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Occupational Asthma and Challenges in Classifying Chemical Respiratory Allergens

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ABSTRACT

Respiratory Sensitisation is a serious health condition that can have life-threatening consequences and that is regulated under the UN globally harmonised system (GHS) and the European system for classification, labelling and packaging of hazardous chemicals and mixtures (CLP). In the absence of widely accepted and validated approaches for the prospective identification of chemicals that induce respiratory sensitisation, classification relies on clinical evidence of causation of substance-specific respiratory hypersensitivity, typically seen as occupational asthma. Significant advances have been made in recent years in the phenotyping of both asthma and occupational asthma since the introduction of criteria and guidance for classification that are not reflected in the current criteria and guidance. Typically generated clinical data, including specific inhalation challenge tests, while sufficient for diagnosis and health management are often deficient for regulatory classification purposes as they are often not sufficiently documented to meet the required standards and fail to reliably distinguish between occupational asthma and non-specific irritant exacerbation of pre-existing asthma that is regulated under another classification endpoint. A multistakeholder forum is proposed to facilitate revision of the now outdated criteria and guidance. Differences between underlying mechanisms of respiratory sensitisation and occupational asthma jeopardise establishment of an Adverse Outcome Pathway for respiratory sensitisation and development of alternative methods, including non-animal methods.

Keywords: Respiratory Sensitisation; Occupational Asthma; Work Exacerbated Asthma; Clinical Data; Specific Inhalation Challenge (SIC) tests; Classification, Labelling and Packaging (CLP); Globally Harmonised System of Classification and Labelling of Chemicals (GHS).

1. Introduction

Respiratory Sensitisation (RS), also known as respiratory hypersensitivity, is an immune response to inhaled substances that can lead to allergic reactions, particularly asthma. It is one of the manifestations of type I allergy. This process, in common with contact (skin) sensitisers (a manifestation of type IV allergy), involves an initial exposure (sensitisation phase) followed by subsequent reactions upon re-exposure (elicitation phase)[1]. RS is identified as a classifiable health hazard under the United Nations Globally Harmonised System of Classification and Labelling of Chemicals (GHS)[2] and as implemented within the EU under regulation 1272/2008 on the classification, labelling, and packaging of chemical substances and mixtures (CLP)[3]. On the basis that type I allergy can cause severe, potentially life-threatening reactions like anaphylactic shock[4] it is recognised under Article 57(f) of the EU's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation[5] as being of equivalent concern to carcinogenicity, mutagenicity and reproductive toxicity[6] and prioritised for regulatory action including restrictions, potentially limiting or banning substances of very high concern (SVHC) that pose unacceptable risks.

Although chemical-induced respiratory hypersensitivity has been known for decades, there are currently no widely accepted and validated approaches for the prospective identification of chemicals that induce respiratory sensitisation. Recent comprehensive reviews exist elsewhere[1,7]. Consequently, GHS and CLP criteria for classification recognise that "*evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience*" and that this is "*normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered.*" In this context, the criteria are referring to clinical evidence demonstrating the intrinsic property of a chemical to cause occupational asthma (OA) and the diagnosis consequently relies upon expert judgement of clinical and other evidence in a weight-of-evidence approach.

Clinical evidence confirming the presence of asthma and demonstrating a work-related pattern of disease indicative of causation of OA draws from a number of sources[8-10]. Initial suspicions of the development of OA can be raised by general practitioners or occupational physicians, where they exist. Asthma diagnosis is typically confirmed through a combination of tests and assessments, including lung function tests like spirometry and peak flow tests, along with a review of symptoms and medical history. Additionally, referral to specialist centres for further evaluation of lung function and airway sensitivity using bronchodilator responsiveness tests and challenge tests may occur. Confirmation of a work-related association is typically done through interrogation of patient medical and work histories combined with robust characterisation of exposure profile by a proficient industrial hygienist, and may lead to the identification of possible causative/exacerbating agents[11-14].

Work-related asthma (WRA)[15], i.e., asthma displaying a pattern of work-related clinical symptoms encompasses both asthma caused in the workplace (sensitiser induced (SIOA) and irritant induced (IIOA)) and asthma that is pre-existing and made worse by exposure to agents in the workplace (Work Exacerbated Asthma or WEA).

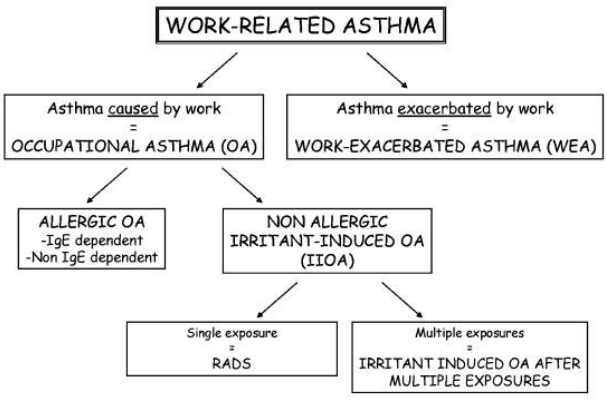

Figure 1. Classification of work-related asthma[15]

While it is generally accepted that it is important to distinguish between OA and non-specific WEA, it may be a moot point from a clinician's perspective whether there is a need to distinguish between SIOA and IIOA for occupational health management. As a result, the extent of the clinical evidence supporting a diagnosis may vary considerably.

Indeed, more often than not, if there is exposure to a putative respiratory sensitiser within the workplace then both a work-related association and causation are assumed[9]rather than identified by thorough workplace analysis. This impacts greatly on the utility of clinical data for regulatory classification purposes and the requirement to demonstrate causation, i.e., to demonstrate that a substance has led to specific respiratory hypersensitivity[16]. This article discusses those aspects of clinical and related data procurement that are essential for effective health management and regulatory classification and labelling purposes.

2. Management of Occupational Asthma (OA)

It is important to recognise from the outset that asthma per se is characterised by a complex pathogenesis[17-19] encompassing several well-defined phenotypes including: allergic, non-allergic, eosinophilic, neutrophilic, exercise-induced, and aspirin-induced[20-24]. Asthma is a very prevalent disorder[25,26] and it is within this setting that OA develops. Namely, a typical workforce will comprise both healthy individuals and asthmatics of varying degrees of sensitivity and susceptibility to WEA. This is reflected, but perhaps not sufficiently emphasised, in the generally accepted paradigm for WRA described by Moscato and coworkers[15] in which there is clear distinction between asthma caused in the workplace (SIOA and IIOA) and pre-existing asthma made worse by exposure to agents in the workplace i.e., WEA.

In practice, however, the distinction between new asthma being caused, and pre-existing asthma being exacerbated, by agents in the workplace is extremely challenging. This is in no small part due to the inevitable retrospective nature of the events leading up to the development of the disease, and difficulties in distinguishing between IIOA and non-specific irritant WEA[16].

Approximately 16% of new asthma diagnoses in adults is thought to be work-related (WRA)[27-29]. OA, or more correctly speaking WRA, is recognised as an important health issue due to its extremely distressing and potentially life-threatening nature[30], high prevalence and social and economic burden[14,31-36]. It has been reported that although the incidence of life-threatening asthmatic events is extremely low[37], individuals with WRA tend to express more severe symptoms when compared with their non-WRA counterparts[34]. In this regard, the incidence of severe asthma has been estimated to be between 16.2%[38] and 18%[39]. The extent to which selection bias impacts on these estimates is unknown.

It is only natural, therefore, that the primary objective of health management professionals is identifying and minimising exposure to workplace triggers, using medications to control symptoms, and implementing strategies to prevent future attacks. In this regard, early diagnosis and removal from the triggering substance are crucial for better outcomes[40]. Some health professionals may even hold the viewpoint that it is unnecessary to determine the underlying mechanism by which causation occurred, or even if it was exacerbation of a pre-existing condition rather than causation. Occupational physicians and industrial hygienists, however, are likely to hold a very different viewpoint as the management of OA risk in an occupational setting is very different. Depending upon whether the underlying mechanism is true respiratory sensitisation or irritant induced asthma, as opposed to exacerbation by non-specific stressor agents including general air pollution such as dusts, irritant chemicals, molds, smoke or fumes and even physical stressors like temperature and humidity, different risk management measures apply.

In the absence of comprehensive and validated approaches for the prospective identification of chemicals that induce respiratory sensitisation[1,7,41-47] it remains beholden upon respiratory physicians to make timely diagnostic decisions, often based upon incomplete data.

Nevertheless, there are unavoidable consequences of not sufficiently distinguishing between SIOA, IIOA and WEA that go beyond the immediate objective of optimising patient well-being and

healthcare outcomes. One likely consequence is that lists of "recognised" respiratory sensitisers in addition to including "true sensitisers" will also contain "false positive agents" that cause WEA as opposed to SIOA or IIOA. Proliferation of such lists based upon insufficiently defined or heterogeneous criteria encourage further a priori misdiagnosis that weakens then not only the basis of evidence-based medicine, but also research into approaches for the prospective identification of chemicals that induce respiratory sensitisation including new approach methodologies (NAMs)[1,7,16].

3. Clinical diagnosis of Occupational Asthma (OA)

Clinical guidelines for the diagnosis of OA have been developed and revised in recent years[9,27,48-53]. These guidelines converge in recommending investigation and comprehensive documentation of occupational and patient/familial clinical histories, and clinical data including a combination of physical examination, pulmonary function tests, allergy testing and bronchial provocation challenge tests. The scope and limitations of these investigations have recently been reviewed elsewhere[7].

Occupational history can provide valuable information on the patient's job history, workplace activities and, if supported by occupational hygiene data, exposure to chemicals that are recognised, or suspected, to be linked to WRA. Patient and familial clinical history, especially of allergies, eczema, or early respiratory infections can indicate not only pre-existence of asthma, but also inherited genetic predisposition and the individual's susceptibility to developing asthma. Additionally, understanding past exposures (like smoking or air pollution) and other respiratory health conditions can help identify potential confounding factors that might influence susceptibility, asthma development and severity. Clinical investigations can confirm the diagnosis of asthma and cross-shift pulmonary function tests like spirometry and peak expiratory flow (PEF) monitoring can confirm that symptoms are work or even task related. Additionally, marked Non-Specific Bronchial Hyperreactivity (NSBH) in a Methacholine challenge test can confirm the diagnosis of asthma and indicate increased susceptibility to non-specific irritation and WEA. While allergy testing has proven to be of value in identifying specific hypersensitivity to high molecular weight allergens, such as proteins, this has proven unreliable for most low molecular weight chemicals suspected of causing OA.

A positive bronchial provocation inhalation challenge tests conducted with specific substances, also known as the Specific Inhalation Challenge or SIC test, if conducted according to recognised guidelines, has been claimed to be the "gold standard" for a diagnosis of OA[9,52]. Indeed, the current criteria and guidance for classification and labelling (GHS and CLP) state that the results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. However, it has to be recognised that the SIC test only demonstrates that the specific substance under the exposure conditions used in the SIC test is capable of provoking a bronchial response in the subject. As such the test does not distinguish between OA and WEA.

The "recognised guidelines" do include recommendations to mimic typical workplace conditions and to monitor exposure levels during the SIC test so as to maintain these below the occupational exposure limit (OEL), thereby assuming that non-specific irritation will be avoided. This is an over simplification of what is often a very complex aspect of occupational health management. Firstly, this approach assumes that the OEL is protective not only for healthy personnel but also for asthmatic individuals that are being subjected to SIC testing. However, this may not necessarily be the case since the OELs are primarily designed to protect the health of the majority of healthy adult workers, they are not always sufficient to protect individuals with pre-existing conditions like asthma, especially those with work-related asthma. While OELs aim to prevent adverse health effects from chemical exposures, they often don't

account for the increased sensitivity of some individuals or the potential for substances to trigger or exacerbate asthma. In this regard, asthmatics have been reported to have up to three-fold greater bronchial sensitivity than their healthy counterparts[55]. Secondly, the profile of workplace exposures is typically complex with workers experiencing varying levels of exposure depending on the tasks they perform. These exposures often include background levels that are relatively consistent, overlaid with brief, but potentially high-intensity, "peak exposures" associated with specific tasks or operations. An individual's exposure profile can be further determined by the availability of engineering control measures, such as local exhaust ventilation, and the use of respiratory protective equipment. Only a comprehensive survey by a trained industrial hygienists will provide a reliable insight into the exposure conditions that are required to be mimicked in a SIC test. Furthermore, since it has been recognised that "*In practice, appropriate techniques for measuring the wide variety of agents causing occupational asthma are seldom available.*"[9] exposure monitoring is rarely done with sufficient rigor. Consequently, the good intentioned use of excessively high exposure conditions in SIC tests so as to maximise test sensitivity can result in non-specific irritation and the triggering of false positive responses[56].

Some respiratory physicians[38] are of the view that observation of a Late Asthmatic Response (LAR) in a positive SIC test, whether present in isolated or dual reactions (DAR), reliably indicate involvement of immune mechanisms thereby confirming OA. However, this viewpoint is not supported by the available science as reviewed elsewhere[57]. Furthermore, LAR are observed during exercise-induced asthma[58,59] so the observation of LAR in positive SIC tests does not necessarily indicate the mechanism by which the challenge substance is acting and substance-specific hypersensitivity cannot be assumed.

It remains the case that thorough interrogation of patient history combined with robust characterisation of exposure profile by a proficient industrial hygienist is still the most reliable means of identifying possible causative/exacerbating agents for OA.

4. Classification and Labelling of Respiratory Sensitisers

With regards to Respiratory Sensitisation[2,3], criteria and Guidance on the Application of the CLP Criteria[60], still reflect closely GHS Revision 1 published in 2003, and unlike information on other hazards that has been revised to reflect developments in toxicological hazard assessment, lag the current state of knowledge on the identification of RS and clinical diagnosis of OA.

For example, current criteria state under §3.4.2.1.2.1 that "*Evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience.*" In this context, the use of the term "*lead to*" conveys the requirement that the substance must have the intrinsic property to cause hypersensitivity to happen or exist as opposed to aggravating a pre-existing condition (WEA). This is consistent with the paradigm of work-related asthma (WRA) described by Moscato and coworkers[15] and the differentiation between OA induced by agents in the workplace (SIOA and IIOA) as opposed to asthma that is exacerbated (WEA). However, the criteria go on to state "*In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.*" This relief from having to demonstrate immune involvement was originally introduced to address uncertainties in the precise nature of the immune response(s) that drive the acquisition of sensitisation and inability to demonstrate substance-specific IgE antibodies (reviewed by Pemberton and Kimber[57]). This is acknowledged in ECHA's guidance[61] §3.4.2.1.3.1 where it states that "*The mechanisms by which substances induce symptoms of asthma are not yet*

fully known. For preventative measures, these substances are considered respiratory sensitisers."

This broadening of the criteria ensured that irritant induced OA (IIOA) fell under the scope of Respiratory Sensitisation classification, but placed greater pressure on the need to distinguish between irritant IIOA and non-specific irritant exacerbation of pre-existing asthma, both in the workplace (WEA) and in SIC tests (false positive results). The criteria and guidance make a single reference to this critical aspect under Annex I: §3.4.2.1.3. of ECHA guidance[61], albeit in a section referring to animal studies, where it states under footnote ** "*The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitisers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyper reactivity, they should not be considered respiratory sensitisers.*" (emphasis added by the authors). It may therefore be justified in claiming that the criteria and guidance do not give sufficiently clear and precise requirements and limitations on the use of clinical data for classification purposes[16].

Revision of the criteria and guidance is warranted to avoid contentious interpretation of clinical data and proliferation of scientifically unsound classifications, and to align clinical and regulatory understanding. This revision must recognise and balance the constraints imposed by medical confidentiality with the adequacy of clinical data in satisfying data quality, reliability and transparency criteria under CLP. A particular focus must be given to the role of the SIC test in decision making. There is growing evidence from recent EU harmonised classification and labelling (CLH) activities[16,56,62,63] that the current requirement for tests to meet "accepted guidelines"[61](Annex I §3.4.2.1.2.3. (b)) is too broad to be of any reliable value. In this regard, detailed guidance is required to highlight the key features, reporting standards and data requirements that are essential for the correct interpretation of SIC tests and the determination of substance-specific hypersensitivity, and compliance with CLP criteria[3] (§ 3.4.2.1.1.3) relating to "reliance on reliable and good quality evidence".

In taking this forward, it should be recognised by all parties that the priorities of clinicians, toxicologists and regulators are in some aspects necessarily different and that the misalignment of GHS/CLP criteria and guidance and the state of knowledge underpinning acquisition and expression of OA inevitably leads to tension over the use and interpretation of human and non-human data. A multistakeholder forum is therefore essential to broker a common understanding of the state of the science and how best to revise the criteria and guidance.

It is also anticipated that this broader awareness by all stakeholder groups of the practical differences between RS and OA, the paradigm of WRA, and the contributions of sensitiser induced OA, IIOA and WEA, will contribute to the refinement of the Adverse Outcome Pathway (AOP) for respiratory sensitisation to recognise the involvement of non-immune mechanisms and future development of NAMs.

Conflict of Interest Statement:

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Abbreviations:

AOP: Adverse Outcome Pathway
CLH: EU Harmonised Classification and Labelling
CLP: Classification, Labelling, and Packaging of chemical substances and mixtures
DAR: Dual Asthmatic Response
ECHA: European Chemicals Agency
GHS: Globally Harmonised System of Classification and Labelling of Chemicals
IIOA: Irritant Induced Occupational Asthma
LAR: Late Asthmatic Responses
NAMs: New Approach Methodologies
NSBH: Non-Specific Bronchial Hyperreactivity
OA: Occupational Asthma
OEL: Occupational Exposure Limit
PEF: Peak Expiratory Flow
REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals
RADS: Reactive Airway Dysfunction Syndrome
RS: Respiratory Sensitisation
SIC: Specific Inhalation Challenge
SIOA: Sensitiser Induced Occupational Asthma
SVHC: Substances of Very High Concern
WRA: Work-Related Asthma