

Cefic views on respiratory sensitisation

Cefic is committed to ensuring that the health of workers and the safety of products are top priorities for the chemical industry. This paper focuses on the management of substances with respiratory sensitising potential. There is ongoing action in Europe to list sensitisers as Substances of Very High Concern (SVHCs) under the “equivalent level of concern” route set out in Article 57(f) of REACH. This would unjustifiably imply that respiratory sensitisers present the same health risks as defined under REACH for carcinogens, mutagens, and reproductive toxicants (CMRs) as trigger for SVHC. Cefic believes the default listing of respiratory sensitisers as SVHCs is unnecessary in controlling their risks for the reasons outlined below. This can only happen on a case by case decision. This position paper includes key messages followed by a detailed discussion of specific aspects of respiratory sensitisation.

Key messages

- **The severity of pathologies associated with respiratory sensitisers is not a trigger for SVHC.**
 - The health impacts are far less serious than the effects of CMRs as defined under REACH where e.g. inherited genetic mutations is a trigger for SVHC. In contrast, the health effects from respiratory sensitisers, i.e. allergic effects associated with elicitation responses, are manageable and generally reversible when exposure to the sensitising agent is removed.
 - Respiratory sensitization is not equivalent to asthma. Asthma is a chronic inflammatory disorder which can have various causes, one being the result of repeated exposure to an allergen, but also non-allergic asthma exists. This inflammatory response may in turn lead to a hyperresponsiveness to a variety of stimuli such as cold air or strong smells.
- **Effects are reversible (contrary to CMRs) and elicitation can be avoided**
 - Respiratory sensitization can be described as an adaptive immune response that is mostly associated with the induction of immunoglobulin E (IgE) antibodies to a specific allergen, e.g. pollen, animal dander or a chemical, and their association with mast cells. Elicitation, following subsequent exposure to the same specific allergen, can result in an inflammatory respiratory allergy response with symptoms such as rhinitis and shortness of breath.
 - Minimizing exposure or remaining away from the sensitizing source reduces the adverse effect on health. It results typically in reversibility and recovery of any physiological symptoms if treated on time.
- **It is possible to mitigate the risks to develop allergy, and maintain quality of life.**
 - Risks of sensitisation can be managed by controlling exposure, as has been demonstrated in the detergent industry.
 - Periodic Health surveillance is very effective in identifying workers with early health effects (including sensitisation) and therefore appropriate actions can be taken if necessary to evaluate and control the exposure to a level that would protect the vast majority of workers.
 - The introduction of appropriate risk mitigation measures (through engineering controls such as ventilation or enclosures of processes and wearing personal protective equipment) can therefore minimize exposure, prevent induction and consequently the onset of symptoms associated with respiratory allergy.

- **Proactive measures can be taken**
 - Respiratory allergy effects manifest quickly. Even if at the beginning it is possible to have a short latency period between exposure to sensitisers and symptoms, risk mitigation measures need to be taken immediately and appropriateness/effectiveness of these can be assessed rapidly after implementation.
 - The burden of the effects is reduced through raising awareness, good risk assessment and effective exposure control for respiratory sensitisers rather than introducing a new “classification” terminology.

- **SVHC identification means stigmatization. Huge impact on the market without systematic added value**
 - Due to market perception, the listing of respiratory sensitisers on the SVHC Candidate List will bring further, unjustified stigmatisation and potentially the loss of beneficial substances for consumers and society. Furthermore, inappropriately having a default listing of all respiratory sensitisers under this article will generalize its message and lead to a disregard for the importance of SVHC as the highest level of health concern.
 - A thorough Risk Management Option analysis (RMOa) will determine the most appropriate route for regulatory management of individual chemicals, provided it takes into account their hazard, potency, exposure and socioeconomic data. This process should be performed on a case by case basis and with contribution from stakeholders, including industry. Different control routes to ensure safe use should be considered before entering any further REACH regulatory processes, including compliance with existing community occupational health and safety legislation.

Cefic opinion

Managing exposure to a respiratory sensitising substance is the primary strategy for both the prevention of potential development and the reversal of already existing allergic symptoms. Measures taken to avoid further exposure of a sensitised individual at an early stage will normally result in disappearance of symptoms and consequently achievement of normal quality of life.

Whilst SVHC listing is a possible route for controlling the safe management of hazardous chemicals, Cefic believes the indiscriminate application of SVHC status to respiratory sensitising substances represents a disproportionate use of the “SVHC label” and a misrepresentation of the original intent of REACH Regulation. When considering the provision of Article 57(f), respiratory sensitisers as a general rule should not be treated in the same manner as Category 1A and 1B CMRs, since sensitisers do not pose serious threats to human health in the same manner.

Note: This position is supported by a scientific explanation and list of references in Appendix.

Scientific explanation why respiratory sensitisers should not be assumed equivalent to CMRs

1. The severity of pathologies associated with respiratory sensitisers is not comparable with CMRs

Article 57 of REACH provides that Category 1A and 1B CMRs and PBT/vPvB substances may be included in REACH Annex XIV (authorisation list). The pathology associated to these endpoints represents serious, irreversible and life-threatening impacts on human health and/or serious long-term environmental impacts.

The health effects typically associated with CMR substances as defined under REACH include death, prolonged hospitalization, persistent or significant disability and congenital abnormalities, all of which can be considered serious in nature and irreversible. In addition, development of such effects is usually such that effective intervention is not possible until after a concern has been identified.

In contrast, for respiratory sensitisers the symptoms of this allergic reaction include persistent sneezing, blocked nose/sinus congestion, watery eyes/runny nose, breathing difficulties and coughing. Such symptoms usually resolve once exposure ceases and removal of the individual from exposure typically results in reversibility and recovery of any physiological impairment that may be associated with the actual elicitation component of the allergy. Only in extreme and rare cases can long-term repeated exposure result in severe forms of asthma. Even though individual susceptibility determines the severity of the allergic response, it is extremely rare for an individual to suffer a life-threatening reaction.

It is important to note that respiratory sensitisation and asthma are not one and the same thing. Development of asthma as a condition requires long-term repeated exposure to the respiratory sensitiser such that significant irreversible airway remodelling occurs. Individuals diagnosed for substance specific respiratory hypersensitivity who are withdrawn from the workplace soon after diagnosis will have a very good prognosis and will live without asthmatic symptoms or impairment of lung function. Therefore cessation of exposure of individuals displaying initial symptoms of respiratory sensitization will prevent further progression and in most cases lead to reversibility.

Consequently when considering Article 57(f), respiratory sensitisers should not be considered as such to pose serious effects to human health or the environment as compared with CMRs and PBT/vPvB substances. A case by case assessment with thorough RMO analysis is needed.

2. Effects are reversible (contrary to CMRs) and elicitation can be avoided

The development of respiratory allergy is a result of two distinct phases:

1. The first is an 'induction' or 'sensitisation' phase during which individuals develop irreversible sensitisation to a respiratory allergen. In this initial phase, a change in immunological status is observed (immunological priming) that is free of symptoms.

2. The second phase, called 'elicitation', occurs following subsequent exposure of the individual to the same allergen. This second or subsequent exposure(s) result in development of symptoms of

respiratory allergy, typically symptoms of rhinitis and asthma. The degree and severity of response is linked to the amount to which the person is exposed and subsequently symptoms disappear when the individual is no longer exposed to the respiratory sensitiser. Therefore, the physiological response that characterizes the effect is reversible. Fundamental changes at the physiological level e.g. changes in the epithelium, smooth muscle hypertrophy, collagen deposition and overall airway remodeling only occur following frequent, prolonged and repeated exposure to the allergen.

The risk of triggering an allergic response can be managed by preventing or controlling the exposure through a number of administrative and technical measures such as ensuring that the sensitised person is kept away from the sensitising source, thus substantially reducing the adverse effect on health (Basketter *et al.*, 2015). In fact, removal of an individual from exposure typically results in reversibility and recovery of any physiological symptoms associated with elicitation (Labrecque *et al.* 2010, Tarlo *et al.* 2008)

3. It is possible to mitigate the risks to develop allergy, and maintain quality of life.

Current risk assessment approaches and risk management measures in the workplace are primarily aimed at prevention of induction. The number of cases of occupational asthma reported in Europe has decreased significantly since the turn of the century as a result of improved industrial hygiene standards and pan-European initiatives, suggesting that current industrial practices are sufficient and substantiating that exposure control measures seem effective.

Work-related asthma or occupational asthma is diagnosed following evaluation of patient history, measurement of lung function periodically both at and away from work, and may include specific challenge testing and in addition specific IgE or skin prick testing (which is particularly sensitive to high molecular weight respiratory sensitisers such as proteins).

Accurate diagnosis, effective intervention and removal of the individual from exposure can result in an effective recovery from the disease. The individual can be protected from further development of symptoms by engineering controls, job re-assignment, or use of appropriate respiratory protective equipment such as commonly employed in animal breeding and testing facilities.

Even for the stage of fully developed respiratory allergy, scientific literature on the prognosis indicates that after removal from further exposure the majority of individuals with e.g. diisocyanate related asthma show significant improvement (see ref in Appendix points 4-5). There is a strong correlation with duration of exposure and several studies have suggested that medical surveillance of exposed workers affects recovery. This indicates that lack of recovery is not an unavoidable outcome but can be influenced by early detection through raising awareness, worker education and medical surveillance.

For most respiratory sensitisers, the risk of exposure can be controlled by existing measures and thereby allows for the safe use of the substance. This has been documented for enzymes used in the detergent manufacturing industry in a recent paper (Basketter *et al.*, 2015). Communication through Safety Data Sheets, Labelling and Safe Use Guidance information with respect to respiratory sensitisation potential to downstream users is an important element already carried out by industry to ensure safe handling and use of these products (*see Appendix for examples*).

4. Proactive measures can be taken

For sensitisers, adverse health outcomes can be prevented due to the possibility to determine thresholds for induction – that is, an exposure level below which sensitisation is highly unlikely. Appropriate risk mitigation measures can therefore be introduced to prevent sensitization and thereby in consequence the onset of symptoms. Risk mitigation measures can be taken immediately and appropriateness/effectiveness of these can be assessed rapidly after implementation.

Example (Enzyme)

Measurement of the specific allergic IgE antibody response and management against this response provides a clear point of control in the successful (and long-term) prevention of occupational allergic respiratory disease to enzymes.

Safe conditions of production and use of industrial enzyme proteins have been investigated for many years by the involved industry, and state-of-the-art has been presented in a joined peer-reviewed publication (see Appendix). In Basketter *et al.* (2010), safe exposure levels for both workers and consumers are proposed based on long-term experience and available data. For workers, a derived minimal effect level (DMEL) of 60 ng/m³ for pure enzyme protein has been shown to be a successful occupational health limit for sensitization, while for consumers, DMELs up to 15 ng/m³ are proposed as highest tolerable level during short term exposure, depending on specific product uses and associated exposures.

5. Conclusion

For the reasons stated above, respiratory sensitisers unlike CMR's do not fulfill all criteria as described in ECHA's document¹ in which ECHA presents its approach regarding the assessment of substances with sensitising properties considering the equivalent level of concern criteria as laid down in Art 57(f) of REACH.

Cefic believes that

- Respiratory sensitisers do not present equivalent level of concern compared to CMR's as laid down in the table annexed.
- The risk of respiratory sensitisation can be adequately controlled. Safety guidance by several industry associations is available, and effectiveness thereof has been documented.
- Managing respiratory sensitisers in the same manner as CMRs fails to take into account the clinical evidence that, for sensitised individuals, early avoidance of exposure to a sensitising substance is effective in reversal of any existing disease symptoms and the prevention of new disease. In contrast to CMR substances (as defined under REACH), in the majority of cases, measures taken to avoid further exposure will result in halting of disease progression, achievement of normal quality of life and in many cases complete recovery.
- Once the potential risk to health is managed effectively, considerations such as severity of health effects, quality of life and societal impact will no longer be relevant.

¹ ECHA document CA/60/2012 presented at Caracal in November 2013.

Table 1: Industry position concerning level of concern comparison between CMR substances and sensitisers

	C & M	R (developmental)	Resp. Sens.	Skin Sens.
Possible serious health effects?	YES <ul style="list-style-type: none"> Serious & permanent organ dysfunction Inheritable defects Could lead to death 	YES <ul style="list-style-type: none"> Serious & permanent organ dysfunction Malformations or death in (unborn) children 	NORMALLY NO <ul style="list-style-type: none"> Serious & permanent organ dysfunction only in cases of long term repeated overexposure despite symptoms 	NORMALLY NO <ul style="list-style-type: none"> Organ dysfunction is reversible
Irreversibility of health effects?	YES <ul style="list-style-type: none"> Irreversible effects 	YES <ul style="list-style-type: none"> Irreversible effects 	NORMALLY NO <ul style="list-style-type: none"> Cessation of exposure before manifestation of asthma prevents irreversible effects 	NORMALLY NO <ul style="list-style-type: none"> The effects on skin (elicitation phase) generally reversible
Delay of health effects after cessation of exposure?	YES <ul style="list-style-type: none"> Long delay until effects manifest 	YES <ul style="list-style-type: none"> Medium delay until effects manifest 	NO <ul style="list-style-type: none"> No health effects in sensitised individuals (non-asthmatic) when no exposure 	NO <ul style="list-style-type: none"> No health effects in sensitised individuals when no exposure
Quality of life impaired?	YES <ul style="list-style-type: none"> Long term illness limiting possibility of living a normal working and private life Possible mental/ psychological impacts 	YES <ul style="list-style-type: none"> Children with developmental effects may need life-long medication/ support in their daily life 	NORMALLY NO <ul style="list-style-type: none"> Long term illness only in cases of long term repeated overexposure despite symptoms Re-training of affected staff 	NORMALLY NO <ul style="list-style-type: none"> Re-training of allergic staff
Societal concern?	YES – <ul style="list-style-type: none"> Widespread concern about cancer Cost implications for society in terms of healthcare 	YES <ul style="list-style-type: none"> Widespread concern about adverse effects in children Cost implications for society in terms of healthcare Disability 	YES <ul style="list-style-type: none"> Cost implications for society in terms of healthcare and retraining but very limited compared to societal concern related to CMR. 	YES <ul style="list-style-type: none"> Cost implications for society in terms of healthcare and retraining but very limited compared societal concern related to CMR.
Is derivation of a 'safe concentration' possible?	NORMALLY YES <ul style="list-style-type: none"> Non-genotoxic Mode of Actions allows definition of threshold DNEL Genotoxic mode of action allows definition of DMEL 	YES <ul style="list-style-type: none"> Possible to determine a safe concentration 	YES <ul style="list-style-type: none"> If available, data from animal models and human experience allow the derivation of safe concentration. 	YES <ul style="list-style-type: none"> Derivation of safe concentration is routinely possible

Appendix: *List of references and safety guidance examples*

List of documents sorted by topic, supporting statements made in the core text.

1. General article on sensitisers and SVHC criteria

- Basketter D and Kimber I, **2014**; Consideration of criteria required for assignment of a (skin) sensitiser a substance of very high concern (SVHC) under the REACH regulation. Regul Toxicol Pharmacol.; 69(3):524-8

2. Case study - subtilisin

- Kimber I and Basketter D, **2014**; Categorization of protein respiratory allergens: The case of Subtilisin. Regulatory Toxicology and Pharmacology, Volume 68, Issue 3, Pages 488–492

3. Threshold for the induction/elicitation

- Scientific articles
 - Basketter DA, Broekhuizen C, Fieldsend M, Kirkwood S, Mascarenhas R, Maurer K, Pedersen C, Rodriguez C, Schiff HE, **2010**; Defining occupational and consumer exposure limits for enzyme protein respiratory allergens under REACH. Toxicology. 268:165-170.
 - Cochrane SA, Arts JHE, Ehnes C, Hindle S, Hollnagel HM, Poole A, Suto H, Kimber I, **2015**; ECETOC Report - Thresholds in Chemical Respiratory Sensitisation. Toxicology, Vol 333, 179-194
 - Pauluhn J, **2014**; Development of a respiratory sensitization/elicitation protocol of TDI in Brown Norway rats to derive an elicitation-based occupational level. Toxicology 319: 10-22

4. Reversibility

- Labrecque, Malo, et al. **2010**. Good clinical references. Occup Environ Med. Medical surveillance programme for diisocyanate exposure.
- Tarlo et al. **2008**. Chest. Diagnosis and Management of Work-Related Asthma: American College of Chest Physicians Consensus Statement

5. RMM

- Basketter D, Berg N, Broekhuizen C, Fieldsend M, Kirkwood S, Kluin C, Mathieu S, Rodriguez C, **2012**; Enzymes in Cleaning Products: An Overview of Toxicological Properties and Risk Assessment/Management. Reg. Toxicol. Pharmacol, 64/1: 117-123

- Basketter DA, Kruszewski FH, Mathieu S, Kirchner DB, Panepinto A, Fieldsend M, Siegert V, Barnes F, Bookstaff R, Simonsen M, Concoby B, **2015**; Managing the Risk of Occupational Allergy in the Enzyme Detergent Industry., *J Occup Environ Hyg.* 12: 431–437
- Basketter D, Berg N, Kruszewski F, Sarlo K, Concoby B, **2012**; Relevance of Sensitization to Occupational Allergy and Asthma in the Detergent Industry. *J. Immunotox.* 9(3): 314-9
- Sarlo K, Kirchner DB, Troyano E, Smith LA, Carr GJ, Rodriguez C, **2010**; Assessing the risk of type 1 allergy to enzymes present in laundry and cleaning products: Evidence from the clinical data. *Toxicology.* 271:87-93
- Basketter D, Berg N, Kruszewski F, Sarlo K, Concoby B, **2012**; The Toxicology and Immunology of Detergent Enzymes. *J. Immunotox* 9(3): 320-6
- Pepys J, Wells ID, D'Souza MF, Greenberg M, **1973**; Clinical and immunological responses to enzymes on *Bacillus subtilis* in factory workers and consumers. *Clinical Allergy* 3:143-160
- Sarlo K, Clark ED, Ryan CA, Bernstein DI, **1990**; ELISA for human IgE antibody to Subtilisin A (Alcalase): correlations with RAST and skin test results with occupationally exposed individuals. *J. Allergy Clin. Immunol.* 86(3):393-399
- Sarlo K, Fletcher ER, Gaines WG, Ritz HL, **1997**; Respiratory Allergenicity of Detergent Enzymes in the Guinea Pig Intratracheal Test: Association with Sensitization of Occupationally Exposed Individuals. *Fundamental & Applied Toxicology*, 39(1):44-52
- Basketter DA, English JSC, Wakelin SH, White IR, **2008**; Enzymes, detergents and skin: facts and fantasies. *Br. J. Dermatol.* 158, 1177-1181
- Kimber I, Basketter DA, **2014**; Categorisation of protein respiratory allergens: the case of Subtilisin. *Reg. Toxicol. Pharmacol.* 68, 488-492.
- Basketter DA, Kimber I, **2011**; Assessing the potency of respiratory allergens: Uncertainties and challenges. *Regul. Toxicol. Pharmacol.*, 61, 365-372.
- Larsen AI, Johnsen CR, Frickman J, Mikkelsen S, **2007**; Incidence of respiratory sensitisation and allergy to enzymes among employees in an enzyme producing plant and the relation to exposure and host factors. *Occup Environ Med* 64; 763-768.
- Sarlo K and Kirchner DB, **2002**; Occupational asthma and allergy in the detergent industry: new developmets. *Curr Opin Allergy Clin Immunol* 2; 97-101.

- Stocks SJ, McNamee R, van der Molen HF, et al. **2015**; Trends in incidence of occupational asthma, contact dermatitis, noise-induced hearing loss, carpal tunnel syndrome and upper limb musculoskeletal disorders in European countries from 2000 to 2012 *Occup Environ Med*;72: 294–303.
- Diagnosis, management and prevention of occupational asthma, Royal college of physicians **2012**, *Clinical Medicine*, VI 12 No 2 156-159
- Tarlo SM, Banks D, Liss G, Broder I. **1997**; Outcome determinants for isocyanate induced occupational asthma among compensation claimants. *Occup Environ Med.*; 54(10):756-61.
- Lozewicz S, Assoufi BK, Hawkins R, Taylor AJ **1987**; Outcome of asthma induced by isocyanates. *Br J Dis Chest.* ;81(1):14-22.
- Gannon PF, Weir DC, Robertson AS, Burge PS **1993**; Health, employment, and financial outcomes in workers with occupational asthma. *Br J Ind Med.*;50(6):491-6.

6. Safety guidance - examples

- Worker safety
 - European Agency for Safety and Health at Work (EU-OSHA):
<https://osha.europa.eu/en/publications/factsheets/39>
- Association websites
 - Amfep, **2013**. Association of Manufacturers of Fermentation Enzyme Products. October 2013; “Guide to the safe handling of industrial enzyme preparations”. 12 pages. Brussels
<http://www.amfep.org/content/safe-handling-guide-2013>
 - Amfep, **2006**. Association of Manufacturers of Fermentation Enzyme Products; “Amfep and ETA position on consumer risk assessments for enzyme-containing personal care products and cosmetics”. Brussels
<http://www.amfep.org/content/personal-care-products>
 - AISE, **2013**. The international Association for Soaps, Detergents and Maintenance Products.; “Guiding principles for the safe handling of enzymes in detergent manufacture”. 122 pages. Brussels
<http://www.aise.eu/cust/documentrequest.aspx?DocID=290>

- AISE, **2013**. The international Association for Soaps, Detergents and Maintenance Products; “Exposure measurements of enzymes for risk assessment of household cleaning spray products”. Brussels
www.aise.eu/cust/documentrequest.aspx?DocID=1923
- AISE, **2006**. The international Association for Soaps, Detergents and Maintenance Products; “Developing consumer products containing enzymes: Ensuring consumer safety”. Brussels
<http://www.aise.eu/cust/documentrequest.aspx?DocID=2785>
- US SDA, **2005**. The Soap and Detergent Association (SDA). *Risk Assessment Guidance for Enzyme-containing Products*. US Soap and Detergent Association, Washington, DC. 58 pages. http://www.cleaninginstitute.org/science/enzyme_safety.aspx
- US SDA, **1995**. The Soap and Detergent Association (SDA). “*Work practices for handling enzymes in the detergent industry*”. New York: The Soap and Detergent Association. 55 pages. http://www.cleaninginstitute.org/science/enzyme_safety.aspx
- SDIA **1991**. The Soap and Detergent Industry Association “*The Standing Committee on Enzymatic Washing Products, Revised Operating Guidelines, Fifth Report*”. London. First edition published in 1969
- SDIA **1971**. The Soap and Detergent Industry Association “*Recommended Operating Procedures for UK Factories Handling Enzyme Materials*”. London. The Annals of Occupational Hygiene, Vol 14 Issue: 2 p71-83.
- MS guidance
 - UK Health and Safety Executive (HSE) ASTHMA Website
<http://www.hse.gov.uk/asthma/index.htm>
 - <http://www.hse.gov.uk/asthma/furtherreading.htm>
- Health Canada
 - <http://www.hc-sc.gc.ca/ewh-semt/occup-travail/whmis-simdut/sensitizers-sensibilisants-eng.php>

For more information please contact:
Amaya János, REACH Manager, Cefic,
+32 2.792.75.12 or aja@cefic.be.

About Cefic

Cefic, the European Chemical Industry Council, founded in 1972, is the voice of 29,000 large, medium and small chemical companies in Europe, which provide 1.2 million jobs and account for 17% of world chemicals production.