensitization and diseases via both routes.^(66–69) However, once an individual or animal is sensitized, elicitation of an allergic response to subsequent chemical exposure may occur independent of the sensitization exposure route.^(54,70–73) Skin exposures to LMW allergens, such as isocyanates and beryllium, may result in, or exacerbate, respiratory hypersensitivity diseases with subsequent airways exposure.^(4,68) This is contradictory to the historic perception that respiratory sensitization is achieved primarily, if not exclusively, via inhalation exposures to the chemical allergen.⁽⁴⁾ In contrast, available data illustrate that it is the immune system that is sensitized and not just the respiratory tract or skin (although allergen specific T-cells will preferentially home back from the lymph node to the site of exposure). For this reason, the contribution of both exposure routes resulting in allergic sensitization to the onset of hypersensitivity reactions, such as asthma or ACD, should not be discounted during the development of OELs or assessment of workplace exposures to allergens.

Most OELs for chemicals that are not allergens are intended to characterize airborne exposure levels that would protect from adverse health effects (i.e., cancer, irritation, or development toxicity) from the inhalation route. These OELs for general toxicity endpoints do not typically rely on dermal toxicity studies as their basis. In contrast, OELs for chemical allergens may need to reflect the combination of inhalation and dermal data. This reflects the absence of quantitative exposure-response data from inhalation studies and contribution of total systemic exposures to the allergic response. While there are methods available to quantitate inhalation exposure to many chemical allergens (especially chemically stable allergens such

as beryllium), the current practice of occupational hygiene is ill equipped to quantitate most dermal or aggregate exposures. Until the science of dermal exposure assessment matures, the focus of OELs for chemical allergens will continue to be placed on inhalation limits with efforts to support qualitative risk management practices for dermal exposures.

Exposure Assessment Challenges for LMW Allergens

An important area not adequately addressed in the current science surrounds accurate characterization of complex exposures to LMW allergens in the work environment. Some LMW allergens are inherently reactive and may occur in multiple chemical states, such as an oxidized byproduct that may be more potent as an allergen.⁽⁷⁴⁾ Capturing and stabilizing both the parent and all byproducts adds substantial analytical challenges. Another exposure assessment challenge reflects the difficulties in characterizing chemical mixtures of allergens. For example, many products contain mixtures of diisocyanates that may have varying allergic potencies, which has led to proposal of establishing both analytical methods and OELs for total diisocyanates.⁽⁷⁵⁾ Whether real-time chemical specific instruments can be developed to quantify mixed allergen exposures in workplace atmospheres is an open area of research. An additional complicating factor is exposures via multiple routes. As previously discussed, allergic sensitization and diseases are systemic in nature and the proportional contributions of the individual exposure routes are usually unknown. Techniques to measure dermal exposures for LMW allergens, in many cases, do not exist. Further, the condition of the skin barrier at the time of exposure is often neglected despite the importance of the stratum corneum barrier in dermal penetration.

Collectively, these exposure assessment challenges fundamentally inhibit the derivation and use of OELs for chemical allergens in two primary ways. First, exposure measurements in existing occupational epidemiological studies may be inaccurate and prevent their use as the basis of an OEL. Second, the workplace environment is dynamic resulting in field level exposure measurements that are subject to the same challenges when used for occupational risk assessment (i.e., comparison of the exposure to the OEL). Improvements in exposure science may facilitate the collection of reliable measurements that accurately describe the workplace conditions.⁽⁷⁶⁾

Techniques for Developing OELs for Chemical Allergens

Despite the challenges in setting OELs for respiratory chemical allergens a variety of approaches have been used or are being developed. Most organizations that set OELs rely primarily on human effects and exposure data. However, research into *in vivo* toxicology methods using laboratory animals shows promise.^(58, 77–79) Alternative approaches that support risk assessments include the use of predictive *in vitro* and *in silico* methods as tools for identifying potential toxicological endpoints for OEL assignment. The following sections highlight each of these techniques in greater detail.

OELs Based on Human Effects and Exposure Data

OELs have been established for a small number of chemical allergens (see Table I). Despite their chemical diversity, these chemicals share the feature of having sufficient human effects and exposure databases that serves as the basis of the OELs. The unique features of the immunological concentration-response behavior of allergens as noted above supports the emphasis on reliable human effects data. This is reflected in the basis for OELs established for known respiratory sensitizers, all of which relied directly on concentration-response data from worker populations. Data of sufficient quality are often not available, which hampers the OEL development process and has led to significant efforts to develop validated animal models for sensitization of the respiratory tract.

Other sources of human data used to confirm allergic sensitization in individuals exhibiting symptoms with a suspected etiology are diagnostic tests. These tests are designed to assess responses in sensitized individuals and are not intended to describe a concentration-response. The results of such tests are useful for hazard characterization purposes, but are not capable of serving as the basis of an OEL.

OELs Based on Data from Animal Test Protocols

Animal data are commonly employed to derive OELs based on non-immune-mediated health endpoints (e.g., cancers, systematic toxicity and irritation) when human effect and exposure data are unavailable.⁽³³⁾ Use of animal toxicology data represents an alternative approach for the derivation for OELs for chemical allergens. Several animal test protocols have been proposed for characterizing and quantifying immune-mediated respiratory diseases, in addition to potentially allowing for construction of a concentration-response relationship for respiratory sensitization.^(4,58,66,78,80–82) The current suite of experimental study protocols rely on different animal species (i.e., guinea pig, mouse, rat), exposure regimens (i.e., route, dose and timing) and health endpoints of interest (i.e., airway response, airway histopathology, biomarkers of exposures).^(4,58,77,78) These techniques have not been validated and their ability to assist in setting OELs for chemical allergens has not been widely accepted.

Currently, efforts are underway to refine and validate *in vivo* respiratory sensitization assays including the respiratory local lymph node assay (LLNA) and other protocols that include direct measures of respiratory response in rodents.^(53–56,78) Several factors influence generation of pulmonary exposures for these tests, including chemical solubility and stability in the vehicle, vehicle selection, and variability in lung deposition between species and cross route exposure (i.e., dermal exposure). As such, requirements for sophisticated equipment and associated expenses have increased the difficulty of these types of tests.⁽⁵⁸⁾ Direct measures of sensitization that may serve as potential points of departure in this model may include production of hapten-specific IgE, cell proliferation in pulmonary-associated lymph nodes, production of specific cytokines, mRNA, miRNA, and proteomic profile. Despite the

promise of this approach, the utility of these alternative models is still questionable. Additionally, few chemical allergens have been examined and the usefulness of data generated from these animal test protocols for OEL development process is unclear. Among the various experimental methods under development, data generated by the Brown Norway rat protocol has been used to derive an OEL for TDI based on the elicitation of allergic respiratory response in sensitized animals.⁽⁸³⁾ A potential limitation of this model is the inability to distinguish between immune mediated and irritant inflammatory and airway responses from the responses. Despite the use of this model to develop an OEL, it is unclear if this can be widely applied to numerous LMW respiratory allergens. Another potential shortcoming is the use of elicitation of an allergic respiratory response as the basis of the OEL instead of respiratory sensitization. As previously discussed, it would ideal if OELs for LMW allergens were based on a concentration-response relationship for sensitization rather than elicitation.

Table II provides brief descriptions of well-validated animal testing protocols capable of assessing the potential of LMW allergens to cause sensitization following dermal application. Of these protocols, the LLNA may be the most widely applied for new chemical hazard characterization. This animal test protocol estimates a concentration of the test chemical that yields a 3-fold increase in lymphocyte proliferation in treated mice (i.e., the EC₃) when compared to a control substance.⁽⁸⁴⁾ The EC₃ value has been suggested as a potential point of departure for quantitative risk assessments when ACD is the critical health endpoint.⁽⁸⁵⁾ For select strong respiratory sensitizers,^(55, 56, 86, 87) dermal LLNA data may serve as a potential source of information considered during the derivation of an OEL developed via route-to-route extrapolation. To conduct route-to-route extrapolation, several core assumptions must be made that result in uncertainties associated with exposure pathway differences and potency. These assumptions are as follows.

- The potential for a chemical to cause sensitization is independent of exposure route. This assumption attempts to account for the biological mechanistic differences between the induction of sensitization via the skin and respiratory routes.
- The potency of the chemical is dependent on the internal concentration of the chemical regardless of route of administration.
- The absorbed dose is assumed to be 100% of the applied dose used during the LLNA study; this allows for the estimation of a respiratory dose equivalent.

These uncertainties have precluded the direct derivation of an OEL from dermal LLNA data. Additional understanding of route specific mechanisms of allergic sensitization and diseases would overcome uncertainties and allow for the use of dermal sensitization data as the quantitative basis of OELs.

TABLE II. Overview of Animal Test Protocols Designed to Determine Skin Sensitization

Name	Protocol/Outcome
Modified Draize Test (MDT; mouse) ⁽¹¹⁰⁾	<ul style="list-style-type: none"> • The assay is conducted in two phases, induction and challenge. Induction phase is conducted by the administration of four intradermal injections in the shaven flanks; injection locations correspond with areas drained by specific lymph nodes. The challenge phase occurs on day 14. Intradermal injections at nonirritant concentrations are administered. At 24 hr, skin responses are examined. • Skin responses to the challenge injection are graded and their size evaluated. Results are subjective in nature.
Buehler Test (guinea pig) ⁽¹¹⁰⁾	<ul style="list-style-type: none"> • The assay is conducted in two phases, induction and challenge. During the induction phase, one to three weekly occlusive topical applications of the test substance at slightly to moderately irritating concentrations are applied to shaven patches on the shoulder of animals. This occurs for 3–9 weeks. Fourteen days after the last induction exposure is conducted, the challenge phase begins. Nonirritating concentrations of the test substance are applied topically to a naïve shaven site and covered for 6 hr. • Skin responses are examined and graded on a scale similar to the one used in the MDT. Evaluation of the graded skin response is based on two parameters. The first parameter, called the incidence index, refers to the percentage of animals that responded positively to the challenge phase. The second parameter, called the severity index, provides an estimate of the total sum of reactions grades divided by the number of exposed test animals.
Guinea-pig Maximization Test (GPMT; guinea pig) ⁽¹¹¹⁾	<ul style="list-style-type: none"> • Procedure designed to subjectively screen the allergenicity potential of test substances. The assay is conducted in two phases, induction and challenge. Induction is conducted in two distinct stages. In stage 1, animals receive paired intradermal injections in the shaved shoulder region along with and adjuvant to boost the potential immune response on day 1. In stage 2, animals receive a topical occlusive patch containing the test substance applied to the shaved shoulder region on day 7; this patch is removed 48 hr after application. Challenge is performed on day 21 by the topical application of a nonirritating concentration of the test substance on an occluded naïve site on the flank of test animals for 24 hr. Responses are evaluated at 24 hr and 48 hr after challenge dose is applied. • Skin responses are graded with a standard rating scale that allows for the standardized classification of allergenic potential. Score assigned ranges from none to extreme responses.
Mouse Ear Swelling Test (MEST; mouse) ⁽¹¹⁰⁾	<ul style="list-style-type: none"> • Procedure designed to quantitatively measure mouse ear thickness as an indication of allergic response. The assay is conducted in two phases, induction and challenge. Induction is conducted in two distinct stages. In phase 1, test animals are pretreated with an intradermal injection in the shaved abdomen. Topical application of the test substance occurs for 3 consecutive days at the site of the injection. The challenge phase begins on day 10 after a 1-week recovery period with the topical application of a lower concentration of the test substance to one ear, while a vehicle is placed on the opposing ear. Ear thickness measurements are taken at 24 hr and 48 hr post topical application. • If the increased ear thickness of one or more test animals is 20% greater than the thickness of the controls' ears, then the test substance is identified as a sensitizer. Potency of the sensitizer is based on both the increased ear thickness and number of animals with positive responses.
Murine Local Lymph Node Assay (LLNA; mouse) ⁽¹¹⁰⁾	<ul style="list-style-type: none"> • Procedure capable of determining the relative allergenic potency of a test substance. Animals are treated topically with the test substance at a selected concentration for 3 consecutive days. Five days after the first treatment, test animals receive an injection of a radiolabelled chemical that is incorporated within lymphocytes contained within the lymph nodes draining the sites of exposure. • Measurement of the proliferation of lymphocytes provides a quantitative estimate of sensitization potential. Results are reported as Stimulation Index (SI), which refers to a comparison of the net increase of lymphocytes or proliferation rate within test animals compared to controls. Skin sensitizers are identified as chemicals that are able to induce an SI of 3 or greater (i.e., a 3 times or greater response in test animals as compared to controls) at a given concentration.

TABLE III. Qualitative Hazard Notations Designations for Chemical Allergens

Organization	Designation	Definition	Reference
ACGIH	SEN	<ul style="list-style-type: none"> • Potential for an agent to produce sensitization, as confirmed by human or animal data; may refer to dermal and/or inhalation sensitization 	ACGIH ⁽¹⁰¹⁾
	RSEN	<ul style="list-style-type: none"> • Respiratory sensitization notation - used in place of the SEN notation when specific evidence of sensitization by the respiratory route; does not imply that sensitization is the critical effect on which the TLV is based 	
	DSEN	<ul style="list-style-type: none"> • Dermal sensitization notation used in place of the SEN notation when specific evidence of sensitization by the dermal route; does not imply that sensitization is the critical effect on which the TLV is based 	
CAL/OSH	“D” SEN	<ul style="list-style-type: none"> • Substances can cause occupational dermal sensitization responses even when exposures do not exceed the values (i.e., PEL) 	CAL/OSHA ⁽¹¹²⁾
	“R” SEN	<ul style="list-style-type: none"> • Substances can cause respiratory sensitization 	
GHS	Hazard statement 317 Skin sensitizer – Category 1	<ul style="list-style-type: none"> • May cause an allergic skin reaction • Substance causes skin sensitization within humans or animals 	UNECE ⁽¹⁰⁰⁾ ; EC ^{(113)*}
	Hazard statement 334*	<ul style="list-style-type: none"> • May cause allergy or asthma symptoms or breathing difficulties if inhaled 	
	Respiratory sensitizer – Category 1	<ul style="list-style-type: none"> • Substance causes respiratory sensitization within humans or animals 	
NIOSH	SEN	<ul style="list-style-type: none"> • Potential for immune-mediated reactions following exposure(s) of the skin 	NIOSH ⁽⁹⁸⁾

ACGIH = American Conference of Governmental Industrial Hygienists; CA OSHA = California Occupational Safety and Health Administration; GHS = Globally Harmonized System for the Classification and Labeling of Chemicals; DSEN = dermal sensitization; PEL = permissible exposure limit; RSEN = respiratory sensitization; SEN = sensitization

Additional Approaches and Impacts on OEL Derivation

Incorporation of data based on chemical and physical similarities to known allergens (i.e., structure-activity relationship approaches) may also provide a means to derive an OEL. The final approach relies on relative potency factors (RPFs), which can be defined as ratios of the toxic potency of a selected chemical relative to an index chemical that exhibits the same toxic mechanism.⁽⁸⁸⁾ A method has been previously applied to characterize the comparative toxicity of specific categories of chemicals, including organophosphates and polycyclic aromatic hydrocarbons, in human health risk assessments.^(89,90) Using the RPF approach for chemical allergens that produce their immune effects through similar mechanisms and especially if they are of the same chemical class may allow for the

establishment of scientifically-defensible OELs for chemicals that independently do not have sufficient data. For example, many diisocyanates have been identified as chemical allergens with varying sensitization potency;⁽⁴⁾ however, availability of data on the individual diisocyanates varies greatly. Application of the RPF approach may allow for the development of OELs for diisocyanates with limited data based on the datasets for those members of the chemical family that are well studied.

The quantitative risk assessments and the development of OELs using the RPF approach may be enhanced through the inclusion of *in vitro* and *in silico* information sources that can provide supplemental information in the absence of human effect and exposure data on each chemical.^(9, 91–95) Efforts to validate these models have been the subject of significant

TABLE IV. Risk Management Guidance for Chemical Allergens

Control Technique	Specific Control	Areas of Increased Emphasis in Allergen Risk Management
Substitution	Molecular substitution	<ul style="list-style-type: none"> • Replace chemical allergen with alternative non-allergenic molecule • Encapsulate or modify chemical at the molecular level to reduce access to allergenic moiety
Engineering	Process Design	<ul style="list-style-type: none"> • Limit the use of chemical allergen at latest possible phase in process to minimize the potential duration of exposure and the need for engineering controls • Select equipment and processes that minimize aerosol generation of LMW chemical allergen • Develop plan for spill containment of LMW chemical allergen
	Isolation	<ul style="list-style-type: none"> • Enclose operations where chemical allergens are added, used, stored, or disposed
	Ventilation	<ul style="list-style-type: none"> • Local exhaust ventilation (LEV) should be used in areas where chemical allergens are added into the process, stored, or disposed • Maintain equipment at a negative pressure to ensure inward flow of air to prevent escape of LMW chemical allergen • Dilution ventilation should be used to supplement LEV
Administration	Work-practice	<ul style="list-style-type: none"> • Management systems should be developed to main hygiene standards within the workplace • Operational controls should be put in place to achieve no visible dust, no recurring spills, no gross skin contact, and prevention of aerosol generation • Worker education program should include an overview of the health effects of LMW chemical allergens, use of controls, safe work practices, and contingency measures for spills or releases of the LMW chemical allergens • Access to high risk activities and locations should be restricted • Safe work practices should be established that provide guidance on good personal and workplace hygiene, storage, use, and disposal of LMW chemical allergens, and clean-up of spills
	Medical monitoring	<ul style="list-style-type: none"> • Medical monitoring should be conducted for workers potentially exposed to LMW chemical allergens to assess and monitor their health. Programs should attempt to identify workers who have early or pre-clinical work-related allergy/asthma • Symptom questionnaires are an essential component of medical surveillance of such workers, in addition to tests for sensitization and exposure biomarkers, where available
	Exposure monitoring	<ul style="list-style-type: none"> • Exposure monitoring should be conducted to validate the efficacy of engineering controls, ensure airborne concentrations are maintained below OELs, hazard banding range, or other exposure recommendations • Exposure monitoring should focus on both air and surface contaminant (wipe and skin) sampling
Personal Protective Equipment (PPE)	PPE program	<ul style="list-style-type: none"> • Programs should emphasis the use of respiratory and skin PPE capable of protecting workers from the specific chemical allergen • Use of PPE should be directly coupled with engineering and administrative controls • PPE reuse should be limited to prevent secondary exposures; if reused, decontamination protocols should be established • Workers should be educated on the use and decontamination of PPE

TABLE V. Checklist Summary of Key Considerations During Assessment of Health Risks Associated with Chemical Allergens

Critical Question(s)
Is there an allergen risk for this task/workplace?
Is the chemical an allergen?
<ul style="list-style-type: none"> ■ What guidelines are available (i.e., OELs, hazard notations)? ■ What data are available (i.e., epidemiology, animal, in vitro)? ■ How can data be integrated?
What are the exposure levels within the workplace?
<ul style="list-style-type: none"> ■ What exposure pathways are important? ■ What are the temporal patterns (i.e., acute [peak] exposure vs. full shift exposure)? ■ What physical forms (particulates, gases/vapors) are important?
For the task/workplace, is there an allergen risk? If so, what is the severity of the risk?
<ul style="list-style-type: none"> ■ Are data capable of deriving an OEL? ■ Are data capable of assigning a hazard band? ■ Are data capable of assigning a hazard notation?
What control strategies are needed to mitigate the risk?
<ul style="list-style-type: none"> ■ Manage to prevent sensitization? ■ Manage to prevent elicitation?
Strategy for communicating in place?

review.^(94,96) These techniques have not yet been adopted as the basis for an OEL on their own, but they have been used for qualitative hazard characterization, including assignment of hazard notations or as one input into a hazard banding process.^(32,97–100)

DISCUSSION

Many OELs for non-allergen chemicals are based on human health effect and exposure data.⁽¹⁰¹⁾ Unfortunately, such data are not available for most chemical allergens. This absence of human data coupled with a lack of established and validated animal models capable of characterizing the concentration-response relationships for respiratory sensitization makes it difficult to develop OELs based on allergic effects as the critical endpoint. Instead, OELs for many chemicals with some potential for sensitization are derived from other non-immune endpoints, such as respiratory irritation or systemic toxicity. The ability of these OELs to be protective against allergic sensitization and diseases is unknown leaving workers potentially vulnerable to life-threatening immune-mediated effects. Until the critical challenges in setting OELs for chemical allergens are addressed, greater emphasis must be placed on the implementation of comprehensive risk management strategies designed to specifically prevent or limit workplace exposures to chemical allergens via the dermal and inhalation pathways. Failure to do so could result in sensitized workers that, upon repeat exposure to an allergen, may experience a continuum of immune-mediated responses ranging from mild ACD to life-threatening cases of asthma.

In the absence of established quantitative risk assessment techniques capable of developing OELs for chemical allergens,

numerous qualitative approaches have been applied to provide alternative exposure recommendations that provide guidance on the health hazards of allergens and assist in the development of a well-informed risk management strategy. Two common approaches are (1) qualitative hazard notations and (2) hazard banding (occupational exposure banding).

Qualitative hazard notations or designations function as a communication tool used for risk management purposes. They are intended to identify specific health concerns, such as sensitization rather than characterize airborne concentrations of a chemical capable of resulting in allergic responses. Table III provides an overview of hazard notations established for chemical allergens by numerous OEL-setting organizations. The criteria, level of documentation and data requirements used to assign these notations vary widely between organizations. For example, NIOSH outlines a systematic approach based on weight of evidence for the assignment of multiple hazard notations that target specific dermal health hazards, including sensitization (SEN).⁽⁹⁸⁾ Each notation is accompanied by a robust summary of the critical data and rationale used to assign a specific notation. However, the NIOSH notations are limited to dermal hazards and do not address respiratory sensitization.^(98,99) In comparison, the Globally Harmonized System for the Classification and Labeling of Chemicals (GHS) assigns notations for several endpoints, including respiratory and dermal sensitization.⁽¹⁰⁰⁾ Governmental agencies, private industry and other groups are using this approach both domestically and internationally to characterize the health and environmental hazards of chemicals. Depending on the organization that generates the GHS notations, the documentation, rationale and data used to assign the GHS notations may not be available to the public. The second qualitative

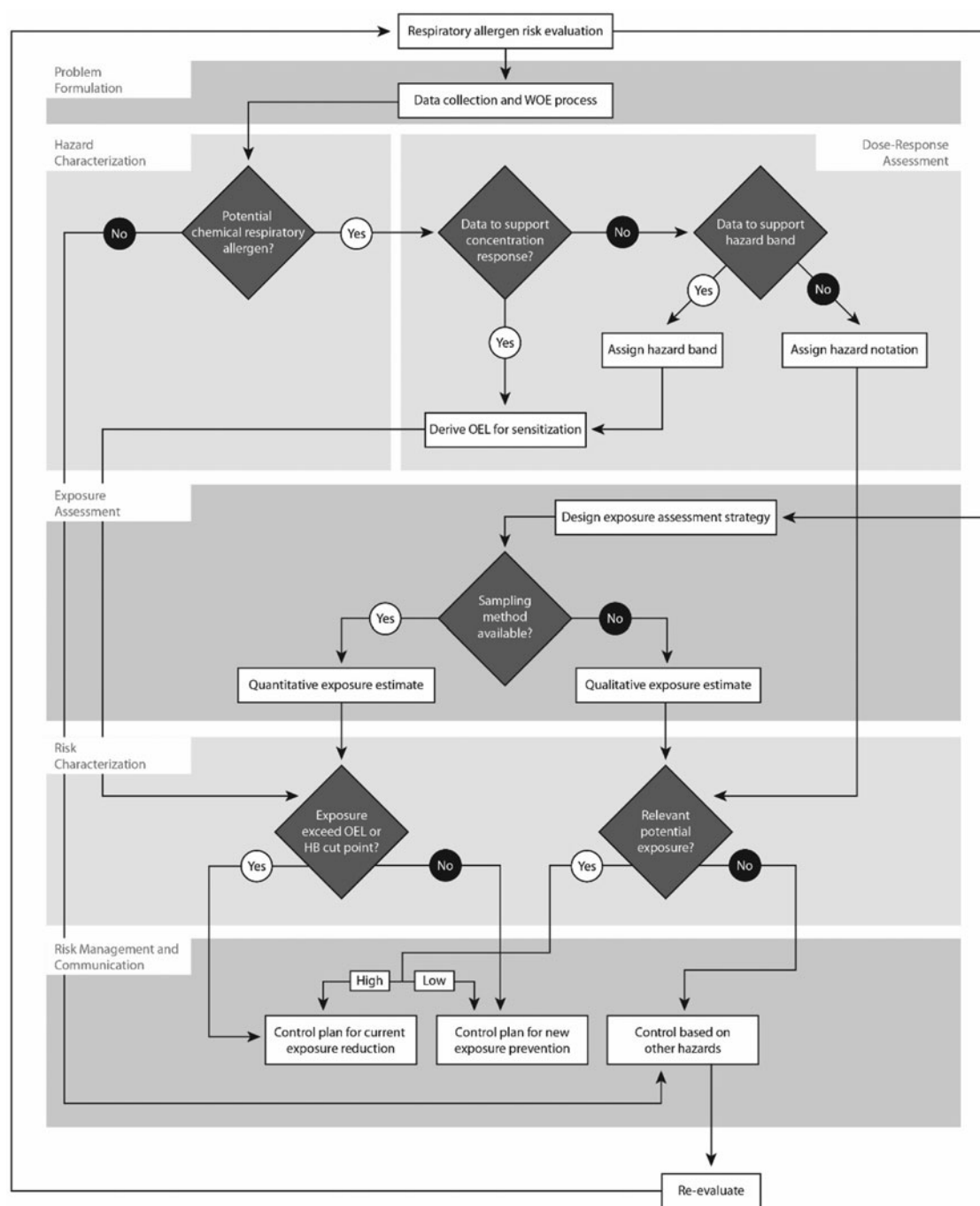


FIGURE 2. Consideration in assessing the health risks of potential chemical allergens. HB = hazard band; OEL = occupational exposure limit; WOE = weight of evidence. The flowchart illustrates key consideration during the risk assessment of potential chemical allergens. On the basis of the risk assessment paradigm, the outlined process relies on a weight of evidence approach to critically evaluate available data. Included within the flowchart are options within each of the primary steps: hazard characterization, dose-response analysis, exposure assessment, risk characterization, and risk management and communication. These options allow for the evaluation of data, determining appropriate level of recommendation developed (i.e., hazard notation vs. occupational exposure limit), type of exposure assessment, and control technique.

approach is hazard banding, which attempts to systematically categorize chemicals in “bands” or categories using predefined criteria based on selected physicochemical and toxicological properties. Criteria typically cover a variety of toxicological endpoints ranging from acute toxicity to systematic toxicity

from repeated exposures to special endpoints of concern (i.e., irritation, sensitization, developmental toxicity and carcinogenicity). Many banding systems link predefined criteria for these health endpoints with hazard labeling and classification schemes, such as GHS. The banding approach has been

successfully applied within the pharmaceutical industry for decades to limit workers' exposures to potent chemicals (not all of which are sensitizers) and is increasingly being applied across other industries.^(32,97) The hazard bands identified are commonly used to guide the selection of exposure control stringency.^(102, 103) Application of hazard banding provides a tool to identify potential respiratory and dermal sensitizers, in addition to assisting in making informed risk management decisions.

A comprehensive risk management strategy intended to protect workers from allergens incorporates several core elements. Primary prevention involves implementing strategies before induction of sensitization occurs. Interventions in preventing sensitization include avoidance of sensitizing agents, modifying the agent (i.e., encapsulation of agent), reduced exposure by containment or personal protective equipment and education.⁽²¹⁾ Secondary prevention involves early detection and limiting progression of disease, such as limiting the clinical manifestations in a sensitized individual. Secondary preventive interventions include: (1) workplace (air and biological) monitoring;⁽¹⁰⁴⁾ (2) medical surveillance;^(30, 105-107) and (3) application of the hierarchy of controls.^(104, 108, 109) These important monitoring and surveillance strategies do not need to be limited to secondary prevention. Table IV provides generalized recommendations for controls to prevent or limit workplace exposures to allergens. Table V and Figure 2 are included to assist users in addressing critical issues and developing risk management strategies aimed at controlling workplace exposures to chemical allergens.

CONCLUSIONS

Chemical allergens represent a significant health hazards for workers. A limited number of OELs have been established for respiratory LMW allergens based almost exclusively on epidemiology and human exposure data that allow for the extrapolation of concentration-response relationships. For most respiratory allergens, such data sets are not available to construct the concentration-response relationship. The absence of human effect and exposure data coupled with other critical limitations, such as the absence of animal test models capable of predicting respiratory sensitization potential, currently inhibits the ability to develop OELs for most LMW allergens. Approaches, such as the *in vivo* assays and biomarkers of sensitization, hold great promise in assisting in the development of concentration-response relationships between exposures to LMW allergens and onset of immune-mediated respiratory diseases and subsequently the development of OELs. Until these approaches are appropriately vetted and refined, the health risk of allergens in the workplace must be addressed via the combination of appropriate exposure control technologies and practices and qualitative hazard characterization approaches, such as hazard banding and hazard notations, with well-informed risk management efforts.

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