

Cefic views on skin sensitisation

Cefic is committed to ensuring that health of workers and the safety of products are top priorities for the chemical industry. This paper focuses on the management of substances with dermal 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 skin sensitisers present the same health risks as defined under REACH for carcinogens, mutagens, and reproductive toxicants (CMRs) as trigger for SVHC. Cefic believes the listing of skin sensitisers as SVHCs to be unnecessary in controlling their risks for the reasons outlined below. This position paper includes key messages followed by a detailed discussion of specific aspects of skin sensitisation.

Key messages

- The severity of pathologies associated with skin sensitisers is not comparable to CMRs. Their health impacts are far less serious than those caused by CMRs. Their health effects are reversible and can be avoided.
- The existing regulatory process through CLP and REACH enables the identification of skin sensitising substances, thereby permitting implementation of intervention measures (such as via targeted communication channels and adapted risk mitigation measures) at an early stage to mitigate risks from exposure.
- Thresholds for skin sensitisers can generally be set, meaning that most individuals will not be sensitised below these levels. The introduction of appropriate risk mitigation measures can therefore prevent induction and, consequently, the onset of symptoms.
- A thorough Risk Management Option analysis (RMOa) determines the best regulatory route to control chemicals, provided it takes into account their hazard identification and characterisation, exposure and socioeconomic data. This process should always be performed by and involve contribution from stakeholders, including industry. Different control routes to ensure safe use should be considered, including compliance with existing Community occupational health and safety legislation, before taking any further regulatory action.
- Due to market perception, the listing of sensitisers on the Candidate List will bring unjustified further stigmatisation and potentially the loss of beneficial substances for consumers and society.

Cefic opinion

In the case of skin sensitisers, measures taken to avoid further exposure will normally result in halting the disease, disappearance of symptoms and consequently increase the quality of life. Avoidance of exposure to a sensitising substance is the primary strategy for the potential reversal of any existing disease symptoms and the prevention of new disease.

Whilst SVHC listing is a possible route for controlling the safe management of hazardous chemicals, Cefic believes the application of SVHC status to skin sensitising substances would represent an inappropriate use of the “SVHC label” and a misrepresentation of the original intent of the REACH Regulation. When considering the provision of Article 57(f), skin sensitisers as a general rule should not be treated in the same manner as Category 1A and 1B CMRs, as they 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.

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

1. The severity of pathologies associated with skin 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 with these endpoints represent serious, irreversible and life-threatening impacts on human health and/or serious long-term environmental impacts. Skin sensitisers, by contrast, differ in the severity of response in that this varies from individual to individual. Usually the potential clinical manifestations after sensitisation are transient and often comparatively minor, yet we also recognise that in rare cases this can be ongoing and severe. These responses are generally local and appear in the form of eczematous lesions. They are caused by direct or indirect contact with an allergen that may induce a skin reaction related to the concentration and exposure level. Many (not all) natural or man-made substances may induce allergic reactions upon contact with the skin. This is the case for plants (e.g. primroses), metals present in leather or in buckles of clothing items or chemical substances in paints or gloves.

In most cases, the symptoms of this allergic dermatitis include erythema, oedema, dry skin and itching. These undesirable effects are, other than in rare cases, temporary and disappear once contact ceases. Serious effects on health in the context of Article 57(f) would include effects likely to cause death in the short, medium or long term or effects that are irreversible and cause disabilities or incapacity. Serious effects for reprotoxic substances may cover teratogenic effects (effects on the descendants of parents exposed to teratogenic agents –i.e. able to disturb the growth and development of an embryo or foetus).

Consequently when considering Article 57(f), skin sensitisers as a ‘class’ should not be considered to pose serious effects to human health or the environment in the same manner as CMRs and PBT/vPvB substances.

2. Contrary to CMRs, symptoms are reversible and elicitation can be avoided

As with all areas of toxicology and chemical hazard evaluation, the exposure to and the potency of the substance – *for example, in relation to acute toxicity potential, chronic hepatotoxicity, sensitisation potential, etc* – will determine the true risk and level of concern. Regulatory systems to address such cases are already in place as well as companies’ own risk management measures.

The risk of triggering allergic contact dermatitis symptoms can be managed by 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 (*see Appendix for example*).

There will be variability in the response:

- Initially whether an individual can be sensitised by a sensitiser and
- Secondly the degree of expression of that response into minor or major.

Whilst sensitisation (getting contact allergy) is irreversible, the health effects from sensitisation, unlike CMRs, are reversible.

Allergic contact dermatitis will only arise as a result of two phases:

1. The first is an induction phase during which individuals develop a contact allergy. This phase is in general irreversible (even so in a few cases complete disappearance of the contact allergy over time has been reported), but it causes no clinical effects.

2. In the second phase, called 'elicitation', the clinical signs of allergic contact dermatitis appear, but the allergic response is generally reversible – symptoms disappear when the skin is no longer exposed to the sensitiser above the individual “own” elicitation threshold level.

It is important to clearly differentiate between the first and second phases as the clinical disease state is only triggered during the second phase of elicitation. The effects of skin sensitisers are therefore reversible when exposure ceases.

3. It is possible to identify potential skin sensitisers early in the regulation process, so measures can be introduced quickly to mitigate the risks.

Once a substance is classified as a sensitiser under CLP, the communication and implementation of risk management measures down the supply chain are ensured. Moreover, data on skin sensitisation is required in a very early stage of the hazard assessment under REACH (Annex VII). This means that users are informed of the risks and (individual or collective) protective measures can be introduced immediately. For most skin sensitisers, the risk of exposure can be controlled by existing measures so that they can be used safely. Communication through Safety Data Sheets, Labelling and Safe Use Guidance information with respect to 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 example)*.

4. Risks can be quantified

Mutagens and some carcinogens (direct genotoxic agents) give additional cause for concern as there is no general consensus on how to establish no-observed-effect levels (NOEL) for these substances. It is however generally possible to determine thresholds for skin sensitisers – that is, exposure levels under which induction is unlikely. Appropriate risk mitigation measures can therefore be introduced to prevent induction and thereby in consequence the onset of symptoms. Toxicology tests conducted using the latest technology (e.g. mechanism using QSAR modelling) can determine the relative potency, and the risk of induction can be adequately managed even through a quantitative risk assessment (QRA) methodology. *(see Appendix for methodology and application)*.

The information submitted in the substance's REACH registration can also be used to show that sensitisation risks are carefully managed for the listed uses. Toxicology tests conducted using older models are sensitive and study direct sensitisation response but cannot determine no-observed-effect levels. In this case risks are assessed from a qualitative perspective. As a result, appropriate preventive measures and handling conditions are systematically applied. These include simple measures such as the wearing of appropriate gloves and protective clothing to avoid skin contact (see Appendix for example).

Further remarks on ECHA document presented at Caracal in November 2013 (CA/60/2012)

In addition to the above, Cefic believes the following points on the CARACAL paper are pertinent:

- Skin sensitisers do not fulfill all criteria as described in the ECHA's document, so they should not be identified as SVHC.
 - Overall, the consideration of skin sensitisers as being of equivalent level of concern to CMRs runs counter to the current scientific understanding in that evidence shows thresholds exist for both their induction and safe use; this has been demonstrated in animal models and/or humans based on epidemiological data. (*see Appendix – Reversibility and Threshold*).
 - The risk of induction of skin sensitisation can be adequately managed even through a Quantitative Risk Assessment (QRA) methodology e.g. for fragrances. QRAs are the cornerstone of health-based exposure limits and are used extensively by both authorities and industry. (*The principles and practical applications of this methodology for fragrance ingredients have been published – see Appendix*).
 - The allergic contact dermatitis caused by a specific substance or group of substances that are chemically similar is generally observed in a minority of people and can therefore be easily managed by preventing further exposure. The rest of the population is not affected and threshold concentrations can be calculated, so as to make sure that those people will not become affected. Once the potential risk to health is managed effectively, as it can be for most cases, considerations such as severity of health effects, quality of life and societal impact will not be relevant anymore.
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Table 1: Comparative level of concern in relation to CMR (Carcinogenicity, Mutagenicity, Reproductive Toxicity)

This table aims to summarise views explained in the position paper.

It is not a stand-alone table; it should be read together with the explanation provided in the position paper.

Issue	Sub issues	C – M – R	Skin sensitisation
Exposure	Route	Dermal, oral, inhalation	Only dermal
	Origin	Naturally and synthesised chemicals	Naturally and synthesised chemicals
Consequences following the cease of exposure	On disease progression	Disease can't be stopped Unless heavy medical treatment Cause of death	Halts disease
	On quality of life	No effect	Increase
	Prevention of new disease	Avoid exposure	Stop exposure even after first symptom
	Reversibility	Irreversible	Reversibility of existing symptom
Severity of the pathology	Cause	By direct and indirect contact with chemical	By direct and indirect contact with allergen inducing skin reaction
	Seriousness -Variability of the response -Degree of expression of the response	Very severe pathology – severe effects - teratogenic effects – Major effects which impact everybody, every time. Cause disability or incapacity or death.	Severity of response varies from individual to individual but not serious effects on human health or environment in the same manner as CMRs/PBT/vPvB. -Clinical manifestation can be severe or minor. -Induce allergic response (eczematous lesions, etc.) only to sensitive subjects.
	Reversibility	Induction and effects are irreversible.	Induction is irreversible but effects (allergic illness) are reversible once exposure ceases.
	Life impact – time of disease	One step process, not reversible once symptom appeared. Heavy pathology. Disease potentially present for ever (unless lucky outcome of heavy treatment-rare).	2 steps process: -induction phase to develop an allergy, no clinical effects present. -appearance of clinical signs = allergic dermatitis (erythema, oedema, dry skin, itching) triggering the allergy.

		Cause death in short/medium/long term.	Temporary disease – disappears once exposure ceases (except very rare cases). Does not cause death.
Risks	Detection - studies	Lack of carcinogenicity studies as source of information. Studies available very late (higher tier studies).	Studies available – in REACH registration dossier (Annex VII requirements). Users informed at early stage on risks. Protective measures introduced as soon as smallest signs detected. Symptoms disappear as soon as exposure ceases (reversibility of the effects observed).
	Quantification	Difficulty to establish NOEL.	Threshold effect meaning determination of exposure level under which induction is unlikely. Meaning measures can be introduced to prevent the onset of the symptoms. Via new technologies, relative potency can be determined and risk of induction can be adequately managed (via QRA methodology) ⇒ Quantitative approach to risk assessment. Via old models, NOEL not determined. ⇒ Qualitative approach to risk assessment.
	Management	Managed by existing regulatory system.	Potency – managed by existing regulatory system and risk mitigation measures. Safe use of sensitisers possible via control of the risk of exposure. REACH dossier mentioning RMM for listed uses. Appropriate handling conditions proposed and applied (PPE, etc.) by industry to protect people and minimise exposure.
Prevention	Communication		Sensitisers early identified (CLP, REACH dossier) – measures

			rapidly introduced, communicated (SDS, label, safe use guidance, etc..) and implemented by industry to minimise exposure, protect human health and prevent the disease.
	Latency period (before effects appear)	Order of magnitude – years, decades Difficulty in introducing mitigation measures on time. Risk identified at a later stage.	Order of magnitude: weeks, months. Early detection of first symptoms. Quick reaction to avoid further exposure.
SVHC identification	Benefit on communication through the supply chain	Increase communication and look at alternatives	DU already informed via labelling (CLP) and company guidance. Phase out not necessary in each case.
	Consequences for industry	Overlapping with other RMO (CMD, CAD, restriction,..)	Direct stigmatisation of supply chain without considering case by case assessment or reversibility of the effect. Reduce marketability due to negative perception.
	RMOa – ensuring coordination between existing legislations.	CMD – REACH	REACH – OSH Compliance with community legislations.

Appendix – List of references

List of document 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) sensitizer a substance of very high concern (SVHC) under the REACH regulation. *Regul Toxicol Pharmacol.*; 69(3):524-8

2. Reversibility

- Clinical evidences
 - Jensen, C.D., Andersen, K.E., **2005**. Course of contact allergy in consecutive eczema patient's patch tested with TRUE test panels 1 and 2 at least twice over a 12-year period. *Contact Dermatitis* 52, 242–246
- Scientific articles
 - Lidholm A.G., Bergfors E., Inerot A., Blomgren U., Gillstedt M., Trollfors B., **2013**; Unexpected loss of contact allergy to aluminium induced by vaccine. *Contact Dermatitis* 68, 286-292
 - Valsecchi R., Rossi A., Bigardi A., Pigatto P.D., **1991**. The loss of contact sensitisation in man. *Contact Dermatitis* 24, 183–186

3. Threshold for the induction/elicitation

- Scientific articles
 - Api A.M., Basketter D., Cadby P.A., Cano M.-F., Ellis G., Gerberick F.G., Griem P., McNamee P.M., Ryan C.A., Safford R., **2008**. Dermal sensitisation Quantitative Risk Assessment (QRA) for fragrance ingredients. *Regulatory Toxicology and Pharmacology*, 52, 3-23
 - Arts J.H.E., Mommers C. and de Heer C.; **2006**; Dose-response relationships and threshold levels in skin- and respiratory allergy. *Crit. Rev. Toxicol.* 36, 219-251
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 - Boukhanan & Maibach, **2001**; Thresholds in contact sensitization: Immunologic mechanisms and experimental evidence in humans – an overview. *Food Chemical Toxicology* 39, 1125-1143
 - Cochrane S.A, Arts J.H.E, Ehnes C, Hindle S, Hollnagel H.M, Poole A, Suto H and Kimber I.; **2015** - *ECETOC Report* - Thresholds in Chemical Respiratory Sensitisation. *Toxicology*, Vol 333, 179-194
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 - Kimber I. Basketter D., Berthold K., Butler M., Garrigue JL., Lea L., Newsome C., Roggebadn R., Steiling W., Stropp G., Waterman S., Wiemann C., **2001**; Skin sensitization testing in potency and risk assessment. *Toxicol. Sci* 59, 198 – 208
 - Lalko J. and Api AM., **2008**; Citral: Identifying a threshold for induction of dermal sensitization. *Regulatory Toxicology and Pharmacology* 52, 62-73

4. RMM

- Evidence on drastic reduction of effects on health while kept away from source
 - Antonov D., Schliemann S. and Elsner P., **2011**; Therapy and Rehabilitation of Allergic and Irritant Contact Dermatitis. In: "Contact Dermatitis", 5th edition, Eds Johansen JD, Frosch PF and Lepoittein J-P, Springer-Verlag, Heidelberg, pp 963-983

5. Safety guidance - examples

- Worker safety
 - European Agency for Safety and Health at Work (EU-OSHA): <https://osha.europa.eu/en/publications/factsheets/39>
- Association website (AISE, Building association, Enzyme trade associations, ISOPA, ...)
 - ISOPA – "Walk the Talk" document: <http://isopa.org/product-stewardship/walk-the-talk/>
 - ALIPA "Safeguard - We care that you care!" <http://www.alipa.org/index.php?page=alipa-safeguard---we-care-that-you-care>
 - 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. February 2006; "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. September 2013; "Guiding principles for the safe handling of enzymes in detergent manufacture". 122 pages. Brussels <http://www.aise.eu/cust/documentrequest.aspx?DocID=290>
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- 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>

6. Test guidelines

- OECD skin sensitisation test guidelines:
 - http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

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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.