

***Chemical Respiratory Allergy:
Clinical Information and
How To Use It and Improve It
Madrid, 27-28th October 2016***

Workshop Report No. 33

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European Centre for Ecotoxicology and Toxicology of Chemicals

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Chemical Respiratory Allergy: Clinical Information and How To Use It and Improve It

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SUMMARY

The workshop identified various areas that can drive improvements in the identification, classification and risk characterisation of respiratory sensitisers and recommended several practical steps to improve the current situation. Identified problems included the fact that, in contrast to the situation for skin sensitisation and skin irritation, where these are clearly distinguished for the purposes of classification and labelling, no similar distinction is drawn between sensitisation of the respiratory tract and respiratory irritation. Other issues include lack of clarity with respect to minimum reporting requirements, with some concern about isolated cases of respiratory allergy being used for classification, contradictions within the regulations and lack of guidance for clinicians with respect to the data that should be recorded when reporting cases of chemical respiratory allergy. A number of recommendations were made to address these problems.

1. INTRODUCTION

1.1 Background

In 2015 an ECETOC taskforce published the results of a review of the available data to consider the relevant endpoints that can be used to describe Chemical Respiratory Allergy¹ (CRA) and to inform our understanding of threshold effects [1]. The aim of that review was to determine whether chemical respiratory allergy should be regarded as a threshold, or as a non-threshold, toxicity, and to recommend appropriate methods for deriving safe concentrations of chemical respiratory allergens.

As discussed in the taskforce publication [1], although there is evidence that the acquisition of sensitisation to chemical respiratory allergens is a dose-related phenomenon, and that thresholds exist, currently the mechanisms involved in CRA are not fully elucidated, there is uncertainty regarding routes of exposure, and no validated models exist for identification of respiratory sensitising substances. Neither are there any methods suitable for the routine assessment of threshold values for sensitisation of the respiratory tract by chemicals. As a result, human thresholds of induction and elicitation are poorly characterised which creates uncertainty about the safe use of H334 (previously assigned the risk phrase R42) classified substances.

More robust human threshold data would help refine the current risk assessment approaches for the use of such materials, both from occupational and consumer exposure standpoints. Additionally, members of the taskforce identified that clearer guidance is required on how best to use existing human data for the evaluation of respiratory sensitisers in weight of evidence assessments.

Therefore, a workshop was convened to:

Develop best practice guidance on how to assess and use available human data for the identification of respiratory sensitisers, including the creation of a framework for the interpretation of quality of evidence and weighting to be applied.

Drive discussions on identifying human biomarkers for respiratory sensitisation to chemical allergens and the use of such tests in prospective monitoring of workforces to identify more accurate threshold data.

Three key publications were highlighted as pre-read material for workshop participants (see Bibliography on page 12 of this report).

1.2 Workshop structure and aims

Sixteen international scientific experts from industry and academia participated in the workshop where on day 1, after a series of expert presentations, participants were split into two break-out groups to discuss the following:

- a) What are the criteria for data admissibility and weighting for classification?
- b) The identification of biomarkers for chemical respiratory allergens and for sensitisation of the respiratory tract?

On day 2 the conclusions from day 1 were reviewed and all participants considered a third discussion point:

- c) Assessment of sensitising potential: relevance for classification and SVHC.

Finally, all key discussion points and conclusions were recapitulated in a final plenary session where several key actions were identified to begin to address the workshop objectives, which were to:

- Define and promote a consistent, best practice, strategy for the evaluation of available human data for respiratory sensitizers, for use by regulators in formal decision-making processes.
- Publish a consensus opinion on the research required for the identification of human biomarkers of chemical respiratory sensitisation, and application in prospective monitoring of workforces with the ultimate aim of refining current human threshold data to reduce uncertainty in current risk assessment approaches.

A list of workshop participants is given in Appendix B, and the programme is detailed in Appendix A.

2. PRESENTATION SUMMARIES

The following abstracts were drafted ahead of the workshop and have not been modified following the workshop discussions.

2.1 Session 1: Guidance Development

2.1.1 Introduction, Aims & Objectives – Plan for the 2 days

Stella Cochrane, Unilever, United Kingdom

Human thresholds of chemical respiratory sensitisation and elicitation are poorly characterised. This coupled with uncertainty regarding mechanisms, exposure routes and a lack of validated hazard identification and characterisation approaches means there is great uncertainty regarding the identification and safe-use of R42 classified substances.

Better guidance on how to use existing human data for the evaluation of respiratory sensitisers in weight of evidence assessments is needed. More robust human threshold data would help refine the current risk assessment approaches for the use of such materials, both occupational and consumer.

2.1.2 Chemical Respiratory Allergy: definitions, mechanisms, hazard identification and characterisation

Ian Kimber, Manchester University, United Kingdom

Allergic sensitisation of the respiratory tract by chemicals posed a number of toxicological challenges, and there remained many controversies. These included, importantly, the mechanisms through which sensitisation is acquired (including particularly the role of IgE antibody), and the relevance of the skin for driving sensitisation. These uncertainties were considered, as their impact on approaches for hazard identification and characterisation.

In addition, this presentation seeks to provide a working definition of chemical respiratory allergy, and will review briefly a recently published Adverse Outcome Pathway that explores the key events resulting in sensitisation of the respiratory tract.

2.1.3 The Case of ADCA – A chemical sensitizer?

Axel Schnuch, University of Gottingen, Germany

Azodicarbonamide (ADCA) is used as a foaming agent in the production of a number of different products (e.g. wallpapers, under-coatings for cars, various building materials). In the 70's and 80's there were some reports on respiratory symptoms suspected to be related to exposure to ADCA.

Data of different sources, all from the 70's and 80's, with decreasing evidence, may support the notion of ADCA being a respiratory allergen: 1. Well documented reports on 3 cases from two centers. 2. Less well documented reports on 8 cases from three centers. 3. "Epidemiological" studies on exposure measurements and on workers with respiratory symptoms from three plants manufacturing or using ADCA. 4. Notification of suspected, yet not diagnosed cases to registers of occupational health (e.g. SWORD).

Evidence:

There are at most 3 reasonable cases in which pulmonary reactions have been verified in published and sufficiently documented provocation tests (1x Korea, 2x Canada). In spite of some shortages, these 2 case reports give some evidence for an immunological mechanism and could therefore be regarded as sufficient to fulfil the criteria for marking ADCA with Sa (sensitising airways), although additional immunological evidence like positive prick tests or proof of specific IgE is lacking.

Shortcomings and unanswered questions:

- The identity of the ADCA as used in provocation tests is not documented in any case report
- No allergological diagnostics have been done in epidemiological studies from the working place and no such information is available for cases from registration systems
- Unlike other low-molecular weight allergens, ADCA is negative in the Local Lymph Node Assay
- Considerations on the reactivity of ADCA and its metabolites do not point to a stable protein binding (necessary for sensitisation)
- The fine dust particles, possibly in combination with other factors (especially in the plastics industry) may also be causative
- The impact of decomposition products has not been evaluated in the plastics industry
- Further exposure scenarios may be involved, regarding information from some patent literature (e.g. the possible role of admixtures like carbonic anhydrides)
- Regarding the (former) relatively wide distribution/exposure (ten thousands of workers exposed per year), just 3 well documented and published cases provide little evidence for a strong sensitising potential

Conclusion:

A respiratory sensitising effect of azodicarbonamide is not sufficiently proven and the substance has therefore not been marked with Sa.

2.1.4 Current status of regulation of respiratory sensitizers

Josje Arts, AkzoNobel, The Netherlands

In this presentation the current status of regulation of respiratory sensitisers was addressed with a focus on classification criteria and risk assessment.

Emphasis was put on the fact that for respiratory sensitisers- in contrast to skin sensitisers - immunological mechanisms do not have to be demonstrated.

2.1.5 Clinical Diagnosis of Occupational Asthma – practice and challenges/opportunities

Paul Cullinan, Imperial College, United Kingdom

The standard approach to – and some recent advances in - the clinical assessment of occupational asthma was discussed using a recent ‘case’ managed at the presenter’s hospital.

The aim is to provide a clinical perspective to discussions around how the sensitising potential of (chemical) agents encountered at work can be assessed.

2.1.6 Moving beyond hazard identification towards hazard characterization: illustrated with case studies

David Basketter, DABMEB Consult, United Kingdom

There is a sense in which moving beyond hazard identification in the area of respiratory allergy is rather easy: we do not have any generally applied, let alone validated, predictive tests. Consequently, the presence of hazard is often based on a simple rule, e.g. if the chemical is an isocyanate, we assume it is a respiratory sensitiser, or, if humans will inhale a specific foreign protein, we should assume that some individuals will raise IgE antibodies. However, in practice, novel respiratory allergens are identified on the basis of the adverse health effects they produce, typically in an occupational setting, a situation unchanged since the dawn of toxicology.

In whatever manner if one arrives at the conclusion that there is a potential hazard present, how can it be characterised? The reality is that very pragmatic approaches have to be adopted. Perhaps a positive result in a skin sensitisation test can be subjected to a cytokine profiling study to determine whether there is a Th2 tendency, although that merely leads to a more confident hazard identification. What is missing, for both

chemical and protein respiratory allergens is a means to measure their relative sensitising potency. Consequently, a primary strategy has been to consider the exposure side of the “risk = hazard potency x exposure” calculation. Perhaps this is far from what is meant by hazard characterisation in most areas of toxicology, but it is how practical progress is made. The presentation offered case studies of exposure to a cosmetic containing a potential respiratory sensitiser as well as an occupational example involving exposure to bacterial and fungal protein allergens. In each case, there are clear limitations on what can be achieved.

To progress beyond the pragmatic cases to be discussed, it is obviously necessary to have clarity of focus on mechanism (IgE mediated reactions), one or more methods to assess potency based on the mechanistic understanding and, probably most crucially, to have access to a sufficient body of clinical data which permits a range of respiratory allergens to be ranked according to their relative potency in humans. Whilst that last element remains absent, efforts to develop new methods have little chance of achieving any degree of scientific or regulatory credibility.

3. ROUND TABLE DISCUSSIONS

Moderator: Alan Poole, ECETOC, Belgium

To focus round table and plenary discussions the workshop participants were asked to address the 5 topics shown below:

- What are the criteria for data admissibility and weighting for classification?
- The identification of biomarkers for chemical respiratory allergens and for sensitization of the respiratory tract.
- Assessment of sensitising potential - relevance for classification and SVHC.
- Steps required to identify biomarkers for sensitization to chemical respiratory allergens.
- Guidance on how to assess and use available human data for the identification and regulation of respiratory sensitizers.

4. CONCLUSIONS OF THE ROUND TABLE AND PLENARY DISCUSSIONS

The following key conclusions emerged:

- Evidence of an immunological mechanism should be required to classify a substance as a respiratory sensitiser, using all available information.

- In contrast to the situation that pertains to skin sensitisation and skin irritation, where these are clearly distinguished for the purposes of classification and labelling, no similar distinction is drawn between sensitisation of the respiratory tract and respiratory irritation. This is very unfortunate because they are different conditions, that are driven by different mechanisms, and which demand different risk management strategies.
- Existing classification guidance needs to be improved, particularly in terms of clarity with respect to minimum reporting requirements, and contradictions within regulations need to be removed.
- Isolated case reports of respiratory allergy were considered insufficient for classification, but the incidence and/ or prevalence rates that would be required for this purpose are not yet defined.
- More robust and complete human clinical and epidemiological data are critical for not only refining thresholds and understanding potency, but also for validating new in vitro approaches and biomarkers for CRA.
- As part of the collection of such data, there is a need for more accurate exposure information both in terms of levels of exposure and chemical characterisation of the materials people are exposed to. Approaches should be used that address the long standing questions in the field of HMW respiratory allergy research such as collection of concurrent data for skin and inhalation routes of exposure, which would provide insight into the impact of peak exposures and robust chemical characterisation of the materials reaching the skin and respiratory tract.
- Guidance for clinicians with respect to the data that should be recorded when reporting cases of CRA needs to be improved.
- Additionally, it is currently not clear who reports clinical data to whom, and there appears to be a potentially large body of data that is not in the public domain that could be used to improve our understanding of potency and thresholds for chemical respiratory allergens. Existing human clinical data and exposure data need to be identified, collated and shared to maximise use of this important source of information.
- The possibility of drawing upon existing clinical and / or occupational surveillance experience to rank chemical respiratory allergens in terms of potency (prevalence and exposure) should be explored.
- There is a need to agree a list of well characterised chemicals to clearly define positive and negative materials for use in investigative studies of CRA, in particular those to enable irritants and sensitisers to be separated and also skin and respiratory sensitisers. The Association of Occupational and Environmental Clinics (AOEC) database could be a useful source of information in this respect.
- The most appropriate potential human immunological biomarkers, and those potentially worthy of revisiting / exploring as new biomarkers, include:
 - sIgE antibody (recognising there is a need to review novel approaches to measurement - e.g. analysis of specific precursor plasma cells - and state of the art diagnostic methodology in this area), total IgE, nasal tryptase and other mast cell degranulation and cytokine markers, the basophil activation test

(BAT) and the lymphocyte transformation assay. Many of these targets are not new but with renewed effort applied to addressing the challenge of correct antigen production, they may be successfully applied.

- There is likely to be value in overlaying what is currently known about the existing respiratory sensitisation AOP on the more fully defined skin sensitisation AOP and linking this to clinical outcomes to help identify where research activities for novel biomarker identification should be focused.
- Given the current use of LLNA data in a negative predictive sense i.e. if a material is negative in this assay it is deemed neither a skin nor respiratory sensitizer, then it is important to understand whether the recently validated in vitro skin sensitisation tests also provide this negative prediction for respiratory sensitizers.
- Based on the evidence that indicates chemical character is most important in driving the Th1/Th2 polarisation between skin and respiratory sensitizers, further work to investigate the chemical characterisation of selected materials to try and understand what is driving this mechanistic difference was deemed an important area of further research.
- There is a need to define a tissue dose-metric for the respiratory tract (considering both upper and lower regions of the respiratory tract), such as the $\mu\text{g}/\text{cm}^2$ for skin sensitisation, and for information and tools to be acquired and developed to enable extrapolation from human in vivo exposures - currently measured as airborne concentrations – to such a metric such that it may be utilised in in vitro studies.

5. RECOMMENDATIONS AND NEXT STEPS

The following activities were identified as next steps to address the workshop objectives:

- A publication overlaying what is currently known about the CRA AOP on the skin sensitisation AOP with consideration of clinical data, with a view to identifying areas of focus to develop new or improve existing human biomarkers, both in vitro and clinical.
- Review available data generated for chemical respiratory allergens in recently validated in vitro skin sensitisation assays and, if necessary, generate data for additional materials to understand the negative prediction potential of such tests.
- Consider working with the European Respiratory Society (ERS) to establish a clinical toxicology group to consider 'clinical information and how to improve it', including how to standardise current diagnostic tests and how to define best practice for data collection. Such a group could rank existing materials in terms of potency based on clinical experience and consider how to develop new diagnostics / human biomarkers.
- A short commentary on current guidance on classification and labelling of chemical respiratory allergens and how to improve it.

- Specific SVHC guidance concerns to be taken forward by CEFIC TF on SVHC sensitisers.

6. CLOSE OF THE WORKSHOP

The organising committee thanked everyone for their participation and agree to pursue the 5 recommendations.

ABBREVIATIONS

ADCA	Azodicarbonamide
AOEC	Association of Occupational and Environmental Clinics
AOP	Adverse outcome pathway
BAT	Basophil Activation Test
CEFIC TF	European Chemical Industry Council Task Force
CRA	Chemical Respiratory Allergy
ECETOC	European Centre for the Ecotoxicology and Toxicology of Chemicals
ERS	European Respiratory Society
H334	Health Hazards classification: may cause allergy or asthma symptoms or breathing difficulties if inhaled
HMW	High Molecular Weight
IgE antibody	Immunoglobulin E antibody
LLNA data	Local Lymph Node Assay
R42	Health Hazards classification: may cause sensitisation by inhalation
Sa	Sensitising Airways
splgE antibody	Specific IgE antibody
SVHC	Substance of Very High Concern
SWORD	Surveillance of Work Related and Occupational Respiratory Disease
Th1	Cells which secrete the cytokines interferon-gamma (IFN-gamma) and tumor necrosis factor-beta (TNF-beta)
Th2	Cells which secrete interleukin-4 (IL-4), IL-5, IL-9 and IL-13

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APPENDIX A: WORKSHOP PROGRAMME

27 October DAY 1 (Modigliani room)		
08:30-09:00	Registration	
09:00–09:15	Introduction, Aims & Objectives, Plan for the 2 days	Stella Cochrane Unilever, UK
09:15-09:50	Chemical Respiratory Allergy: definitions, mechanisms, hazard identification and characterisation	Ian Kimber Manchester University, UK
09:50-10:20	The Case of ADCA – A chemical sensitizer?	Axel Schnuch University of Gottingen, DE
10:20-11:00	Coffee break (Hall Atocha)	
11:00-11:30	Current status of regulation of respiratory sensitizers	Josje Arts AkzoNobel, NL
11:30-12:00	Clinical Diagnosis of Occupational Asthma – practice and challenges/opportunities	Paul Cullinan Imperial College, UK
12:00-12:30	Moving beyond hazard identification towards hazard characterization: illustrated with case studies	David Basketter DABMEB Consult, UK
12:30-13:30	Lunch (Restaurante Nacional)	
13:30-14:30	Panel Discussion + Q&A with morning speakers: setting the scene for the Round Table Discussions to follow	All speakers (above) Moderator: Alan Poole
14:30-14:40	Details for Round Table Discussions	Madeleine Laffont

27 October DAY 1 (Modigliani & Picasso rooms) cont...**14:40-15:40 Round Table Discussions (held in parallel):****1. What are the criteria for data admissibility and weighting for classification?****Green Group (Modigliani room)****Chair:** David Basketter**Rapporteur:** Danielle Botelho*Possible Questions to prompt – but not constrain - discussion:*

- *Should evidence of an immunological mechanism be required to classify a substance as a sensitizer?*
- *How much is enough? What are the quantitative and qualitative classification criteria to label a substance as a sensitizer?*
- *What should be the minimum reporting requirements for chemical evidence of sensitization?*

2. The identification of biomarkers for chemical respiratory allergens and for sensitization of the respiratory tract?**Blue Group (Picasso room)****Chair:** Ian Kimber**Rapporteur:** Stella Cochrane*Possible Questions to prompt – but not constrain - discussion:*

- *What are the most appropriate potential immunological biomarkers?*
- *Are there potentially relevant non-immunological biomarkers?*
- *Are there lessons to be learned from skin sensitization?*
- *Are there lessons to be learned from respiratory allergy to proteins?*

15:40-16:15 Coffee break (Hall Atocha)

27 October DAY 1 (Modigliani room) cont...

16:15-17:00	Plenary & reporting back	Chair & Rapporteur from each Roundtable
17:00-17:20	Conclusions & details for tomorrow	Stella Cochrane Unilever Danielle Botelho RIFM, USA
17:20-17:30	Details for Museum visit & dinner	Madeleine Laffont ECETOC
18:45-20.00	Reina Sofia Museum Visit	All
20:00	Dinner: Rest. Arzabal (Museum, Sabatini building)	All

28 October DAY 2 (Modigliani room)

08:45-09:00	Welcome and proceedings	Ian Kimber Manchester University, UK
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09:00-10:15	Roundtable Discussion 3: Assessment of Sensitising potential - Relevance for classification and SVHC	All participants <i>discuss the same question</i>
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Chairs: David Basketter and Ian Kimber**Rapporteurs:** Danielle Botelho and Stella Cochrane*Possible Questions to prompt – but not constrain -
discussion:*

- *Is it necessary for the substance to provoke allergic symptoms (e.g. during a provocation test) in order to be eligible for classification – or is it sufficient that it provokes a biological response (e.g. antibodies) in the absence of clinical symptoms?*
- *How can we ensure that biomarkers are adequately specific and sensitive?*

10:15-10:45	Coffee break (Atocha Hall)
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10:45-11:30	Plenary & Discussion	Chairs & Rapporteurs
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11:30-13:00	Drafting:	All
	1. Describe steps required to identify biomarkers for sensitization to chemical respiratory allergens – and their use for prospective monitoring of workforces to more accurately identify threshold data	Chair: I. Kimber Rap: S. Cochrane

13:00-14:00	Lunch (Restaurante Nacional)
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14:00-15:30	Drafting:	All
	2. Guidance on how to assess and use available human data for the identification and regulation of respiratory sensitizers (include interpretation of strength of evidence and weighting)	Chair: D. Basketter Rap. D. Botelho

15:30-16:00	Conclusions, Wrap Up and Close	Ian Kimber Manchester University, UK
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16:00-16:30	Closing Coffee break (Atocha Hall)
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APPENDIX B: WORKSHOP PARTICIPANTS

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