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Use and limitations of clinical data in the identification and classification of low molecular weight chemicals (LMWCs) as respiratory sensitizers: recommendations for improvement

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ABSTRACT

While progress has been made in recent years, there are still no suitable and accepted *in silico*, *in vitro,* or *in vivo* models that can be used to accurately predict whether a chemical substance has the intrinsic property to cause immune-mediated chemical respiratory allergy, typically manifested as allergic asthma or allergic rhinitis which represents a severe health hazard. Regulatory authorities have relied primarily on clinical evidence (case reports, clinical databases, worker exposure studies) to classify substances as respiratory sensitizers, but this evidence can lack a proven immunological mechanism which is necessary to identify substances which can cause life-long sensitization and clinically relevant allergic symptoms in the respiratory tract in an exposed population (such respiratory allergens may be considered as "true" sensitizers, in analogy to the definition of skin sensitization, and in contrast to respiratory irritants). In light of this, the European Center for Ecotoxicology and Toxicology of Chemicals convened a Task Force to evaluate the types of clinical methods and data sources and the implications of relying on such data for regulatory decision making from a scientific perspective. Recognizing that there are benefits and important insights from using such data, significant shortcomings were identified. With clinical work being focused on treatment and diagnosis of individual patients, the approaches and methods used for clinical guidance, diagnostics and reporting have serious limitations in proving the respiratory sensitization potential of a specific chemical, definitely restricting their suitability in deriving legally binding hazard classifications for human health protection. Even within the current broader regulatory definition of respiratory sensitization, a robust assessment and sound evidence of causation by a specific chemical seems mandatory in order to avoid misclassifications. Application of a systematic weight-of-evidence approach is considered suitable to determine the level of confidence, including a thorough assessment of the specificity or non-specificity of observed bronchial hyperreactivity. Recommendations proposed in this publication may not only aid industry and regulators in their decision making but also facilitate a further exchange between stakeholders to improve the data used to (a) more precisely identify true respiratory sensitizers to effectively protect human health, (b) aid evaluation of potential predictive models, and (c) encourage regulators to clarify guidance and to consider a re-evaluation of the current regulatory definition of respiratory sensitizers.

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Occupational elicitation data; occupational asthma; respiratory sensitization; diagnostic methods; UN Globally Harmonized System (UN GHS)

Abbreviations: ADCA: Azodicarbonamide; AHF: Americas Health Foundation; ALAT: Latin American Thoracic Association; ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health & Safety); AOEC: Association of Occupational and Environmental Clinics; AOP: Adverse outcome pathway; AR: Allergic rhinitis; ATS: American Thoracic Society; BAL: Bronchoalveolar lavage; BAT: Basophil activation test; BOHRF: British Occupational Health Research Foundation; BPO: Benzoyl peroxide; BTS: British Thoracic Society; CLH: Harmonised Classification and Labelling; CLP: Classification, labelling and packaging; CMR: Carcinogens, mutagens, and reproductive toxicant; CRD: Component-resolved diagnosis; CTS: Canadian Thoracic Society; DAR: Dual asthmatic response; DFG: Deutsche Forschungsgesellschaft (German Research Foundation); DGAKI: German Society for Allergology and Clinical Immunology e.V.; DGAUM: German Society for Occupational and Environmental Medicine e.V.; DGP: German Society for Pneumology and Respiratory Medicine e.V; DoL: Department of Labour; EAACI: European Academy of Allergy and Clinical Immunology; EAR: Early asthmatic response; EBC: Exhaled breath condensate; ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals; ECHA: European Chemicals Agency; ELISA: Enzyme-Linked ImmunoSorbent Assay; E-PHOCAS: European Network for the Phenotyping of Occupational Asthma; ERS: European Respiratory Society; EU: European Union; FEIA:

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Fluorescent enzyme immunoassays; FeNO: Fraction exhaled nitric oxide; FEV_1: Forced expiratory volume in one second; FROD: Finnish Registry of Occupational Diseases; FVC: Forced vital capacity; GHS: Globally Harmonized System; GINA: Global Initiative for Asthma; HEMA: 2-hydroxyethylmethacrylate; HMWC: High molecular weight chemicals; HPMA: N-(2-Hydroxypropyl) methacrylamide; ICS: Indian Chest Society; IDT: Intradermal testing; IgE, IgG: Immunoglobulin E, Immunoglobulin G; II(O)A: Irritant-induced (occupational) asthma; IIDB: Industrial Injuries Disablement Benefits; IPCRG: International Primary Care Respiratory Group; KATRD: Korean Academy of Tuberculosis and Respiratory Diseases; KoSAR: Korean Severe Asthma Registry; KOWAS: Korea Work Related Asthma Surveillance; LAR: Late asthmatic response; LLNA: Local lymph node assay; LMW: Low molecular weight; LMWC: Low molecular weight chemicals; MAK Commission: German Research Foundation (DFG) Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area; MAT: Mast cell activation test; MMA: Methyl methacrylate; NAM: New approach methodologies; NCCP: National College of Chest Physicians; NIAID: National Institute of Allergy and Infectious Diseases; NICE: National Institute for Health and Care Excellence; NIH: National Institutes of Health; NIOSH: National Institute for Occupational Safety & Health; NO: Nitric oxide; NODS: Notifiable Occupational Disease System; NSBHR (equivalent to NSBR and NSBH): Non-specific bronchial hyperresponsiveness; NVL: National Care Guidelines (Nationale VersorgungsLeitlinie); OA: Occupational asthma; OECD: Organization for Economic Co-operation and Development; OEL: Occupational exposure limit; OHAT: Office of Health Assessment and Translation; OISP: Occupational Immunosurveillance Program; ONAP: National Observatory of Occupational Asthma; ORDS: Occupational Respiratory Disease Surveillance; OSHA: Occupational Safety and Health Administration; OSHRI-KOSHA: Occupational Safety and Health Research Institute of the Korea Occupational Safety and Health Agency; PA: Phthalic anhydride; PEF: Peak expiratory flow; PEF(R): Peak expiratory flow (rate); PMMA: Poly(methyl methacrylate); PriOR: Surveillance program of exposures and health impairment from work in Italy; (Q)SAR: (Quantitative) structure–activity relationship; RAC: Committee for Risk Assessment; RADS: Reactive airways dysfunction syndrome; RAST: Radioallergosorbent tests; REACH: Registration, Evaluation, Authorization and Restriction of Chemicals; Resp. Sens.: Respiratory Sensitizer; RNV3P: National Network for the Monitoring and Prevention of Occupational Diseases; R-phrases: Risk-phrases [Note: R-phrases are no longer in regulatory use but they appear in references cited herein dating from before the implementation of H-statements under GHS]; RS: Respiratory sensitizers; SABRE: Surveillance of Australian Workplace Based Respiratory Events; SAR: Structure–Activity Relationship; SIC: Specific inhalation challenge; SPT: Skin prick testing; SRROD: Swedish Register or Reported Occupational Diseases; STOT: Specific target organ toxicants; SVHC: Substances of very high concern; SWORD: Surveillance of Work-related and Occupational Respiratory Disease; TDI: Toluene diisocyanate; Th: T helper cells; THOR: The Health and Occupational Research; TMA: Trimellitic anhydride; TWA: Time-weighted average; UN: United Nations; US: United States of America; WEA: Work-exacerbated asthma; WoE: Weight of evidence; WRA: Work-related asthma

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Introduction

Chemical respiratory allergy, as with other hypersensitivities such as allergic contact dermatitis, is a two-step process whereby initial exposure to a substance results in priming of the immune system (sensitization) which upon subsequent exposure to the same (or similar) substance provokes an immunologically mediated hypersensitivity reaction (elicitation). Chemical respiratory sensitization is mechanistically not fully understood, but there is evidence that an antibody Immunoglobulin E (IgE)-mediated immune response for which a threshold is assumed but often difficult to determine plays a key role, and a prominent role of a preferential T helper 2 (Th2) cell response is assumed (Cochrane et al. 2015). While IgE-mediated immune responses toward high molecular weight chemicals (HMWC), that is, environmental proteins in pollen, dust, or food, are more common among the general population, this review focuses on low molecular weight chemicals (LMWCs)[1]. As reviewed elsewhere, LMWCs often require haptenization to trigger an immunological response and do not necessarily elicit an IgE-mediated response but may exert other non-immunological responses (irritants) and/or immunological responses involving different T helper cell types (also compared to skin sensitizers) (Schwab and Poole 2023). LMWCs that cause allergic respiratory symptoms *via* specific-antibody mediated immunological mechanisms are in the following text referred to as "true" respiratory sensitizers or respiratory allergens, a terminology that had been employed by other authors before (Arts 2020; Pemberton et al. 2024). According to Arts (2020) "true chemical respiratory allergy is characterized by immunological priming that results in allergic sensitization of the respiratory tract. If the sensitized subject is exposed subsequently by inhalation to the same chemical then an accelerated and aggressive secondary immune response will be provoked that elicits a respiratory reaction recognized clinically as respiratory allergy, and in a workplace setting described as occupational asthma (OA)", with the severity of reactions becoming "more severe with repeated exposure as the level of sensitization increases" (Kimber et al. 2011). Such "true" sensitizers can cause a broad variety and severity of potential clinical symptoms that usually manifest in allergic asthma but also other hypersensitivity reactions like rhinitis, whereas nonallergenic, irritant substances can cause similar respiratory symptoms. Unfortunately, in contrast to other toxicological endpoints including skin sensitization, until today there are no standardized nor formally accepted *in vivo*, *in vitro,* or *in silico* models in place to evaluate a substance for its respiratory sensitization hazard, an issue which is also reflected in chemicals legislation. The definition for respiratory sensitization included in the United Nations (UN) Globally Harmonized System for classification and labeling (GHS) and its implementation in the European Union (EU) *via* the Classification, Labelling and Packaging (CLP) Regulation and related guidance (European Parliament and Council 2008; UN 2023; ECHA 2024c) states "respiratory sensitization means hypersensitivity of the airways occurring after inhalation of a substance or mixture", followed by an acknowledgement that respiratory sensitization represents an immunological hazard: "Sensitization includes two phases: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen" [...] "for respiratory sensitization, the pattern of induction followed by elicitation phases is shared in common with skin sensitization." The regulation also states that "evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience. 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", with the last part obviously representing a precautionary compromise accounting for the above-mentioned lack of validated methods, the incomplete understanding of the underlying complex mechanisms, and the challenge to discriminate clinical symptoms between truly sensitizing and irritant substances. As mentioned in guidance (ECHA 2024c), "mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitizers. 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 sensitizers." For respiratory irritants, a dedicated hazard class is available in GHS. Chemicals (or mixtures if chemical is present at $\geq$20%) classified for causing respiratory tract irritation upon single exposure (STOT SE 3) are labelled with the Signal word "Warning", the exclamation mark (GHS07) as pictogram and the Hazard statement H335 "May cause respiratory irritation".

Respiratory irritants are assumed to induce asthma only at exposures with high concentrations (for review see e.g. Pemberton et al. (2024)), whereas for elicitation thresholds the situation is less clear.

While it could be argued that the described regulatory indistinctiveness and potential overlap between the two hazard classes and a potential over-classification of substances that only act *via* an irritant mechanism should be acceptable as a precaution, the approach bears some unfortunate implications with regard to scientific correctness, suitable benchmarks, the development and validation of new methods, and appropriate risk management measures. Nevertheless, also with the existing regulations, a thorough assessment can counteract a scientifically questionable outcome, whereby utmost care needs to be taken to analyze whether a specific

substance (or mixture) really is causing the observed effects and to avoid potential misinterpretations.

The GHS hazard classification of a substance as a respiratory sensitizer (Resp. Sens. 1) has the potential for far-reaching societal and economic consequences. A chemical (or mixture, if chemical is present at $\geq$1%) that is classified as Resp. Sens. 1 (Hazard statement H334 "May cause allergy or asthma symptoms or breathing difficulties if inhaled"; Signal word "Danger"), is labelled with the health hazard pictogram GHS08 (EU Regulation 2006; UN 2023)[2]. The same pictogram, which is important to communicate the hazard, is used for chemicals (or mixtures) classified as Category 1 or 2 carcinogens, mutagens, and reproductive toxicants (CMRs), specific target organ toxicants (STOTs), and aspiration toxicants (referring to acute injury or death after aspiration). For comparison, chemicals (or mixtures if chemical is present at $\geq$20%) classified for causing respiratory tract irritation upon single exposure (STOT SE 3) are labeled with the Signal word "Warning", the exclamation mark (GHS07) as pictogram and the Hazard statement H335 "May cause respiratory irritation". Currently, 120 substances, high molecular weight chemicals (HMWC; $n = 17$), such as industrial enzymes, as well as low molecular weight chemicals (LMWCs, $n = 103$), such as anhydrides, diiscocyanates, chloroplatinates, and metals, have a harmonized classification as Resp. Sens. 1. The majority (59%) of these substances are not classified for any other serious health hazard endpoint (Annexe VI to CLP (European Parliament and Council 2008) updated *via* 20th Adaptation to Technical Progress (ATP) (European Parliament and Council 2023)[3]).

None of these currently classified substances are sub-categorized as Resp. Sens. 1 A (high sensitization rate and/or severity) or 1B (low to moderate sensitization rate and/or severity), as their reason for classification is primarily based on human (occupational) elicitation data. In the absence of induction threshold data, human elicitation data is considered too variable to define potency of the respiratory sensitization hazard (OECD 2006). As a result, the category of respiratory sensitizers (Resp. Sens. 1) includes both potentially highly potent and less potent substances.

Specifically in the EU, chemicals and/or mixtures (if specific concentrations limits are exceeded) that are classified, and therefore labelled as Resp. Sens. 1, are currently in scope for the Candidate List of substances of very high concern (SVHCs) due to the potential to cause serious/irreversible effects on human health that are considered to be of equivalent concern to carcinogens, mutagens, or reproductive toxicants. SVHCs that are prioritized from the Candidate List to the Authorization List (e.g. Glutaraldehyde) require authorization for market, which needs to be granted by the European Chemicals Agency (ECHA) for each specific use (EU Regulation 2006). While the protection of human health is the utmost priority for regulators and industry, the regulatory hazard-based approach (the assessment of the potential to cause harm) does not account for the risk (the likelihood to cause harm), which allows consideration of risk mitigation measures and exposure restrictions. Indeed, whilst hazard-based and risk-based approaches have the same goal, i.e. the protection of human health, the accuracy and reliability of the hazard-based approach heavily depends on the accuracy and reliability of human-relevant methods and approaches to identify substances with the true, intrinsic ability to cause sensitization of the respiratory tract.

While new toxicological methods and tools to identify LMWC that are respiratory sensitizers are still being developed (Chary et al. 2018; Arts 2020), it is crucial to emphasise the significance of evaluating these new methods using LMWCs with substantial evidence supporting their clinical relevance for respiratory sensitization (Sadekar et al. 2021; Ponder et al. 2022). One of the key challenges for the robust evaluation of new methods is the full understanding of underlying immunological mechanisms of respiratory sensitization which would justify the hazard classification as Resp. Sens. 1.

Due to the lack of suitable methods and tools to identify respiratory sensitizers, there has been an increasing reliance on the use of human data, that is, clinical evidence (case reports, clinical databases, worker exposure studies), to justify the classification of substances. The UN GHS states that "evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience" and in general that reliable human data should be taken into account for hazard identification purposes (UN 2023). Such human experience is typically based on clinical observations reported in the context of occupational exposure (Baur et al. 2019). However, such observations have many limitations which include fit-for-purpose data quality for identification of and predictive potential for respiratory sensitizers, as elaborated in the relevant sections of this paper. They are also highly dependent on multiple factors such as, exposure to mixtures in the workplace, route and duration of exposure, implementation of accurate exposure monitoring and dose methods, as reviewed previously elsewhere (Chary et al. 2018; Arts 2020; Pemberton and Kimber 2021).

Linked to this complexity is the lack of a definitive clinical test to diagnose asthma or occupational asthma (OA), itself often a process of elimination, which has led to significant debate on whether asthma is under- or over-diagnosed in the general population (Aaron et al. 2018; Kavanagh et al. 2019). To date, health surveillance and clinical case study data have primarily been used in the clinical context for the management of asthma or OA where limitations in predictive value, including differentiation between sensitizer-induced versus irritant-induced asthma, are often considered acceptable by clinicians. The different forms of work-related asthma (WRA) have been reviewed before (Vandenplas et al. (2017), and references therein), encompassing "both asthma caused by work (i.e. OA) and pre-existing or coincident asthma exacerbated by non-specific stimuli at work (e.g. irritants), the latter condition commonly referred to as 'work-exacerbated asthma' (WEA)" while OA "may result either from immunologically mediated sensitization to a specific substance at work (i.e. 'immunologic' OA or 'sensitiser-induced' OA) or from exposure(s) to high concentrations of irritant compounds (i.e. 'irritant-induced asthma')" (Figure 1). Irritant-induced (occupational) asthma (II(O)A), which is mechanistically not fully understood, may be typified by the "reactive airways dysfunction syndrome" (RADS) and by other symptoms (Lantto et al. 2022). The complexity of different terms is often oversimplified by using insufficiently specific terms such as "asthmagen". The term "asthmagen" encompasses both HMWC and LMWC, without discriminating

between substances that act as true respiratory sensitizers or nonallergenic irritants, all of which have the potential to induce asthma symptoms. Overall, significant challenges arise in differentiating between sensitizer-induced and irritant-induced asthma, or its absence, and whether symptoms observed with clinical testing are the result of elicitation in a sensitized individual by a tested agent or are the triggering of pre-existing asthma originally induced by different causes or different LMWCs which require a thorough scientific analysis.

For LMWC that are suspected to have respiratory sensitization potential (e.g. based on existing human clinical data), the process of identifying and classifying a substance as a respiratory sensitizer under chemicals law, schematically outlined in Figure 2, is complex, especially in view of the lack of standardized methods for respiratory sensitization. The underlying assessment to conclude on classification or nonclassification should, from a scientific and risk assessment perspective, follow a systematic and transparent weight-of-evidence (WoE) approach. WoE is a well-established but not a harmonized term or approach which is primarily used in situations where

Figure 1. Classification of asthma due to workplace exposure [adapted from Barber et al. 2022].

accepted state-of-the art studies and/or quality is not sufficiently available and sources of information should be considered in a comprehensive assessment. As reviewed by OECD 2019, WoE concepts have been established in various contexts. OECD derived a number of overarching guiding principles to enable "a consistent, clear and transparent delivery of evidence". Within the UN GHS and CLP regulation, and as described by ECHA, WoE combines several lines of evidence and assesses the strength of all relevant information (ECHA 2016, 2017c, 2017b; OECD 2019). With regard to respiratory sensitization, human clinical data and other *in vivo* data is given preference within the CLP Regulation over data from other sources (CLP Regulation Annexe I, 3.4.2.1 (European Parliament and Council 2008)) (ECHA 2024c): "Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for respiratory sensitizers. Substances may be allocated to one of the two sub-categories 1 A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.1 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals"; "Relevant information with respect to respiratory sensitization may be available from case reports, epidemiological studies, medical surveillance, reporting schemes"[4], and while several aspects are listed that should be considered in evaluating human data, the regulation states that "the results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own … ." based on "data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for

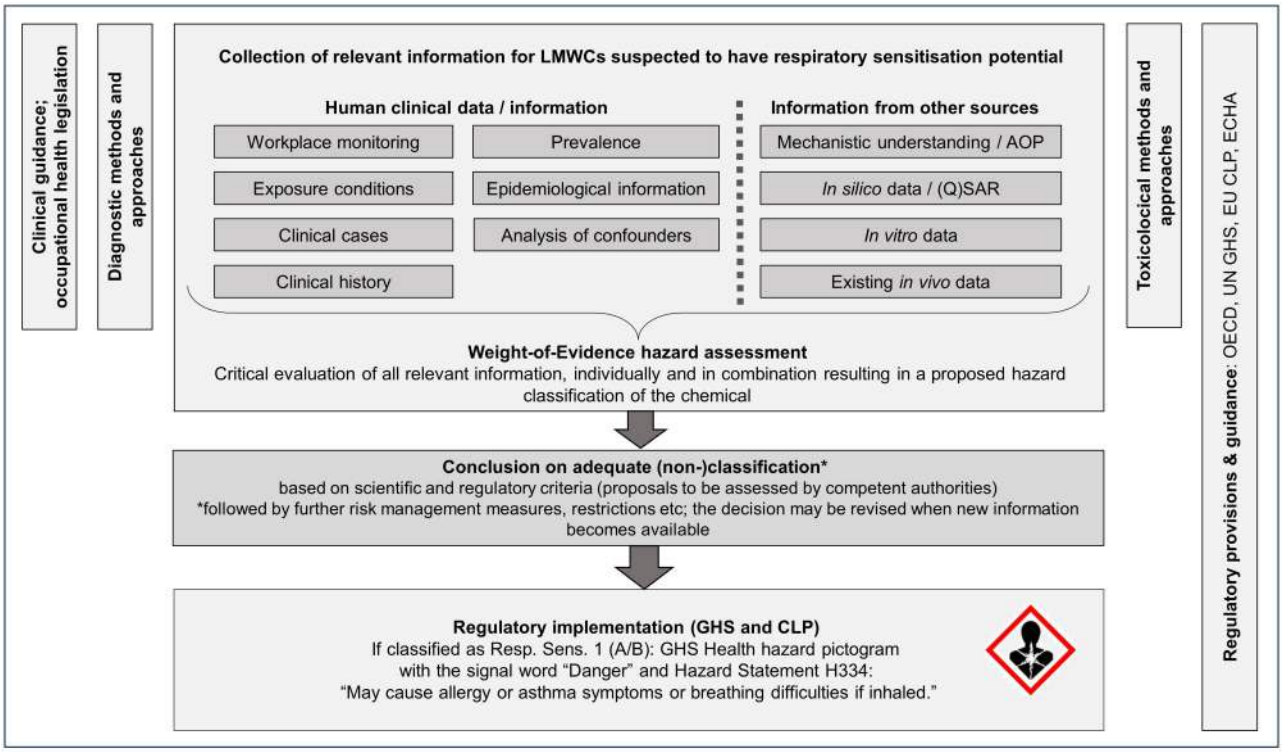

Figure 2. Overview of the process of hazard assessment based on a weight-of-evidence approach and subsequent classification according to UN GHS for chemicals suspected to have respiratory sensitization potential. AOP = adverse outcome pathway; ECHA = European Chemicals Agency; CLP = classification, Labelling and Packaging Regulation; (Q)SAR = quantitative structure-activity relationship; RAC = risk assessment Committee.

the determination of a specific hypersensitivity reaction", while information from non-human sources "may provide supportive evidence in case human evidence is available" and "should be used in a weight of evidence assessment".

In Figure 2, generation, collection and interpretation of data and information are schematically flanked by the legal provisions and guidance from the clinical and chemical fields (with some cross references). The relevance of expert judgement based on a WoE approach and its specific elements for identifying true respiratory sensitizers was recently also highlighted by others (Sadekar et al. 2021; Meek et al. 2023; Pemberton et al. 2023). However, in the absence of other data from suitable methods, a recent harmonized classification and labeling (CLH) opinion by ECHA's Committee for Risk Assessment (RAC) resulted in classification of a chemical as a respiratory sensitizer primarily based on national health surveillance data, worker health studies and specific inhalation challenge (SIC) tests, which emphasizes in our view the need for a systematic and robust WoE approach to increase transparency and objectivity in weighting evidence, as recently highlighted by others (Meek et al. 2023) and to ensure adequate control for non-specific irritant provocation of pre-existing or concurrent asthma.

Due to the scientific relevance and complexity of the topic, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) convened a Task Force to provide an overview of the available clinical data sources and regulatory guidance for the identification of respiratory sensitisers as well as diagnostic methods for the detection of respiratory sensitisation in humans and to evaluate the state of knowledge with respect to their value in regulatory hazard classification. More information on the Task Force approach can be found in Supplement 1. Recommendations on best practices and potential improvements of regulatory guidance resulting from the work of the Task Force are provided in this manuscript as well as a critical reflection on the role of human clinical data and suggestions for further research.

Evaluation of the current state of knowledge

In the following sections, the various elements that should be considered in a comprehensive WoE assessment for the identification and classification of LMWC respiratory sensitizers with regard to human clinical data are explained in more detail and evaluated for their use and limitations for regulatory hazard classification.

The first section provides insight into key sources of human clinical data that may be used for assessment and classification of respiratory sensitization of LMWCs, including important considerations on quality and reliability. The second section summarizes the legal provisions and/or official guidance from the clinical and chemicals regulation fields, highlighting the differences in perspectives between the two. In the third section, the human clinical diagnostic methods and approaches are briefly reviewed related to their implications for the identification of LMWC respiratory sensitizers, and how they should be embedded into a WoE assessment. Current clinical data and approaches, including case studies and epidemiological reports, are described, and whether they allow for a firm diagnosis of respiratory sensitization in the context of exposure to a specific chemical, and/or for distinguishing between true respiratory sensitizers and nonallergenic irritants. The fourth section presents some practical case study examples of the use of human clinical data to identify and classify LMWCs in a regulatory context, further highlighting the complexity and crucial aspects of the decision-making process for LMWC classification.

For the convenience of the reader, each of the following sections contains another brief introduction.

Key sources of clinical and exposure data for LMWCs

Herein, insight is provided into key sources of human clinical data that may be used for assessment and classification of respiratory sensitization potentially caused by LMWCs, including quality and reliability aspects. The primary information is usually related to human case reports, mostly in an occupational context, which may be documented, reported and/or published *via* different channels and may also become part of regulatory dossiers for individual LMWCs.

Publicly available literature

Instead of a comprehensive *ab initio* literature search, selected key overview publications, containing extensive and systematic literature searches for clinical and exposure data for a larger number of LMWCs, were used. Some specific case examples are further highlighted in the later section "Regulatory implementation with examples of practical application of criteria for LMWC classification".

There have been several publications in recent years aimed at curating the scientific evidence of the relationship between exposure to LMWCs and development of allergic asthma (a summary is provided in Table 1). These publications either provide curated lists of respiratory sensitizers, with different approaches to analyze and assess the data, or guidance in data collection and curation itself. For instance, the studies conducted by Sadekar et al. (2021) and Ponder et al. (2022) offer reference lists of chemicals with high confidence for their respiratory sensitization potential based on clinical and epidemiological data and outline specific criteria used to evaluate the available evidence regarding the respiratory sensitizing potential of a LMWC. Different criteria and approaches were employed, resulting in overlapping outcomes (Pemberton et al. 2024). In both publications more than 100 chemicals were reviewed, with the approach by Ponder et al. (2022) resulting in a list of 28 chemicals with evidence for clinically relevant respiratory sensitization potential while the approach by Sadekar et al. (2021) identified 7 compounds (overlapping with the list of 28) with compelling evidence. There are also other comprehensive lists of occupational exposures with limited evidence for correlation with sensitization of the respiratory tract, but which emphasize the value of considering immunological evidence (Part IV "Specific Agents Causing Immunological Occupational Asthma" of Asthma in the Workplace, in particular in chapter 18 (Tarlo et al. 2021)). Hargitai et al. (2024) recently collected literature on respiratory sensitizers including the above-mentioned lists from Sadekar

Table 1. Key overview publications on the identification of respiratory sensitisers (and irritants) from clinical and exposure data.

Publication	Approach to identify respiratory sensitizers (and irritants)	Data interpretation criteria	Lines of evidence	Recognised knowledge gaps
Sadekar et al. (2021)	Out of a list of 97 reported respiratory sensitizers from six sources, 52 LMWCs were identified. The corresponding data for these LMWCs from epidemiological or case studies were further reviewed and assigned to four evidence categories based on a set of scoring criteria. Categories were based on whether the supporting evidence is compelling, reasonable, inadequate or questionable. The classification takes into account the different data types (immunological, lung function related, and others), whether it was evaluated by a medical professional or not, presence of underlying health conditions such as atopy, and whether evidence came from a single case report or self-reported cases.	Classification of data based on compelling, reasonable, inadequate or questionable evidence.	History of exposure, immunological and pulmonary function data, chemical identity, review by medical practitioner	Robust quantification of strength of relationship and level of confidence in data, use of reactivity mechanism, exposure inputs
Ponder et al. (2022)	A list of 118 chemicals identified primarily by a structure-based literature search was curated to identify human clinical indication of respiratory sensitization. Using this curated list, an additional list of compounds, that may have clinical data on respiratory sensitization, was generated by querying the EPA literature database (EPALitDB), and for these compounds the literature data-based curation was repeated. The authors outlined specific clinical diagnostic criteria to conclusively demonstrate occupational asthma as a result of sensitization, rather than irritation. The criteria were based on exposure history to the LMWC, lung function effects, and specific immune responses. Those compounds with unequivocal positive evidence were further differentiated into high or low classes based on the number of supporting reports available. In addition to the clinical evidence, they demonstrated the use of other types of data such as reactivity mechanism as part of WoE.	Classification of evidence into clinical respiratory sensitizers, equivocal and no information categories based on presence of unequivocal immunological data.	History of exposure, immunological data with criteria for positive results, lung function tests, confounding exposure	Robust quantification of strength of relationship and level of confidence in data, exposure inputs
Flemish Institute for Technological Research VITO (2009)	Analysis conducted on incidence and severity of skin and respiratory allergy related to exposure of chemicals from non-food sources carried out for the European Commission. It includes literature searches on respiratory sensitization for 152 chemicals spanning multiple data sources and also includes Risk-phrases (as per Regulation (EC) 1272/2008; European Parliament and Council (2008)) and animal LLNA data in addition to clinical data comprising questionnaires, immunological and pulmonary tests and data on duration of symptoms, time of exposure and latency.	Weight of evidence for consideration as respiratory sensitizer included prevalence rates in surveillance schemes, published human data with cause and effect relationship, R-phrases and LLNA data	Worker/ patient questionnaires, immunological and pulmonary tests, data on duration of symptoms, time of exposure and latency, R-phrases, animal LLNA data	Bias due to use of R-phrases and LLNA data, use of chemical characteristics, exposure inputs

EPA: Environmental Protection Agency; LLNA: local lymph node assay.

and Ponder and compared their hits with the existing entries of classified respiratory sensitizers in Annexe VI of CLP without an in-depth evaluation on the reliability of the data and mechanistic aspects. Dalbøge et al. (2023) conducted a meta-review to address the relationship between potential occupational sensitizing exposure and asthma which followed the specific guidelines from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The authors provide a ranking of confidence levels, covering a large variety of exposures and their potential relation to asthma but without providing insight with regard to immunological information.

From these publications (Table 1), the main sources of primary data besides review articles were found to be case reports in the general scientific and medical literature, books related to asthma, records of workers' experience or questionnaires (workplace monitoring), exposure studies, epidemiological studies, and results of national medical surveillance schemes as usually documented in national health surveillance databases (see below subsection on "Data within national health surveillance programs and related sources"). Various deficiencies in clinical data reporting, including data quality and accessibility, are highlighted, as well as knowledge gaps which arise either due to the specificity of the goals outlined by the respective authors or the limitations of existing clinical reports. They highlight the much-needed additional considerations, such as exposure inputs, chemical reactivity mechanisms and robust quantification of the causal relationship and level of confidence in the data, amongst others.

Data within national health surveillance programs and related sources

Some further insight into available clinical and exposure data was sought from geographically representative, but not fully comprehensive, sets of national repositories. These included:

- US: National Institute for Occupational Safety & Health (NIOSH) Occupational Respiratory Disease Surveillance (ORDS)[5] is one of the programs that gathers state-wide statistics on WRA, although neither the process for reporting into nor collection of data is harmonized across all states and nor is there a record of participation by all states. Metrics are recorded either as confirmed cases further classified under WEA or WRA (new-onset asthma with RADS or occupational asthma [known or unknown asthma inducer]) categories or are simply recorded as confirmed cases but unclassified. Clear guidelines and a decision tree are available[6] to aid with and harmonize the assignment of cases to the different classes, which are provided by NIOSH as the federal agency responsible for conducting research and making recommendations to prevent work-related injuries, illnesses, and deaths. While the most recent data are not publicly available, some historical data have been published (Rosenman et al. 1997; Jajosky et al. 1999).
- UK: The Surveillance of Work-related and Occupational Respiratory Disease (SWORD) scheme under The Health & Occupational Research (THOR)[7] network collates the incidence and pattern of occupational respiratory disease, including occupational asthma, within the UK, through physicians reporting into the scheme. SWORD's findings are published annually. However, specific guidance for physicians on confirming and classifying cases of asthma is not published. The UK's Midland Thoracic Society's Rare Respiratory Disease Registry Surveillance Scheme of Occupational Asthma, or Shield scheme[8], studies the general and specific incidence of occupational asthma within a defined geographic area, determines the proposed mechanisms of asthma, and audits the diagnostic methods and objectives. It is currently one of the most active and data rich networks with publicly available details through reported statistics, anonymized case reports and list of agents considered to be associated with OA. The Industrial Injuries Disablement Benefits (IIDB)[9] can also be a source for trends in occupational asthma reports or cases. While its reports or diagnostic requirements are not publicly available, IIDB lists several substances considered to cause asthma.
- EU: The reviewed national programs or registers related to occupational diseases in the EU included the surveillance program of exposures and health impairment from work in Italy (PriOR), the Finnish Register of Occupational Diseases (FROD), the Swedish Register or Reported Occupational Diseases (SRROD), the French National Observatory of Occupational Asthma (ONAP) and the French National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P). Some of these schemes have published reports of incidence related to OA (Torén 1996; Bena et al. 1999; Ameille et al. 2003; Barbier and Lasfargues 2016; Oksa et al. 2019). However, many publications are not current, and neither recent data nor statistics are published in a harmonized manner nor always on a recurrent basis. Clear harmonized guidelines on diagnostic criteria are also not publicly available. In addition, there are other schemes such as the statutory accident insurance system in Germany[10], which can be a source of metrics and other details regarding occupational diseases in general.
- Australia and New Zealand: The Surveillance of Australian Workplace Based Respiratory Events (SABRE)[11] collects and reports data on occupational respiratory disease specifically, in Victoria and Tasmania, through physicians reporting into the scheme. However, standardised diagnostic criteria have not been published and the key focus is on prevalence. Under the Notifiable Occupational Disease System (NODS) scheme of WorkSafe New Zealand[12], health professionals and other individuals can notify any health-related condition that is suspected to arise from work. However, it seems to have a low potential for aggregation of data for surveillance purposes and thereby, its reporting.
- Korea: The reporting sources of Korea Work Related Asthma Surveillance (KOWAS) scheme, set up under Occupational Safety and Health Research Institute of the Korea Occupational Safety and Health Agency (OSHRI-KOSHA)[13], include the Korea Workers' Compensation and Welfare Service, occupational physicians, and allergy and chest physicians. There are clear definitions and criteria for classifying as WEA or WRA. However, it is mainly reliant on spirometry and there is no explicit requirement for immunological tests. Further, the reporting is dependent

on publications, which have not been recently updated (Kim HR et al. 2003; Kwon et al. 2015).

The national health surveillance programs are set up to identify any ill health caused in the work environment and implement effective control measures to ensure worker health and safety. Given this intended purpose, it is not surprising that the review of such programs and related clinical sources of information revealed significant gaps in knowledge necessary to identify chemical respiratory sensitizers for classification purposes, as these sources typically report on OA and not specifically on allergic, sensitizer-induced asthma. Reporting standards employed in such databases usually do not contain enough detail to adequately characterize the causative agent responsible for the development of asthma in the individual. There is no uniform practice globally regarding what is reported as OA, that is, diagnostic criteria for new cases of OA versus WEA, or to distinguish between an immunological and non-immunological mechanism within an OA classification. Focus may be on the prevalence and occurrence of OA, rather than the causation of it, possibly also due to a lack of standard guidelines for reporting clinical data and the primary concern of healthcare experts being management of occupational asthma without necessarily requiring knowledge of the underlying cause. Similarly, some published epidemiological studies or case reports do not consider or do not include data related to respiratory sensitization, thus not providing sufficiently relevant information to identify true LMWC sensitizers.

The extent of publicly available information, or even recording of data on a regular basis, varies significantly between the different surveillance programs and national registries. Some programs publish information as (retrospective) studies, aggregated statistics or public health reports, often with limited details on patient history and not always on a regular or periodical basis. Restricted access and incomplete data and/or documentation often hamper the direct possibility for a transparent and independent analysis of the reliability and relevance of primary human information. Clinical data or metrics on incidence or prevalence within health surveillance programs, that pertain to different forms of OA or WEA, are not always easy to identify, for example either all respiratory diseases or all occupational diseases are grouped together within a certain geography. Overall, data from such databases should be carefully evaluated including potential deficiencies.

Legal provisions and official guidance from the clinical and regulatory domains

This section gives a brief overview of available legal text or guidance on the clinical diagnosis of asthma and the classification of chemicals as respiratory sensitizers, from regulatory bodies and professional societies. The purpose of the review was to capture a general overview of available official expert guidance. The two major limitations of this review section are: (1) the literature search was not systematic as it is only intended to provide a perspective of how disparate the considerations can be for clinically diagnosing respiratory sensitization in humans; and (2) references captured under this section are mainly limited to those available in English. Since human data are often derived from and documented in a clinical context, this analysis aims to elucidate to what extent such provisions match regulatory requirements for chemical hazard classification (Resp. Sens. 1), especially in the field of occupational hygiene.

Table 2 provides an overview of clinical guidance documents for evaluation and management of asthma or OA and Table 3 lists key chemicals legislation and associated guidance for evaluation of respiratory sensitization. The references, i.e. clinical guidance documents and chemicals legislation or guidance, were reviewed to capture the following information:

1. Scope of the document: regulatory purposes (i.e. chemical classification and labeling) and/or clinical evaluation purposes; Definition of causative agents and/or clinical condition;
2. Classification criteria of causative agents;
3. Classification criteria for the clinical condition;
4. Recommendation for diagnostic methods;
5. Questionnaire (if any);
6. Revisions in the last 5 years.

In summary, there are several established guidelines, across different geopolitical regions, to either aid in identifying the chemicals that cause respiratory sensitization or to facilitate the effective evaluation of symptoms and management of asthma from a clinical perspective. While these guidelines share some commonalities in the diagnosis and management of OA, such as the importance of a thorough clinical history, assessment of symptoms, lung function and immunological tests, they vary in their focus and scope (asthma versus OA), the level of detail and specific recommendations, as well as the inclusion of guidance on conducting occupational exposure assessments to identify potential respiratory sensitizers in the workplace (for more details see Supplement 2).

Clinical guidance

Existing guidance focuses mainly on asthma or OA, which may be interpreted as the outcome of respiratory sensitization from occupational exposures to causative agents but can also be based on other mechanisms such as irritant-induced or non-allergic asthma (Pemberton and Kimber 2021). Consequently, the clinical guidance captured in this review covers asthma and OA and may not be sufficiently specific for the identification of true respiratory sensitization, particularly when this is used in a regulatory context. Some but not all clinical guidelines address the difference between irritant-induced non-immune-mediated asthma and allergic or immune-mediated asthma (Vandenplas and Malo 2003; Lemiere et al. 2022; Ronsmans et al. 2023). Although, diagnostic tests are common for clinical diagnosis of asthma and OA (a subset of which may be true respiratory sensitizers), in the case of OA the interpretation of the test results is complicated due to the variability of the symptoms displayed and

Table 2. Clinical guidance documents for evaluation of symptoms and management of asthma (A)/occupational asthma (OA) in different regions.

Regions	Authority or Institution/Association	Scope	Year	Reference
Global	Global Initiative for Asthma (GINA)	A/OA – clinical	2022	Global Initiative for Asthma (2022)
China	Asthma Workgroup, Chinese Thoracic Society, and Chinese Society of General Practitioners	A – clinical	2013	Asthma Workgroup Chinese Thoracic Society & Chinese Society of General Practitioners (2013)
India	Indian Chest Society and National College of Chest Physicians (ICS, NCCP)	A/OA – clinical	2015	Agarwal et al. (2015)
Japan	The Japanese Society of Allergology	A/OA – clinical	2020	Nakamura et al. (2020) Niimi et al. (2023)
Korea	The Korean Severe Asthma Registry (KoSAR)	A – clinical	2022	Kim et al. (2022)
	The Korean Academy of Tuberculosis and Respiratory Diseases (KATRD)	A – clinical	2016	Kim et al. (2016)
Europe	European Respiratory Society (ERS)	OA – clinical	2012	Baur et al. (2012)
	European Academy of Allergy and Clinical Immunology (EAACI) Task Force	OA – clinical	2012	Moscato et al. (2012)
General (Possible EU-US centric)	International Primary Care Respiratory Group (IPCRG)	A/OA – clinical	2006	Levy et al. (2006)
	Guidelines for the Clinical Evaluation of Occupational Asthma due to Small Molecular Weight Chemicals	OA – clinical	1989	Butcher et al. (1989)
Canada	Canadian Thoracic Society (CTS)	OA – clinical	1998	Tarlo et al. (1998)
		A – clinical	2021	Yang et al. (2021)
South America	Americas Health Foundation (AHF, Brazil)	A – clinical	2021	Pitrez et al. (2021)
North and South America	Joint perspective of the Brazilian Thoracic Society, CTS, the Latin American Thoracic Association (ALAT), and the American Thoracic Society (ATS)	A – clinical	2022	Forno et al. (2022)
United Kingdom	British Thoracic Society (BTS)	OA – clinical	2022	Barber et al. (2022)
	British Occupational Health Research Foundation (BOHRF)	A/OA – clinical	2010	BOHRF (2010) Nicholson et al. (2010)

Table 3. List of chemical regulations and guidance documents for evaluation of respiratory sensitizers (RS) for different regions.

Regions	Authority	Scope	Year	Reference
Global	Association of Occupational and Environmental Clinics (AOEC)	OA – chemical classification	2008	Beckett (2008)
	United Nations Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS) and its national/regional implementation	RS – chemical classification	2021	GHS 10th revised edition (UN 2023)
Europe	European Chemicals Agency (ECHA)	RS – chemical classification Follows GHS criteria	2017	Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint-specific guidance (ECHA 2017a) Guidance on the Application of the CLP Criteria (ECHA 2024c) (Same as Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures – 2023) (European Parliament and Council 2008)
Germany	Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Germany	RS – chemical classification	2023	DFG, Deutsche Forschungsgesellschaft (2023)
United States of America	Occupational Safety and Health Administration (OSHA), Department of Labor (DoL)	RS – chemical classification Follows GHS criteria	2021	Occupational Safety and Health Administration (2021)

the challenges encountered in associating symptoms with workplace exposures. As such, a definitive process is not available for diagnosing immune-mediated asthma because of the limitations of current methods (see section "Clinical diagnostic methods and approaches for the identification of LMWCs as respiratory sensitizers") and therefore lack of data from relevant tests.

The chapter on Assessment of the Worker by Cartier et al. in the 5th edition of Asthma in the Workplace (Cartier et al. 2021) reviews the importance of good health surveillance practices, documentation and diagnostic criteria for OA, which need to be considered while accessing either published data or data within occupational databases.

It is apparent from the distribution of provisions available on clinical guidance, that there is a widespread region-specific effort for standardizing the diagnosis of occupational asthma. For example, an EAACI task force (Table 2) provides guidance on investigating WRA in nonspecialized centers (Moscato et al. 2012) including linking to further investigations at specialized centers.

As another prominent example (not listed in Table 2), the ERS Task Force on Specific Inhalation Challenges with Occupational Agents along with other experts published a consensus statement on the specific inhalation challenge (SIC) test in the diagnosis of occupational asthma (Vandenplas et al. 2014). The SIC as a workplace-related inhalation test is also issued in the S2k Guideline of the German Society for Occupational and Environmental Medicine e.V. (DGAUM), the German Society for Pneumology and Respiratory Medicine e.V. (DGP) and the German Society for Allergology and Clinical Immunology e.V. (DGAKI) (Preisser et al. 2021). There is also other guidance on general asthma which is available in German language only and therefore not the main focus of this review (Nationale Versorgungsleitlinie (NVL)[14]). A guideline for evaluating and diagnosing clinical cases of general asthma in different age groups is available from the National Institute for Health and Care Excellence (NICE) in the UK (NICE guideline NG80, 2021[15]). Overall, it is noted that the prevalence of regional rather than global guidance further complicates the interpretation of clinical data, due to the non-uniformity in data collection and documentation practices of diverse clinical observations, when attempted to be used and integrated in an overall WoE assessment.

Current regulatory perspective on using clinical data for chemical classification

As mentioned in the Introduction the UN GHS states that "evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience". As per GHS criteria, clinical evidence of specific respiratory hypersensitivity, the severity of the reaction, and supporting evidence of the positive results e.g. in animals, forms the basis of the regulatory decision-making process. GHS is implemented in the EU *via* the CLP Regulation. ECHA provides endpoint-specific guidance which includes an assessment strategy for respiratory sensitization data (Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint-specific guidance (ECHA 2017a)). This guidance, and the CLP Regulation guidance (ECHA 2024c), highlight several existing data sources and proposed models to predict or test respiratory sensitizers and associated adverse health effects (either *in vivo*, *in vitro*, or *in silico*), as well as guidance on evaluating human data. However, it is acknowledged that internationally accepted non-human methods for identifying LMWC respiratory sensitizers are not yet available and the clinical data are often limited in nature. While such clinical data has been found reliable and relevant for HMWC (e.g. enzymes), the chemical classification criteria do not distinguish between HMWC and LMWC respiratory sensitizers.

Occupational hygiene provisions also play an important role (e.g. occupational exposure limits, OELs) as a protective exposure level mitigates the risk of adverse events such as occupational asthma cases. The German List of Maximum Concentrations and Biological Tolerance Values at the Workplace provided by the German Research Foundation (DFG; Deutsche Forschungsgesellschaft) Commission for the Investigation of Health Hazards in the Work Area (MAK Commission; an advisory body to the government that derives workplace limit values) emphasizes the relevance of an immunological mechanism, specifically in human cases of sensitization where IgE antibodies are detected at significant levels but lacks accompanying symptoms or functional impairment (DFG, Deutsche Forschungsgemeinschaft 2022). Thus, the MAK Commission recognizes the significance of IgE-mediated sensitization to establish protective occupational exposure limits, even in the absence of apparent symptoms.

Clinical or occupational health perspective vs. regulatory classification requirements

It is noted that both clinical or occupational health and chemical regulation share a common underlying goal of protecting human health. Additionally, another common theme is that while an allergic mechanism in respiratory sensitization is acknowledged there are no sufficiently robust provisions to reliably differentiate between allergic and irritant forms (see Supplement 2).

However, based on this review, some significant differences in perspective have been observed between the two areas. In general, it should be noted that clinical work on respiratory allergy is focused on diagnosing and treating individual patients and by no means designed to aid in classification decisions in regulatory toxicology. Consequently, the clinical focus is on accurate diagnosis for appropriate remedial action rather than necessarily identifying the primary cause of the symptoms and its control, which falls within the domain of occupational hygiene. Clinical guidelines therefore focus primarily on correctly diagnosing the clinical condition and the management of the associated symptoms or disease, without necessarily conducting a refined and complete anamnesis (medical history) and analysis of the mechanism and causation by a specific agent. The clinical focus is usually not on the active search for potential confounders and other potentially sensitising exposures.

The regulatory guidelines, such as those by the OSHA and the MAK Commission, primarily focus on hazard classification of specific substances which in turn is used in the supply chain as a basis for risk communication and risk management measures (labels, safety data sheets, OELs, protective measures, etc.). However, the caveat is that if in the clinical diagnosis of OA a connection between occupational exposure to the chemical agent and symptoms occurrence is presumed without sound evidence regarding the causation, such a report subsequently can still influence regulatory decisions on the substance under evaluation. Though it is understandable that data interpretation can easily be complicated due to the variability of the symptom portrayal and challenges

encountered in associating symptoms with workplace exposures, clinicians and regulators should both be aware of such issues and be transparent in documenting uncertainties. CLP and accompanying guidance (European Parliament and Council 2008; ECHA 2024c) outline a "base-set" of clinical history required when assessing the clinical information, but often this information is lacking as is harmonized diagnostic criteria. In addition, the prevalence of respiratory sensitization in humans and supporting evidence for the specific chemistry, e.g. chemical reactivity similar to diisocyanate or anhydride respiratory allergens, are important factors for evaluating chemicals as potential respiratory sensitizers.

Clinical diagnostic methods and approaches for the identification of LMWCs as respiratory sensitizers

This section provides more detailed insights into clinical diagnostic methods and their use and limitations for the accurate identification of the causal agent of symptoms, understanding the underlying mechanisms (such as sensory effects, irritation, sensitization) caused by the agent, and recognizing the conditions that lead to symptoms and potential disease development. The precise identification of the causal agent and its potential origins facilitates successful, effective and timely treatment and management of the condition, as well as prevention of additional cases but is often difficult to retrieve. Moreover, any research opportunities to enhance the accuracy and applicability of diagnostic methods can drive prevention and improve the success of treatments (Papadopoulos et al. 2012). As mentioned above, the use of clinical diagnostic methods is, however, not intended for classification for respiratory endpoints in a chemical regulatory setting. Research gaps and limitations of the method and applicability should be taken into consideration when the identification of a LMWC respiratory sensitizer results in subsequent implications for regulatory classification.

As can be seen from the previous two sections, both official guidelines and peer-reviewed publications provide criteria and guidance for diagnosing respiratory sensitization. To some extent these sources demonstrate the use of specific combinations of criteria and methods to assess whether a LMWC has strong evidence of causing respiratory sensitization in humans. Overall, it can be stated that diagnostic methods are well advanced to diagnose respiratory sensitization to HMWC in humans as well as to accurately identify the causative protein allergen, e.g. by using component-resolved diagnosis (CRD) for specific IgE antibody (Raulf 2018). However, it is much more challenging to diagnose respiratory sensitization to LMWC (Baur et al. 2019). No single test can reliably diagnose or exclude sensitization of the respiratory tract towards LMWCs in humans (Wang et al. 2023). In this section, following a brief reflection on the assessment schemes for OA, the most commonly used diagnostic methods and procedures are reviewed, with a focus on how they might be used for the identification of LMWC respiratory sensitizers.

Assessment schemes for the diagnosis

Clinical diagnostic procedures are often related to the diagnosis of OA for which a variety of usually complex schemes can be found in several of the aforementioned official guidance documents as well as in key expert literature like the expert book Asthma in the Workplace (Tarlo et al. 2021) or other review articles (Vandenplas et al. 2017). These resources provide detailed guidance on conducting health surveillance, documenting exposure history, symptoms, and testing. For example, in the book "Asthma in the Workplace" (Tarlo et al. 2021) guidance is provided on collection and use of information related to health surveillance data, case reports, chemical identity, and history of exposure, with emphasis on the importance of good health surveillance practices, documentation and diagnostic criteria for occupational asthma, which need to be considered while accessing either published data or data within occupational databases, as well as a decision tree on building WoE for confirmation of OA (For a summary, see Supplement 3). A decision tree by Cullinan et al. (2020) offers a step-by-step approach to confirm or exclude the diagnosis of OA and thus the relation of symptoms to exposure in the workplace. Multiple lines of evidence are necessary to determine OA. However, the approach does not differentiate between OA caused by immunological mechanisms and OA caused by non-immunological mechanisms. If no immunological data are available, the algorithm and decision tree developed by Cullinan et al. (2020) and Tarlo et al. (2021) rely on a positive response from a SIC test (for details see below) or serial monitoring of peak expiratory flow (PEF) as sufficient evidence to confirm a diagnosis of OA.

Cormier and Lemiere (2020) and Vandenplas et al. (2017) highlight the importance of timely and accurate diagnosis of occupational asthma and propose a stepwise algorithm for its diagnosis. The guidance includes investigating non-specific bronchial hyperresponsiveness (NSBHR)[16] and immunological sensitization in the occupational setting, along with considering clinical and occupational history, documentation of functional and inflammatory changes, and conducting SIC with suspected agents in laboratory and workplace settings. The authors also acknowledge the challenges in establishing the immunological basis of occupational asthma and suggest adding fraction exhaled nitric oxide (FeNO) and sputum cell count tests to NSBHR for increasing sensitivity.

Recognizing the need for early diagnosis and intervention for better management and care of respiratory sensitization cases, including HMWC and LMWC respiratory sensitizers, an international multidisciplinary group of experts has published the International Consensus Statement on Allergy and Rhinology which provides a critical review of the existing literature on allergic rhinitis (AR) as well as recommendations for its diagnosis and treatment, and emphasizes the importance of the evaluation of sensitization through skin testing and/or evaluation of chemical-specific IgE antibodies (Wise et al. 2018).

Despite variations in approaches and consideration of different target populations, these assessment schemes share key elements that are critical for the diagnosis of non-immunological OA versus immunological OA. In the following

subsections, the diagnostic tools and methods that are used in diagnostic assessment schemes are further explored with regard to their strengths and limitations to identify LMWC respiratory sensitizers. While the initial tier usually involves assessing whether a patient has asthma through a questionnaire and supported by lung function tests, it is the immunological evaluation that plays a crucial role in uncovering the underlying immunological mechanisms behind the symptoms.

Clinical history/questionnaires

Patients who undergo a hierarchy of diagnostic methods typically experience respiratory symptoms, such as asthma (e.g. cough, shortness of breath, chest tightness or pain, wheezing when exhaling, sputum production, and reduced exercise tolerance), rhinitis, and alveolitis, and occasionally conjunctivitis (Singh 2023). It is also of relevance to note that there are temporal relations between some symptoms, for example allergic rhinitis precedes allergic asthma (Thomas 2006). Before specialists administer diagnostic tests to a patient, they capture the clinical history to determine the appropriate method, how it should be conducted and if the results are in line with the clinical history of the patient (Tarlo et al. 2021). An important first step in the evaluation process is to identify a work-related pattern by examining medical history and identifying a suspected agent(s). This includes conducting an occupational exposure assessment and reviewing work history. In certain instances, occupational physicians may request additional data on exposure levels from the factories where they routinely see cases, incidence of spills or accidents, and similar conditions in other workers. This information can be evaluated alongside the clinical diagnosis and published as part of case studies. Different questionnaires are used depending on the need to obtain the medical history of a patient with symptoms or to assess specific symptoms in a group of workers exposed to a presumed causative agent (Tarlo et al. 2021). The latter typically collects data on job description, exposure level and duration, and symptoms to assess the prevalence and type of effects potentially related to the agent. The medical history of a patient with symptoms aims to assess the possible work-relatedness of the symptoms in context of the exposure history. Generally, questionnaires are important to determine factors that can increase the risk of asthma, such as pre-existing diseases (atopy, previous allergic diseases), a family history of allergies or asthma, and smoking. The clinical history and accurate assessment of temporal patterns of symptoms related to workplace exposure is crucial, specifically for workers compensation claims. While questionnaires do not distinguish between allergic and non-allergic asthma, they do identify risk factors (Janson et al. 2007). Another use of questionnaires is prevention strategies for occupational asthma, which comprises medical surveillance for early detection of affected workers so that early diagnosis and intervention can occur. However, to date, there is no generally accepted nor validated respiratory questionnaire for medical surveillance, and the frequency of such repeat assessment during work exposure remains undetermined (Lau and Tarlo 2019).

Immunologic evaluation

Once suspected LMWCs have been identified, multiple immunological methods can be conducted to investigate the presence of an underlying immunological mechanism. However, the following methods discussed typically require the preparation of conjugates with a carrier protein (see below) to be able to identify specific IgE antibodies towards the alleged LMWC respiratory sensitizer (Baur and Czuppon 1995):

- Skin Prick Testing (SPT), a scratch test or intradermal testing (IDT) can be performed in a minimally invasive, cost and time efficient way to identify a wheal and flare reaction to the suspected agent (Ansotegui et al. 2020).
- Enzyme-linked immunosorbent assays (ELISAs), ImmunoCAP^{TM}, fluorescent enzyme immunoassays (FEIAs), chemiluminescent assays, and the less sensitive radioallergosorbent tests (RASTs) are IgE blood tests that quantify the level of specific IgE antibodies towards the conjugated suspected agent by testing serum from the patient (Ansotegui et al. 2020). It should be noted that since 2010, the National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) has advised against using radioallergosorbent assays (RASTs) due to the lack of sensitivity. Moreover, the measurement of total IgE (instead of LMWC-specific IgE) antibodies in serum is not considered as indicator for sensitization to the suspected LMWC as there are many unspecific factors that can influence total IgE levels in serum (Ansotegui et al. 2020).
- Immune cell-based tests like the basophil activation test (BAT) or mast cell activation test (MAT) reflect a functional cell response such as upregulation of cell surface marker or IgE and non-IgE associated degranulation and histamine release (Vera-Berrios et al. 2019) and thus can be a valuable test in addition to the detection of LMWC-specific IgE antibodies.

While these methods are very well established and reliable for testing protein allergens, they have limitations when applied to LMWC testing. The preparation of a conjugate with a carrier protein is specifically challenging (Baur and Czuppon 1995). There is only a limited number of LMWCs for which conjugates (typically with human serum albumin) are commercially available due to the lack of standardization and complexity to prepare the appropriate testing materials (Budnik et al. 2013) to reliably detect LMWC-specific IgE antibodies. Using conjugates of the suspected LMWC respiratory sensitizer covalently bound to a carrier-protein can pose a risk for false-positive results as serum IgE may bind non-specifically to the protein, irrespective of the suspected respiratory sensitizer. It is therefore advised to test variations of conjugates to discriminate LMWC-specific IgE from protein-specific IgE (Pronk et al. 2007). In addition to the immunological evaluation, an assessment of airway inflammation in sputum can help to identify whether symptoms are driven by an ongoing unspecific inflammation that are exacerbated by the suspected agent in a rather irritant and non-immunologic way (Moscato et al. 2012).

In conclusion, various immunological methods are available but further research and standardization is needed to enhance the accuracy and reliability of these methods for identifying clinically relevant LMWC respiratory sensitizers.

Functional assessment/physiological evaluation

In addition to the clinical history questionnaire and the immunological evaluation, the physiological evaluation is the key component to measure respiratory symptoms and to assess the severity of the condition (for review see Suojalehto et al. (2021)). This evaluation aims to determine the individual's lung function (lung function test) and response to suspected causing agent(s) of the condition (provocation test). Lung function and condition tests such as spirometry, plethysmography, maximal respiratory pressures, diffusing capacity, bronchodilator responsiveness, oxygen saturation/desaturation during exercise, arterial blood gases, fractional exhaled nitric oxide (FeNO), methacholine test, peak expiratory flow (rate) (PEFI), exhaled breath condensate (EBC), bronchoalveolar lavage (BAL), and induced sputum can typically be conducted at physicians and/or specialised pulmonologists. However, the interpretation of such complex lung function data has been found to result in marked variations and errors among pulmonologists (Topalovic et al. 2019).

The following subsections offer a broad overview of the topic, providing a general, but not exhaustive, understanding of the most common and advanced lung function and provocation tests which have been proven useful in diagnosing asthma. However, it is important to note that none of these tests have been specifically developed nor evaluated to identify respiratory sensitization in humans nor identify a LMWC as respiratory sensitizer. Moreover, due to the complexity of the tests, they may not be readily accessible to all individuals, and their results may not always be easily interpretable nor suitable to identify a chemical as respiratory sensitizer.

Lung function tests. Lung function tests (or pulmonary function tests) aim at measuring changes in lung volumes and capacities from a healthy population and help in diagnosing and monitoring respiratory conditions. Certain lung function tests can be conducted at home (self-measurements) and over a longer period of time using portable instruments. Overall, the objective of lung function tests is to provide quantitative measurements and objective data about lung health. These tests assist in diagnosing respiratory conditions, evaluating lung function parameters, monitoring disease progression, and guiding treatment decisions for better management of respiratory health.

A commonly used lung function test method is spirometry, which records the volume of air exhaled and the rate at which it is exhaled. It measures the maximum volume of air that can be exhaled forcefully after a maximal inhalation (forced vital capacity; FVC), the volume of air forcefully exhaled in the first second (forced expiratory volume in one second; FEV_1), the ratio of FEV_1 to FVC, which helps determine the presence and severity of airflow limitation, and the maximum flow rate achieved during forced exhalation (peak expiratory flow rate; PEFR).

A more advanced lung function test can be conducted with the FeNO analyzer, which is a device designed to detect and quantify the amount of nitric oxide gas present in the exhaled breath. FeNO tests are used to assess and monitor airway inflammation by measuring the concentration of nitric oxide (NO) in the exhaled breath and is based on the hypothesis that activated immune cells release inflammatory mediators, which induce the production of NO, a defence mechanism to increase e.g. vasodilation, immune cell activation, regulation of inflammation, and potential tissue damage. However, it is important that lung function test results be considered in conjunction with other clinical information and diagnostic tests, as many factors can influence the results (Heffler et al. 2020).

Provocation tests. Provocation tests, such as the conjunctival provocation test, NSBHR tests, and the SIC test are highly complex tests which are typically conducted under supervision of a pulmonologist in specific diagnostic centers (Vandenplas et al. 2019a).

NSBHR tests are commonly conducted as a first provocation test, which – in contrast to bronchial challenge tests using specific suspected allergens – uses agents that have a generalized effect on airway constriction to provoke a response, such as methacholine, histamine, adenosine monophosphate or mannitol (Vandenplas et al. 2014). The goal of the test is to determine the concentration of methacholine or histamine that causes a specified decrease in FEV_1, typically $\geq$15 or $\geq$20%, known as the provocative concentration or dose. The lower the concentration or dose required to produce the defined decrease in FEV_1, the more hyperresponsive the airways are considered. This test is useful when the causing agent has not yet been identified or to confirm the diagnosis of substance-unspecific asthma in individuals with inconclusive clinical or diagnostic findings, but it has a low specificity for diagnosing OA (Pralong et al. 2016). Taken together, NSBHR results are not a proof of allergic asthma, or a proof of causation by a specific chemical.

Specific inhalation challenge (SIC) test. The SIC test, formally developed in the 1970s to diagnose OA by simulating workplace exposure conditions, is typically conducted in specialized laboratory or clinic with monitoring devices in controlled exposure conditions, and can be considered a more specific follow-up test to basic NSBHR testing (Suojalehto and Cullinan 2014; Preisser et al. 2021). Although the SIC test is considered as the "gold standard" for asthma diagnosis, its presumed high specificity and sensitivity are difficult to quantify. SIC tests should be conducted with considerable care to ensure patient safety and relevance in terms of composition and concentration with respect to workplace exposure, ensuring the test protocol mimics as closely as possible exposure in the workplace e.g. dose, duration and nature of the agent (e.g. monomer vs. polymer, vapor, fume, or dust aerosol). A key reference for the identification of immunologically mediated OA of both HMWC and LMWC is the

consensus statement of the European Respiratory Society (ERS) Task Force which addresses best practice in the field but provides no standardized or mandatory approach (Vandenplas et al. (2014), together with the complimentary online handbook (original version June 2013, last update 2019 (ERS Task Force 2019)). The test design includes a control challenge followed by a gradually increased exposure to the test agent. NSBHR measurements are conducted before and after the challenge. The outcome is led by measuring airway obstruction (FEV_1) in the first place, and development/increase of NSBHR and/or airway inflammation. NSBHR when increased after the challenge while the challenge itself is not showing positive results is not necessarily interpreted as a positive response but may trigger the request for subsequent challenges to exclude OA; the authors state it remains debateable whether an isolated increase in post-challenge NSBHR can be considered a positive SIC. There are many variables that can impact the test results such as duration of the challenge, exposure level of the tested material, and the clinical history of the tested individual with a key challenge being to discriminate between unspecific reactions and symptoms which are truly related to an agent causing the effects by an intrinsic, sensitizing property.

The authors provide a series of recommendations that aim to balance patient safety with the accurate identification of potential causative agents while minimizing false-positive results. They particularly emphasize results caused solely by irritant effects, since "a false-positive reaction may theoretically result from non-specific irritant bronchoconstriction which does not fit the definition of occupational asthma due to specific bronchial hypersensitivity to an occupational agent". Additionally, they suggest that "exposure to a control substance may allow the identification of subjects who are likely to develop non-specific reactions on subsequent challenge with occupational agents" (Vandenplas et al. 2014).

Proposed measures are:

- In the case of irritant agents, the use of a control substance that is comparably irritant and shares the same physical appearance
- Delivering the suspected agent in the same exposure conditions as those that prevail in the workplace, gradually increasing the exposure concentration, and ensuring that exposure does not exceed the relevant OELs (the consensus statement does not specify which OELs should be used under which conditions)
- Continuous measurements to closely monitor and control exposure to mitigate the risk of non-specific reactions

In practice, however, appropriate techniques for monitoring and controlling exposure to the wide variety of agents that can potentially cause respiratory symptoms are seldom available or thoroughly implemented. As can be seen from the ERS Task Force handbook (ERS Task Force 2019), controls to minimize false-positive reactions do not seem to be regularly or consistently used (for example, see the methyl methacrylate (MMA) case study covered later in this paper). Also, the recommendations provided are not mandatory and as acknowledged by the authors the exposure during SIC is not always monitored closely; therefore, exposure concentrations may be increased to levels above standard working exposure conditions which may result in conclusions that are biased by too high exposure conditions during testing. Although testing concentrations that reflect accidental exposure conditions (such as spills) may be relevant for the diagnosis of an individual, these concentrations typically do not represent standard working conditions or OELs. It must be noted that the conduct of such tests is of course voluntary for patients, and due to ethical considerations, no threshold of concern levels can be established. In order to make maximum use in the interpretation of SIC tests, a proper conduct and documentation of all details including substance identity and exposure conditions is essential.

With regard to the underlying mechanisms relevant for SIC outcomes, it is widely accepted that Early Asthmatic Reactions (EARs) reliably hint to irritant mechanisms of OA, while the hypothesis that late asthmatic reactions (LARs) are indicative of an allergic mechanism is less certain (Pemberton and Kimber 2021).

Several investigations deal with potential differences between LMWCs vs. HMWCs in SIC outcomes (Dufour et al. 2009; Vandenplas et al. 2019b). It has been observed that for certain proteins and LMWCs, an adverse response can be as an EAR (usually defined as a FEV_1 $\geq$20% within the first hour of exposure), as a LAR (FEV_1 $\geq$15-20% between 2 and 8 h after exposure), but also as dual asthmatic responses (DAR, combination of EAR and LAR) as well as atypical responses (Dufour et al. 2009). These differences need to be evaluated with care as exposures can influence the development of symptoms and due to the variability among affected individuals, the data does not provide a clear differentiation between LMWC respiratory sensitisers (irritants versus non-irritants) and protein allergens.

In a retrospective multicenter study between 2006 and 2015 covering 20 centers from 11 European countries (European Network for the Phenotyping of Occupational Asthma [E-PHOCAS]), it was found that there are phenotypic differences between reactions to LMWCs compared to protein allergens (Vandenplas et al. 2019b). A basic criterion for selecting subjects was an available "diagnosis of OA ascertained by a positive SIC". However, while the number of tested individuals ($n = 544$) is high, the description of respiratory symptoms (chest tightness, daily sputum, late asthmatic reaction, severe exacerbations) is too vague to conclude with sufficient certainty on immunological relevance compared to irritation.

It should be noted that the group of LMWC referred to in these studies also include polymer molecules like resins, particulate matter like wood dusts, as well as metals, which renders them a group with quite heterogeneous chemical groups and underlying mechanisms. Moreover, among the true respiratory sensitizers, which represent only a limited number of very distinct chemical groups, the type of adverse responses may also vary among affected individuals and/or overlap with those of HMWC.

Further research is needed to better understand the underlying mechanisms of LMWC respiratory sensitizers and the relevance of EARs and LARs to be able to identify

respiratory sensitization to LMWCs with high confidence in such provocation tests. Additionally, a more precise analysis and definition of the inherent properties of the causative agents are necessary, along with proof of their role in causing the effects in SIC tests.

Selected practical issues with clinical diagnosis

Accessibility to clinical expertise or expert diagnostic centers for confirming (occupational) asthma cases is one of the major challenges for individuals affected by respiratory symptoms, which can result in prolonged and unnecessary exposure to the causing agent, exaggerated symptoms and consequently contribute to the development of more severe cases. An observational cohort investigating the utilization of specialized opinion in adult asthma was carried out in England (Blakey et al. 2019). The report addresses the difference between the number of patients eligible to receive expert or specialist referrals and those who received timely referrals. The results indicated that only 4% of the 19837 eligible patients received referrals with an average wait time of 880 days (about two and a half years) between 2007 and 2015. This indicates a potentially high number of clinical cases that remain unresolved. Rui et al. (2022) highlighted the importance of reducing the timing between onset of symptoms and diagnosis for OA prognosis and the knowledge needs related to improvements. There seems to be a need for more specialists (allergologists or allergy trained physicians) to identify and to treat asthma cases in a timely manner (EFA 2011).

Importance of a thorough weight-of-evidence (WoE) assessment as a basis for classification of LMWC respiratory sensitizers

A WoE assessment constitutes an evaluation procedure wherein a thorough scientific assessment of different lines of evidence is conducted to provide a transparent and sound basis for a subsequent classification decision. The key lines of evidence are summarized in Figure 2 of the Introduction. Though in practice this may often be challenging, the authors of this publication conclude that it is of utmost importance for a sound and responsible risk management that the underlying hazard assessment takes into account all relevant information and is done according to state-of-the art or state of knowledge, including the application of good scientific practice and principles. The assessment of potential respiratory sensitizers should in particular aim to distinguish between an allergic and irritant mechanism, and whether exposure to a substance had exacerbated symptoms of a pre-existing disease or is the causative agent. Such approaches typically contain elements of the classic Bradford Hill considerations for the determination of a plausible causal relationship between an observed effect and substance exposure (Hill 1965), including strength (effect size), consistency (reproducibility), specificity, temporality, biological gradient (dose-response relationship), plausibility, coherence, experiment, and analogy. Several modifications from the original criteria have been proposed since then. As reviewed previously (Meek et al. 2023), the WHO IPCS framework on MoA and Species Concordance Analysis proposed criteria to "address the concordance and consistency of the evidence across different lines of evidence and levels of biological organization for mechanistic hypotheses". which are deemed suitable for use in WoE assessments and AOP work.

Therefore, while evaluating the potential of a LMWC to sensitize the respiratory tract, all available data sources must be considered. The uncertainty and level of confidence associated with each information source, including the quality of documentation and potential confounders, needs to be evaluated. ECHA has provided a WoE template and related documents on their website (ECHA 2024b).

Regarding the regulatory perspective towards identification and classification of LMWC respiratory sensitizers, some key areas have been identified which merit thorough consideration to allow for adequate classification and appropriate risk management (Pemberton and Kimber 2021; Meek et al. 2023).

In an ideal case scenario with existing clinical data, respiratory sensitization hazard classification will be based on the following parameters:

- Integration of multiple well-documented human case reports and/or human data from different sources (e.g., epidemiology studies) and tests that provide evidence for respiratory sensitization;
- Symptom evaluation and firm diagnosis of OA by a medical expert, including background information – medical history and exposure analysis revealing potential confounders or additional risk factors;
- Well-characterized specific pulmonary function tests conducted under relevant exposure conditions and immunological tests to confirm causation by the substance under evaluation;
- Distinction between true LMWC respiratory sensitizers and chemicals that cause asthma (or other respiratory symptoms) through a non-immunological mechanism;
- Dose-metrics for respiratory irritation vs. respiratory sensitization;
- Exposure analysis, prevalence and worker history;
- Consideration of physico-chemical properties of the LMWC, including electrophilicity and reactivity mechanisms.

Regulatory implementation with examples of practical application of criteria for LMWC classification

In this section a more detailed view is provided on how criteria are applied in practice as part of the classification and labelling of chemicals. Some case study examples are presented as well as general observations of use of human clinical data in regulatory assessment and classification of respiratory sensitisers. It is illustrated what is currently feasible, and where potential deficiencies exist, be it with the available data or the applied guidance and criteria. The aim is not to provide a comprehensive review of the classification of potential respiratory sensitizers or respiratory irritants, but merely to illustrate critical areas in the assessment of data for hazard classification and labeling purposes.

General observations

Beyond a purely science-driven assessment, it is a matter of regulatory decision-making and the underlying respective risk acceptance as to which classification is ultimately derived, and subsequently what protection and exposure level is considered acceptable, in a specific use context (e.g. workplace with risk protection measures, consumers). From a scientific perspective a state-of-the art assessment is always recommended which includes a reliability assessment of the available information. The various key elements that need to be considered and weighted can be approached from different perspectives, i.e. what are suitable requirements for classification decisions, where are data-gaps, and which criteria or additional information and data can be suitable to complement human data in the context of such a WoE assessment and justification for LMWC classification. It also needs to be noted that the use of WoE is not (fully) harmonized between different legislations but is well established at the Organization for Economic Co-operation and Development (OECD) level.

Though it is generally accepted that consideration of clinical history is crucial (including atopic dermatitis, pre-existing asthma, etc.) as well as the prevalence of effects, such information is often missing. Some important aspects are included in ECHA guidance, as reviewed by Meek et al. (2023). The relevance of this aspect is underlined by the current understanding that sensitisation of the respiratory tract upon exposure to LMWC respiratory sensitizers is less common than either acute effects and/or multiple environmental and genetic factors leading to chronic respiratory symptoms (Schwab and Poole 2023).

Beyond such science-driven considerations, classification decisions by regulators can take into account other factors relating to risk acceptance or the so-called precautionary principle. There sometimes seems to be a conflicting set of imperatives in the regulatory perspective, with precautionary classification on the one hand and the request to use high quality data and mechanistic understanding as a key driver on the other hand. In practice this may lead towards classification even if the underlying information is sparse and/or of poor quality and comes with a high level of uncertainty (for example see MMA case). Finally, and as mentioned earlier, currently no distinction for potency (Resp. Sens. 1 A/1B) can be made in the classification due to lack of methods and relevant data. Thus, all substances classified as Resp. Sens. 1 are currently considered equally potent.

Many LMWC are clinically relevant skin sensitizers, but only very few LMWC are clinically relevant respiratory sensitizers. The initial key events of the Adverse Outcome Pathway (AOP) of skin sensitization are somewhat similar to the initial key events that have been defined for the AOP for respiratory sensitization (Sullivan et al. 2017; Kimber et al. 2018), which explains that some respiratory sensitizers have been tested positive in *in chemico* and *in vitro* methods that were developed and validated to identify skin sensitizers. However, there are only very few clinical cases related to predominantly isocyanates that indicate the potential to cause both, skin and respiratory sensitization (Goossens et al. 2002; Scholten et al. 2020).

Currently, the available guidance on respiratory sensitization classification is limited and partially vague, resulting in simplified and practical criteria for hazard classification decisions, including the following aspects:

1. to abstain from classification
   - In case of proven respiratory symptoms, e.g. ECHA indicates that the substance should not be classified as a respiratory sensitizer if it is proven that symptoms are caused only by an irritant mechanism.
   - According to ECHA, substances which do not belong to a group of well-recognized respiratory sensitizers (anhydrides, diisocyanates) and for which there is no information about respiratory sensitizing effects (e.g. evidence in humans, in animals, *in silico* or *in vitro* to lead to specific respiratory hypersensitivity) are not classified for respiratory sensitization ("classification not possible").
2. to consider classification
   - Substance belongs to a group of well-recognized respiratory sensitizers (anhydrides, diisocyanates)
   - Proven causal relationship between exposure and symptoms, together with positive SIC test results.

It should be reminded in this context that according to the above-mentioned assessment schemes (c.f. section on clinical diagnostic methods an approaches), a positive response in SIC tests or serial monitoring of PEF will usually be considered sufficient evidence to confirm a diagnosis of OA, and together with the current CLP criteria where an immunological mechanism does not need to be demonstrated, a positive response from a SIC test might be considered sufficient evidence of substance-specific respiratory sensitisation (while, as described above, a positive SIC does not necessarily give definitive information on the mechanism involved).

The following case examples further illustrate this complexity in practice and highlight critical factors at the interface between evaluation of clinical information and regulatory classification decisions.

Case examples for the application of current classification criteria

Data-rich compounds: Trimellitic anhydride and toluene diisocyanate, and a structurally related compound with inadequate data: Phthalic anhydride. Phthalic anhydride (PA) CAS No. 85-44-9, Trimellitic anhydride (TMA) CAS No. 552-30-7, and Toluene diisocyanate (TDI) CAS No. 26471-62-5 all have a harmonized classification as respiratory and dermal sensitizers (Annex VI to CLP (European Parliament and Council 2008) updated *via* 20th Adaptation to Technical Progress (ATP) (European Parliament and Council 2023); DFG, Deutsche Forschungsgemeinschaft (2022)). However, only TMA and TDI are considered as true respiratory sensitizers with clinical evidence of sufficient quality. Both are shown to have multiple detailed epidemiological reports from manufacturing facilities that confirm their potential for causing respiratory sensitization from occupational exposures in humans. The clinical evidence contains well-documented physiological and immunological

responses with confirmatory tests using respiratory re-challenges and skin tests, well-characterized chemical identities and their exposure, and detailed medical histories of affected workers. There are a few reports that also mention the role of specific IgE corresponding to the outcome of occupational asthma (Porter et al. 1975; Patterson et al. 1978; Karol et al. 1979). Kimber et al. (2014a) presented an argument for specific-IgE as a marker of respiratory allergy. The authors mention the difficulties of detecting specific-IgE antibodies, specifically in the cases of diisocyanate exposures, which may be in part due to the short half-life of the unbound plasma IgE. More recently, an occupational immunosurveillance program (OISP) demonstrated the importance of longitudinal monitoring of exposed workers for TMA-specific Immunoglobulin G (IgG) and IgE for determining occupational asthma outcomes (Ghosh et al. 2018). It was observed that the TMA-exposed workers that showed higher titres of specific IgG in a significantly shorter duration more frequently developed chemical-specific IgE responses, indicating that regular monitoring of subjects might prove beneficial for early identification of respiratory sensitization cases. However, it is cautioned against misinterpreting specific IgG levels as indicators of specific IgE levels or as having a causal connection between the two markers.

Detailed clinical cases of PA exposures are presented in several published reports (Kern 1939; Chester et al. 1977; Wernfors et al. 1986; Baur et al. 1995; Piirila et al. 1997). Data interpretation is challenging for drawing definitive conclusions regarding occupational cases of respiratory sensitization that are assigned to PA since the relevant reports also mention the use of other well-known respiratory sensitizers, such as TMA and TDI, in the same facilities. The variability observed in capturing immunological biomarkers further complicates diagnosing work-related immune-mediated asthma (Maccia et al. 1976; Chester et al. 1977). Evaluation by Wernfors et al. (1986) of 118 affected workers from two plants showed that 18% of the patients suffered from PA-associated OA, whereas 24% had work-related irritation of the upper respiratory tract (including rhinitis). Of the 21 asthmatic patients (out of 118), 48% had rhinitis preceding bronchial symptoms as opposed to 19% of the non-asthmatic patients. This report provides a critical insight into the spectrum of symptoms associated with respiratory sensitization and the importance of patient medical history. However, the observations documented in these reports together with the reactive anhydride chemical functionality of PA, provide a sufficient level of confidence for regulatory decision-making purposes.

Key learnings. For cases similar to TDI, TMA, and PA, it is important to identify opportunities for a timely intervention and effective risk mitigation measures to prevent cases of OA. For workers, using diagnostic markers, such as chemical-specific IgE antibodies at chemically relevant or quantifiable levels as highlighted for TMA and regular health monitoring of susceptible individuals with detailed documentation is necessary. These details eventually feed into the regulatory decision-making process, thus significantly enhancing the reliability of hazard classification and labelling practices for LMWC respiratory sensitizers.

A classified respiratory sensitizer based on very limited data, not classified as dermal sensitizer: Azodicarbonamide. Azodicarbonamide (ADCA, CAS No. 123-77-3) has a harmonized classification as a respiratory sensitizer and is listed on the Candidate List of SVHCs under Article 57(f) of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Regulation as having "equivalent level of concern" to substances which are CMRs (ECHA 2012). The evidence for causation of occupational asthma underlying the decision for classification relies principally on three strands of information:

1. A number of case studies (ca. 9) reported in the literature of development of OA following workplace exposure to ADCA.
2. Workplace health studies indicating high prevalence of symptoms associated with OA in defined worker populations.
3. National Health database records where OA has been diagnosed and attributed to ADCA exposure in the workplace.

A common feature across all three lines of evidence is that such reports were compiled in the 1970–2000 period with very few, if any, cases of occupational asthma associated with ADCA exposure recorded more recently (Hartwig and MAK Commission 2018). ADCA did not elicit a positive response in predictive tests for skin sensitization and does not seem to be able to form stable associations with proteins (Arts and Kimber 2017). The lack of skin sensitization potential of ADCA is also further supported by the very few numbers of cases (<5 globally) of allergic contact dermatitis (Arts and Kimber 2017).

Of the OA case studies published involving ADCA only nine can be considered sufficiently reported (Malo et al. 1985; Kim C et al. 2004; Arts and Kimber 2017; Suojalehto et al. 2018); however, even here significant details are lacking, and the evidence cannot be described as conclusive. In all cases, co-exposures to other respiratory irritants or sensitizers in the workplace cannot be excluded, and therefore exacerbation of pre-existing asthma cannot be ruled out. Further, NSBHR was not determined in many cases, sufficient details on the purity of the test materials used during challenge is not provided and the methods employed (duration, quantity of exposure) are not uniform thus making it difficult to directly compare clinical outcomes. It is noted that there is no common response following challenge to ADCA, that is, a mixture of early/late responses but one predominant feature is a progression of symptoms which whilst observed with some known respiratory sensitisers is also known to occur following exposure to respiratory irritants. Furthermore, of note is that when conducted, skin prick testing was universally negative.

The workplace health studies reported in the literature add little more than circumstantial evidence to the conclusion that ADCA is a respiratory sensitizer. In all cases it is not possible to determine exposure to ADCA alone and whether it could be the causative agent in the development of OA or merely a factor in exacerbation of pre-existing asthma. In all cases there is no correlation between workplace exposure

levels and onset of symptoms, and it must be noted there was no difference in spirometry between ADCA-exposed and non-exposed workers pre- and post-shift.

National health databases do not provide details to allow meaningful analysis of probable causality of OA by ADCA. Typically, cases reported in these databases do not contain the clinical details required to ascertain a plausibility that the individual is indeed sensitized to ADCA. Clinical details of the cases are scantly reported and do not contain elements required by current regulatory guidance (ECHA 2017a).

Key learnings. This case study highlights several areas of concern when concluding on the classification of a substance as a respiratory sensitizer and identifies areas of potential improvement, in particular in reporting standards, which would assist in regulatory decision making. The consequences of classification can be significant, in this case determination as a SVHC. Therefore, it is crucial to conduct a thorough and rigorous evaluation of the evidence that underpins such decisions. However, the feasibility of such evaluation may vary depending on availability of data and literature. To ensure inclusion of reliable evidence in legislative processes, it is recommended to adhere to a minimum reported standard that all available evidence should meet when considering it as part of the body of evidence.

A classified respiratory irritant with classification for respiratory sensitization currently under evaluation: Methyl methacrylate. Methyl methacrylate (MMA, CAS No. 80-62-6, EC No. 201-297-1) is an unsaturated methyl ester of methacrylic acid that is used as a monomer for polymer production (Poly(methyl methacrylate); PMMA). The monomer is primarily handled in industrial production of MMA and its polymers and there are also widespread professional uses of the monomer, for example in adhesives and sealants, coating products and fillers, dental and surgical cements, as well as consumer uses.

MMA is classified as an irritant to the skin and respiratory tract and as a weak/moderate skin sensitizer. MMA is of low systemic toxicity and workplace threshold limit of 50 ppm (8h time weighted average (TWA)) has been proposed in the EU (European Commission 2006). A comprehensive risk assessment for MMA has been conducted in the EU (ECB 2002) which reviewed the available clinical evidence at that time and concluded that there was "no convincing evidence that MMA is a respiratory sensitizer in humans", as was also confirmed by a later review from Borak et al. (2011) which took into account various lines of evidence including human data.

Following a CLH proposal by the French authority ANSES (French Agency for Food, Environmental and Occupational Health & Safety) in 2019, the RAC adopted ANSES' recommendation to classify MMA as a respiratory sensitizer. The evidence relied upon by the RAC in their 2nd opinion from 2021 included reports of six positive SIC tests attributed to MMA, supported by information from National Surveillance databases that claimed occupational asthma to be caused by MMA. Another RAC mandate to review new information (ECHA 2023c) was recently published (ECHA (2024a) and references therein). Two of six cases that had been previously considered as key evidence (ECHA 2021) were, upon re-evaluation, considered either as not relevant (case 4: SIC was conducted with a product other than MMA) or assigned with a lower relevance (case 5: PMMA dust not MMA was applied in the SIC test, but nevertheless RAC considers this test as still contributing to their concern). For overview and additional information on the cases see Supplement 4. RAC confirm their previous overall conclusion that a classification would be justified primarily based on the remaining four cases. It should be noted that due to several critical aspects these cases do not allow to draw reliable and robust conclusions, including: (a) missing documentation of clinical history and workplace analysis which would be important to assess if there was pre-existing asthma or other substances (confounders) could have caused the asthma; and (b) missing exposure information for the SIC, making it impossible to judge whether the well-known irritating effects may have caused the positive result. Whereas RAC did state that they performed their assessment based on "weight of evidence determination applying expert judgement", such insufficient information should be more critically weighed. A comprehensive WoE assessment for MMA has previously been published in the peer reviewed scientific literature (Pemberton and Kimber 2022). For this assessment, 368 records from a literature search on MMA were generated, classified as per six separate lines of evidence and weighted with respect to causation and levels of confidence including worker health studies, case studies, QSAR, exposure, national surveillance data and SIC test data. The authors applied a modified version of the Bradford Hill criteria and a four-point scoring system based on the US Office of Health Assessment and Translation (OHAT) handbook to the available data to assess the strength of causal relationship and the level of confidence in the data. The authors concluded that the available evidence for MMA does not support classification. Another group of experts (Meek et al. 2023) have highlighted important aspects of the WoE assessment that need to be considered, using MMA as an example.

Key learnings: Overall, the MMA case study points to several critical aspects including:

- The necessity for a comprehensive weighing of the relevance of available information;
- A low quality and transparency of documentation of clinical case study reports hamper a robust assessment, especially when not sufficiently documented in peer reviewed literature or at least made publicly available to allow for an independent assessment;
- The general use of mixtures in the workplace and in SIC tests if not carefully investigated and documented, possibly leading to low confidence in linking observed clinical responses with a specific substance;
- The insufficient consideration of confounding factors, most notably irritant provocation of pre-existing disease and co-exposure to other chemicals or dust;
- The level of exposure used in SIC tests and its control, allowing for comparability with typical exposures in the workplace, including consideration of peak exposures with the low confidence that can be ascribed to interpreting possible mechanisms involved in clinical responses (namely irritation vs. immunological pathway).

In another recent publication (Pemberton et al. 2023) the authors highlight that clinical examinations "do not reliably identify specific chemicals within the workplace that are the causative agents", and they critically analysed examples where SIC tests had been published with the claim that they demonstrate causative effects with regard to two other methacrylates, 2-hydroxyethylmethacrylate (HEMA) and N-(2-hydroxypropyl) methacrylate (HPMA). Since these tests had been performed with mixtures they do not allow to determine a probable causal relationship to a single substance. In their opinions on HEMA and HPMA, RAC plausibly concluded that a classification for respiratory sensitization is not justified with the major reason given that there was insufficient information on the materials of the SIC tests (ECHA 2023b, 2023a).

Single cases and broad exposure: Formaldehyde is not classified as Resp. Sens. 1. Formaldehyde is an example of a chemical with suspected respiratory sensitization potential and widespread use that was not classified as Resp. Sens. 1 according to the opinion of the RAC (RAC and SEAC 2020). Formaldehyde (CAS No. 50-00-0) is a recognized skin sensitizer (Skin Sens. 1), skin corrosive (Skin Corr. 1B), and irritant to the respiratory tract. Only a very limited number of case reports are related to respiratory sensitization. Data include rare cases of anaphylaxis, SIC tests triggering immediate, but no late reactions, specific IgE (if found at significant levels) did not correlate with respiratory symptoms and differentiation from irritation often was difficult. Animal data do not indicate formaldehyde as a respiratory sensitizer (ECHA 2019). Overall, the small number of reliable findings in comparison to the broad exposure potential were considered to not warrant the classification of formaldehyde as a respiratory sensitizer (Resp. Sens. 1) according to the criteria for marking of an agent as an allergen of the MAK commission (DFG, Deutsche Forschungsgesellschaft 2023).

Key learnings: Chemicals that are suspected to have respiratory sensitization potential due to single case reports, but are widely used with broad opportunities of human exposure, do not necessarily warrant a regulatory hazard classification. This case also highlights the need for methods and/or defined approaches that can be used to support the non-classification for respiratory sensitization of a chemical.

Role of clinical data in the development of new methods, a better mechanistic understanding and further research

It is desirable that human data derived by clinical diagnostic methods and approaches can be used to establish a basis for research and method development *in vitro* and *in silico* to identify true respiratory sensitisers without the need of *in vivo* data. Equally, a better mechanistic understanding could aid interpretation of clinical data, and simple additional diagnostic tests may allow for a more accurate diagnosis. However, only accurate clinical data combined with an investigation on the underlying causes and mechanisms can provide a sound basis for the identification of reliable reference substances against which new methods and approaches can be validated. This is another crucial argument to strive for a better discrimination of non-allergic asthmagens and true respiratory sensitisers in the context of clinical diagnosis and potential subsequent use of the data for chemicals classification purposes. High quality data in that regard could support the increasing efforts that are being made to provide an improved understanding of underlying mechanisms and the development of tools, methods and approaches. In case this understanding could be well established, it can be helpful in turn to better interpret human data in the future, especially within the overall context of a WoE assessment. At OECD level the AOP concept has been established and has been developed or is being progressed for various toxicological endpoints[17] (Ankley et al. 2010). While the AOP for skin sensitisation, along with key events, corresponding test batteries, OECD test guidelines, and databases containing test results, was developed and validated by the OECD ten years ago (OECD 2014), and has been further advanced since then (Ezendam et al. (2016); AOP 40 in AOP Wiki database[18]). In contrast, there remains limited understanding of the underlying mechanisms of action for respiratory sensitizers.

Several publications have considered the challenges of building an AOP for allergic respiratory sensitization: (a) Kimber et al. (2014b) used a number of plausible hypotheses to reverse-engineer an AOP, identifying preferential reactivity of respiratory sensitizers with lysine residues to form hapten-carrier complexes as well as a preferential Th2 response which can favor the development of LMWC-specific IgE antibody; (b) an outline of available evidence supporting an AOP for respiratory sensitization with focus on the discrimination between skin and respiratory sensitizers and human relevance as well as to allow identification of gaps in knowledge and research needs (Sullivan et al. 2017); and (c) a hybrid AOP to highlight those areas where the pathways to skin sensitization and respiratory sensitization might diverge and specific research needs and questions that may provide a step forward in understanding mechanisms (Kimber et al. 2018). The authors also highlight major uncertainties associated with the mechanistic understanding of chemical-induced respiratory allergy, in particular: (a) the relevance of routes of exposure, since there is evidence that respiratory sensitization may also occur *via* skin exposure; and (b) the scientific uncertainty and controversy about the role IgE which is also related to difficulties with its detection. As reviewed by Schwab and Poole (2023) both classical IgE-mediated responses but also other non-IgE immunological mechanisms are possible for LMWCs with their exact nature still requiring further investigation.

Recently, Hargitai et al. (2024) analyzed the current state of knowledge with regard to mechanistic understanding in relation to the available AOP concept (draft AOP 39 in AOP Wiki[19]; Sullivan et al. (2017)) and suggested potentially useful models to fill identified knowledge gaps in order to picture presumably relevant key events of the immunological mechanism but not covering HMWCs or respiratory irritants which are acting through different mechanisms. It would have been important in this context to more critically review the literature findings with regard to true respiratory sensitizers in order to make best use of that data to identify suitable reference compounds for the design of the AOP and potential

new methods. This example also shows that the current rather broad regulatory definition of respiratory sensitizers does not seem to be helpful to promote a better mechanistic understanding which would be necessary to aid the development of new methods and approaches.

While as indicated by Kimber et al. (2018), both true respiratory and skin sensitization are likely to involve similar initial key events, there are important differences between skin and respiratory AOPs, including the differential induction of cytokines and chemokines, different dendritic cell populations and differential activation that induce divergent T cell sub-populations, which in turn drive a specific IgE antibody-mediated immune response, but not a cell-mediated immune response as skin sensitizers. Other key events such as preferential binding towards amino acids in proteins, have been found to be driven by chemistry rather than influencing a certain immune response (Lalko et al. 2012; Dik et al. 2016; Hemming et al. 2019; Krutz et al. 2021).

Besides *in vivo* and *in vitro* data, information may include mechanistic insights *via* (quantitative) structure-activity relationships ((Q)SARs), which in a WoE assessment are often combined with *in vitro* tests (OECD 2017). Identification of such substructures associated with respiratory sensitisation using computational tools has been published (Cui et al. 2021). However, one needs to be cautious about the data that underpin the reference compounds used to develop these predictive models. The achievements and gaps with regard to such methods in the light of the current mechanistic knowledge have previously been reviewed (Arts 2020).

As highlighted by ECHA in their review and guidance on non-human data for respiratory sensitisers (ECHA (2017a), Section R.7.3.9.1), care should be taken with SARs related to chemicals that are not "specifically chemical respiratory allergens" but causing asthma-like symptoms in humans without further exploration of the mechanism.

Various efforts have been made to develop screening methods for the identification of true LMWC respiratory sensitizers. In the absence of understanding the underlying mechanisms leading to respiratory sensitization, it is critical to consider how these methods are evaluated for relevance and which LMWCs were used as positive controls in the training data set considering the difficulty in identifying such chemicals with a high degree of confidence based on the limitations of the available diagnostic methods. While well-documented human data may assist in method development, unclear/possibly unreliable cases as positive reference data would lead to unreliable predictions (Sadekar et al. 2021; Ponder et al. 2022). Importantly, despite the potential of LMWC respiratory sensitizers resulting in positive results in alternative methods developed for skin sensitizers as highlighted by Basketter et al. (2017), only very few recognized LMWC respiratory sensitizers are clinically relevant skin sensitizers (e.g. certain diisocyanates); the reasons could be diverse, including potential low potency of specific substances and/or low exposures. Evaluating the weight of available evidence and basing further assay development and data generation (e.g. *in silico*, *in vitro*, clinical parameters) for respiratory sensitization along the lines of this mechanistic outline may also assist in a better interpretation of human data. Further developing diagnostic methods to specifically identify true respiratory sensitization and sensitizers may further strengthen the reliability of human data and possibly assist in the identification of additional human biomarkers for respiratory sensitization that are needed to develop more specific testing methods for hazard identification. The OECD has recently initiated an activity to develop a detailed review paper with the aim to facilitate the development of test methods to predict the respiratory sensitization potential of substances (Project 4.166)[20].

Main observations regarding strength and limitations in using human clinical data for the purpose of hazard classification

Strengths of clinical data:

- From a hazard perspective the obvious benefit of using clinical data is its direct human relevance.
- When reported in a standardized and timely manner, the use of clinical data can help better understand chemical-specific types of symptoms, prevalence of symptoms, and exposure conditions. Such information can also assist in identifying effective risk mitigation measures and function as a monitoring system to prove effectiveness of measures.
- Clinical data, if deemed sufficiently robust, can aid in the identification and benchmarking of true respiratory sensitizers as well as respiratory irritants and skin sensitizers, and a reliable discrimination between these categories is needed for a successful evaluation of *in silico* or *in vitro* models.

Limitations of clinical data:

- Clinical data is based on elicitation, but not induction of sensitization. Human elicitation data has significant variability and inconsistency which undermines its suitability for hazard classification. As described in the sections above, several aspects contribute to these inconsistencies, including non-standardized methodologies, protocols, quality criteria and documentation.
- Clinical data is currently based on data from diagnostic methods that are insufficient to accurately identify respiratory sensitization to LMWCs in humans or to identify the causative LMWC as respiratory sensitizer with high confidence.
- There are inconsistencies in the types of diagnostic methods and significant gaps in reporting, which are a consequence of the absence of standardized testing and guidance.
- SIC testing requires significant technical and clinical expertise and can only be conducted in specialized centers with long waiting times for patients suffering from symptoms. When conducted, there are several potential pitfalls that may lead to false positive results, like lack of exposure control and/or appropriate irritant controls and thus irritating effects being the cause of the positive

result; missing information on clinical history and analysis of confounders and test materials which are insufficiently documented and/or not suitable to analyze substance-specific properties (for example mixtures) which altogether makes it usually difficult to identify specific chemicals as the true cause of a sensitising effect in these tests.

- The most commonly available data are from non-specific provocation tests (NSBHR tests), which are useful to confirm diagnosis of substance-unspecific asthma. However, such data is insufficient to identify respiratory sensitization or the causative LMWC as respiratory sensitizer.
- In many cases, clinical diagnosis of (occupational) asthma and the focus on alleviating patient symptoms and determining work-relatedness tend to take precedence over efforts to uncover underlying immunological mechanisms, resulting in limited discrimination between allergic and non-allergic symptoms. Also, once a likely suspect substance (recognised respiratory sensitizer) is known to be used in the workplace further analyses concerning confounders or other causes may not be conducted.
- There are no standardized approaches and criteria to differentiate between OA vs. WEA cases, which is essential to differentiate between asthma directly caused by exposure to substances in the workplace and pre-existing asthma that is worsened or exacerbated by factors present in the work environment.

Key recommendations & conclusion

Having reviewed the clinical sources and types of information available we herein provide some recommendations as to how clinical data could be used and might be further improved for making informed classification decisions:

1. **A differentiation on a scientific and regulatory level between LMWCs with an intrinsic ability to cause induction and elicitation of allergic respiratory symptoms from those which may provoke non-specific respiratory responses.** Due to the relatively greater severity of potential adverse health effects of respiratory sensitizers compared to irritants, such differentiation is considered helpful to ensure clear risk communication and effective risk management measures. Thus, guidance documents for hazard classification should establish provisions and criteria how an immunological mechanism can be investigated and, consequently, a re-evaluation of legal provisions is recommended with the proposal to classify respiratory sensitizers as Resp. Sens. 1 only where there is robust evidence for an underlying immunological mechanism. Also, clinical data should only be considered as a proof of respiratory sensitization if an adequate control for non-specific irritant provocation of pre-existing or concurrent asthma has been applied and the proof for causation by a specific substance is provided.
2. **A differentiation on a scientific and regulatory basis between potent (Resp. Sens. 1A) and less potent (Resp. Sens. 1B) LMWC respiratory sensitizers.** A clear guidance to be able to differentiate potent true respiratory sensitizers from less potent respiratory sensitizers is deemed necessary, especially to assess how far risk management measures (such as OELs) may be considered as effective to protect human health or more severe restriction measures are required (e.g. identification as an SVHC). Here, exposure data in the context of severity of symptoms and prevalence should be considered as important factors to assess the frequency or probability of occurrence for the exposed population.
3. **Harmonized diagnostic criteria and clinical reporting standards.** Greater consistency in reporting and accessibility of clinical databases (within the framework of patient confidentiality) and published case reports would enable improved identification and monitoring of substances suspected of causing respiratory sensitization. This would also greatly assist regulators and industry alike in identifying substances of potential concern and allow an early intervention with effective risk management strategies. If health surveillance and clinical case study data is used to identify respiratory sensitizers, then data need to be captured in a thorough, transparent, and harmonized way to ensure that true effects requiring hazard classification of a chemical as a respiratory sensitizer can be identified accurately. Guidance is needed to enable clinicians to align on terminologies and clinical reporting standards within the clinical domain but also with regulatory needs.
4. **Advancement of current diagnostic tools and methods to demonstrate LMWC-specific causation of respiratory sensitization effects**. Moving forward, non-invasive and simple diagnostic methods that can accurately identify respiratory sensitization (vs. respiratory irritation, skin sensitization), and the causative LMWC respiratory sensitizer inducing and eliciting the symptoms in humans, are needed in order to use clinical data to determine an appropriate hazard classification. More advanced diagnostic methods and standardization of clinical practices can also help in improving care for patients through targeted therapeutics. Guidance documents should be further developed to: (a) establish more clearly how to provide sound evidence for causation of the observed effects by a specific substance; and (b) provide further insight and evaluation with regard to the specific advantages and disadvantages of diagnostic methods for the purpose of identification of true LMWC respiratory sensitisers. The assessment needs to investigate whether there is an inherent property of a LMWC to cause a substance-specific effect as opposed to a nonspecific effect like irritation, or an effect produced by confounders or poor and/or incorrect documentation.
5. **Requirements for SIC tests when used to diagnose respiratory sensitization to LMWCs and hazard classification.** The following aspects should be considered as critical: (a) control and continuous measurement of exposure, with the gradually increasing exposure not exceeding relevant OELs; the selection and use of OELs (STEL, TVLs, etc) for this purpose should be standardized

and further specified in the guidance; (b) use of similar chemistries with comparable irritancy as control; c) test materials that are mixtures should not be used for classification of substances or need to also be tested individually for their constituent components. In case of positive results in the SIC test, a follow-up test specifically with the suspected LMWC as well as a further immunological evaluation is recommended, together with a general requirement for a proper characterization and documentation of the tested material; and (d) documentation of the clinical history and a workplace analysis to identify confounders have to be provided. In light of the discussed weaknesses and pitfalls when using SIC data for classification purposes, it is suggested to reconsider the regulatory provision that more positive SIC are seen as sufficient for classification, and an improved guidance that better clarifies the criteria and limitations with regard to the reliability/quality and overall relevance of such data for classification purposes should be established. Such criteria should include the relevance of the profile of responses obtained (i.e. DAR and LAR). SIC data should not be used in isolation for classification purposes but be part of a thorough WoE assessment to evaluate their relevance and reliability in the overall context with other relevant information.

6. **A thorough state-of-the art WoE assessment conducted by qualified experts as basis for hazard classification.** To ensure the scientific relevance and reliability of the information used, the principles of WoE should be applied to the assessment of human clinical data. The quality and strength of all lines of evidence should be evaluated for their relevance and level of confidence that a certain chemical is the causative agent for the observed effects. This should be complemented by practical applications of clinically and mechanistically sound diagnostic criteria within a WoE approach by using case studies and (sufficiently reported) prevalence data from surveillance programs. Isolated case reports with unclear mechanistic background should not be considered for hazard classification, especially if the chemical has been used extensively with a history of safe use.
7. **Further elucidate the mechanistic understanding of respiratory sensitization and LMWC respiratory sensitizers for hazard classification.** It is important to emphasize that future classifications and labeling do not necessarily have to rely primarily on clinical data. New approach methodologies (NAMs) based on an agreed AOP for respiratory sensitization could provide a more mechanistic-based approach to testing. Thus, hazard classification for respiratory sensitizers should in future be based on, or at least complemented by, a better mechanistic understanding, additional NAMs and data. While such methodologies and AOPs are still under development, care should be taken as to which data are to be used as a benchmark, since the focus should be on true respiratory sensitizers. The further development of a previously suggested hybrid AOP that not only reflects differences between skin and respiratory sensitizers, but also respiratory sensitizer and irritants, is encouraged.

To conclude, despite an overall rather low reliability, in practice the relevance of reliance on human clinical data for identifying respiratory sensitizers is high, especially in the absence of suitable and standardized toxicological test systems. The considerable uncertainties and pitfalls when using such data for classification purposes often leads to low confidence in the outcome. Though some issues could be partially overcome by tailor-made and standardized diagnostic approaches, good quality documentation and guidance, ethical, technical and scientific limitations remain inherent and need further consideration and thorough investigation. Especially in the light of these uncertainties, application of a systematic WoE approach using appropriate guidance is deemed necessary to determine the level of confidence, including a thorough assessment of the specificity or non-specificity of observed bronchial hyperreactivity. Isolated NSBHR measurements are not considered sufficient for classification. With regard to SIC testing, adequate measures need to be taken to avoid false-positives and to analyze the causality of an effect with regard to a specific LMWC, especially when data are used in the context of chemical classification. The over-interpretation of positive test results, often with mixtures, the lack of following clinical guidance to exclude non-specific irritation and to control exposure, and the interpretation of LAR indicating involvement of immune mechanisms and hence assumed specificity to the test agent, is not sufficiently justified by current scientific knowledge to act as a single criterion for classification but should be embedded in a formal and comprehensive WoE assessment following recognized criteria. An ongoing exchange on these critical topics with relevant stakeholders would be helpful to promote further progress in the field.

Notes

1. It should be noted that there is no standard definition of LMWCs. Different thresholds have been cited [<0.9 kDa (Krutz et al. 2021), <1 kDa (Vandenplas et al. 2019a), <5 kDa (Baur et al. 2019), or higher values)]. The authors of this paper do not endorse a specific value but emphasise the distinction between allergy to LMWCs and allergy to proteins, which have different molecular events.
2. According to ECHA guidance, an exception is foreseen in cases where it can be shown that effects are related to irritant properties only and a classification as respiratory irritant (H335) is considered more appropriate.
3. https://echa.europa.eu/information-on-chemicals/annex-vi-to-clp.
4. For more details including table 3.4.1 please see (ECHA 2024c).
5. https://www.cdc.gov/niosh/topics/surveillance/ords/.
6. https://www.cdc.gov/niosh/topics/surveillance/ords/pdfs/DecisionLogicWRA.pdf.
7. https://sites.manchester.ac.uk/thor/.
8. https://www.occupationalasthma.com/shield.aspx.
9. https://www.gov.uk/government/publications/industrial-injuries-disablement-benefits-technical-guidance/industrial-injuries-disablement-benefits-technical-guidance#appendix-1-list-of-diseases-covered-by-industrial-injuries-disablement-benefit.
10. https://www.dguv.de/de/mediencenter/hintergrund/berufskrankheiten/statistik/index.jsp.

11. https://www.monash.edu/medicine/sphpm/coeh/research/completed/sabre.
12. https://www.worksafe.govt.nz/notifications/notify-worksafe/.
13. https://oshri.kosha.or.kr/eoshri/about/history.do.
14. https://www.leitlinien.de/themen/asthma/4-auflage.
15. https://www.nice.org.uk/guidance/ng80/chapter/Recommendations.
16. There are different abbreviations in use for non-specific bronchial hyperresponsiveness, including NSBR, NSBH and NSBHR. Here we use NSBHR which is meant to be equal to NSBR and NSBH.
17. https://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm.
18. https://aopwiki.org/.
19. https://aopwiki.org/.
20. https://www.oecd.org/chemicalsafety/testing/work-plan-test-guidelines.pdf.

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Declaration of interest

The co-authors of this manuscript consist of members of an ECETOC Task Force (comprising members from industry and research institutes) and one of the stewards from the ECETOC Scientific Committee. The views expressed in this article are solely those of the co-authors and may not represent those of their organisations.

While the common understanding of ECETOC and the Task Force members is to provide an objective assessment, for reasons of transparency we like to disclose that members from industry are employed by companies producing a range of chemicals with the issue of respiratory sensitiser classification having an impact on substances of interest to these companies. The latter does not apply to the Task Force member from a research institute (RIFM). Dr. Julia Scheel is an employee of Röhm GmbH, a manufacturer of MMA and other methacrylates. She has been and will be involved in regulatory activities related to the contents of this paper. Dr. Scheel is contributing to science-based advocacy activities of the Cefic methacrylates sector group (MSG). Dr. Stuart Hindle is employed by Dow Europe GmbH and is involved in regulatory activities related to the contents of the paper. Dow manufactures acrylates and methacrylates. This manuscript was subjected to the usual internal peer-review process required by the companies and institutes of the participating Task Force members. This manuscript was also reviewed by the ECETOC Scientific Committee consisting of representatives of academia and industry (http://www.ecetoc.org/about-ecetoc/scientific-committee/). Both these reviews yielded relatively minor clarification comments.

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Data availability statement

All studies reviewed in this manuscript are available in the published literature. Any further details may be requested from the corresponding author.

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