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Workshop report

Developing a framework for assessing chemical respiratory sensitization: A workshop report

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ABSTRACT

Respiratory tract sensitization can have significant acute and chronic health implications. While induction of respiratory sensitization is widely recognized for some chemicals, validated standard methods or frameworks for identifying and characterizing the hazard are not available. A workshop on assessment of respiratory sensitization was held to discuss the current state of science for identification and characterization of respiratory sensitizer hazard, identify information facilitating development of validated standard methods and frameworks, and consider the regulatory and practical risk management needs. Participants agreed on a predominant Th2 immunological mechanism and several steps in respiratory sensitization. Some overlapping cellular events in respiratory and skin sensitization are well understood, but full mechanism(s) remain unavailable. Progress on non-animal approaches to skin sensitization testing, ranging from *in vitro* systems, –omics, *in silico* profiling, and structural profiling were acknowledged. Addressing both induction and elicitation phases remains challenging. Participants identified lack of a unifying dose metric as increasing the difficulty of interpreting dosimetry across exposures. A number of research needs were identified, including an agreed list of respiratory sensitizers and other asthmagens, distinguishing between adverse effects from immune-mediated versus non-immunological mechanisms. A number of themes emerged from the discussion regarding future

Abbreviations: AOP, adverse outcome pathway; APC, Antigen Presenting Cell; BAL, bronchoalveolar lavage; CLP, Classified, Labeling and Packaging Regulation; DC, dentritic cell; DNCB, 2,4-dinitrochlorobenzene; DPRA, direct peptide reactivity assay; EC, endothelial cells; ELoC, equivalent level of concern; GARD, Genomic allergen rapid detection; GHS, Globally Harmonized System; ITC, Immunotoxicology Technical Committee; KC, Kupffer cells; LC, Langerhans cells; LLNA, Local Lymph Node Assay; LMW, low molecular weight; LRI, Long Range Research Initiative; MDI, diphenylmethane-4,4′-diisocyanate; MIE, molecular initiating event; MOA, mechanism of action ; NOAEL, no-observed-adverse-effect-level; OA, occupational asthma; OECD, Organization for Economic Co-operation and Development; OVA, ovalbumin; JCIA, Japanese Chemical Industry Association; PMN, polymorphonucelar leukocytes; PRR, pathogen recognition receptors; REACH, Regulation concerning the Registration, Evaluation, Authorization and Restriction of Chemicals; SAF, sensitization assessment factor; SAR, structure activity relationship; SVHC, substance of very high concern; TDI, toluene diisocyanate; TMA, trimellitic anhydride; WoE, weight-of-evidence.

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testing strategies, particularly the need for a tiered framework respiratory sensitizer assessment. These workshop present a basis for moving towards a weight-of-evidence assessment.

1. Introduction

Respiratory sensitization is a health hazard that can occur following exposure to chemical or biological materials. The adverse outcome is an allergic-type response of the airways, mostly asthma or rhinitis. The disease develops in two phases: the sensitization or induction phase in which the immune system is primed and the elicitation phase in which the allergic symptoms occur. Respiratory sensitization/allergy is characterized by a progressive increase in immune system responsiveness, such that sensitized individuals respond to exposures that elicit no effect in non-sensitized populations. Accurate identification of respiratory sensitizers is important because the health effects can be severe and long-lasting. At the same time, incorrect identification of a material as a respiratory sensitizer can result in unnecessarily stringent restrictions on use.

From a toxicological perspective this human health hazard presents a number of challenges, including the uncertainty regarding the mechanisms through which sensitization of the respiratory tract to chemicals is acquired. This has hindered development of methods for the identification and characterization of chemical respiratory allergens. The Globally Harmonized System (GHS) for hazard classification considers evidence from human responses, or "appropriate animal models" which are not standardized. Unlike other hazard endpoints used for classification, there is not an internationally accepted animal test guideline. Different published protocols exist for assessing respiratory sensitization, but no systematic undertaking has validated any of the methods for a broad range of materials. Historically, the guinea pig has been the species of choice for research on respiratory sensitization due to physiological similarities of respiratory reactions compared to humans. Time and cost considerations, as well as a lack of suitable immunochemical or molecular probes for mechanistic evaluations, have led many to look for other animal, and non-animal alternative, test systems. Experimental models using rats and mice have been successful in inducing chemical respiratory sensitization, but the parameters providing best predictive performance remain unknown. Current alternatives face challenges in the form of a relatively limited chemical respiratory sensitizer database and knowledge limitations related to which exposure-response parameters are the best predictors of respiratory sensitization. The ability to accurately detect potential respiratory sensitizers is ultimately hindered by the absence of standard, validated and regulatory accepted methods to identify potential respiratory sensitizers and distinguish them from irritants and skin sensitizers for hazard identification. The difficulty in distinction is further compounded by absence of generally accepted methods to define dose thresholds for irritation, which may make distinguishing between immune-mediated and non-immunological responses unclear.

The lack of defined approaches for evaluation of respiratory sensitization potential has necessarily represented a major constraint on effective risk assessment and risk management, and on addressing satisfactorily the requirements of regulations such as the Regulation concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH). There is increasing regulatory pressure to list respiratory sensitizers as substances of very high concern (SVHC) based on an "equivalent level of concern" as set out in REACH Article 57(f). This approach assumes that in certain cases, the impacts caused by sensitizers (respiratory or dermal) on the health and quality of life of the affected individual and the negative impacts on society as a whole are comparable to those elicited by carcinogens, mutagens, and reproductive toxicants (CMRs). Potential factors for comparison include severity of the effect, delayed onset and/or irreversibility of effects, potency, mode of action, degree of impairment of life quality or uncertainty about the dose–response relationship. As there are currently no applicable guidelines or generally accepted assays that can accurately identify respiratory sensitizers nor distinguish between respiratory and dermal sensitizers, all materials with sensitizing potential, despite their potency, may be inaccurately considered for inclusion as SVHC. If an evidence-based, adverse outcome pathway (AOP)-informed approach to assessment is desired there is an increasingly important need, therefore, to seek integrated approaches to toxicity testing and assessment to bridge this gap.

The Immunotoxicology Technical Committee (ITC) of the International Life Sciences Institute-Health and Environmental Sciences Institute previously organized two activities centered on the state-of-the-science of testing methods to identify proteins and chemicals that pose a risk of immune-mediated respiratory hypersensitivity. An expert roundtable discussion, held in 2003 at the Annual Meeting of the Society of Toxicology in Salt Lake City, Utah, was followed by a two-day international workshop in June 2004 that addressed the appropriate methods for identifying and characterizing respiratory hypersensitivity hazards and risks, and the key gaps and related research needs with respect to respiratory hypersensitivity/allergy for proteins, low molecular weight drugs, and chemicals (Holsapple et al., 2006). Key research gaps identified for chemical-specific respiratory hypersensitivity included (1) understanding structure activity relationships for chemical allergies, including understanding the mechanism(s) for respiratory hypersensitivity and identifying distinctive characteristics of the respiratory hypersensitivity allergic response, and continuing to build databases of sensitization until chemicals can be clearly identified as respiratory allergens; (2) better understanding of mechanisms for sensitization; and (3) fully characterizing cytokine profiling as a possible approach for hazard identification.

Given a decade's passage and expectation of continuous progress of science, in 2014 the ITC organized a two-day international workshop in Alexandria, Virginia, towards identifying a framework for developing a standard approach for identifying chemical respiratory sensitizers. (The workshop agenda and materials can be found here: http://hesiglobal.org/event/workshop-on-the-assessment-of-respiratory-sensitizers.) The workshop opened with a presentation on the clinical manifestations of respiratory sensitization. The subsequent series of lectures provided a foundation for the current state-of-the-science for identification and characterization of respiratory sensitizer hazards, using both conventional and non-conventional approaches, and the regulatory and practical needs regarding risk management, with the ultimate aim of identifying near-term and long-term information to facilitate development of validated standard methods and frameworks. The ~75 participants were asked to consider a series of questions that provided a framework for discussions during the break-out sessions. The lectures and break-out discussions provided the