Identification of substances as SVHCs due to equivalent level of concern to CMRs (Article 57(f)) – sensitisers as an example

In Article 57 of the REACH Regulation, criteria are laid down to identify substances of very high concern (SVHCs):

- CMR cat 1A and 1B (article 57 a-c, criteria defined in the CLP Regulation),
- PBT/vPvB substances (article 57(d-e), criteria defined in Annex XIII of REACH) and
- Substances of equivalent level of concern to CMR or PBT (article 57(f)).

Several MSCAs and the Commission / ECHA have been considering the possibilities for and need to identify substances with sensitising properties as SVHC under the 'equivalent level of concern' route set out in Article 57(f) of REACH. To support this work ECHA has prepared the annexed discussion paper elaborating factors, which can be used when assessing whether substances with sensitising properties could be identified as substances of very high concern (SVHCs), under the 'equivalent level of concern' route set out in Article 57(f) of REACH.

The draft document has been discussed in:

- 1st Risk Management Expert meeting (RiME-1/2012, 24 Feb 2012)
- 2nd RiME meeting (RiME-2/2012, 1 Jun 2012)
- Ad hoc meeting of Competent Authorities for REACH (28 Jun 2012)
- 25th meeting of the Member State Committee (20 Sep 2012)
- 11th CARACAL meeting (Nov 2012)

After each of the above meetings, COM and MSCAs and MSC-members (including stakeholders) were invited to provide written comments on the document. These comments were subsequently taking into account in the annexed document.

A similar approach, amended as necessary, can be used when assessing whether substances with other properties could be identified as SVHCs based on Article 57(f).

Annex I Potential of sensitisers to be identified as SVHCs under the 'equivalent level of concern' route (Article 57(f)) – Factors for case-by-case assessment

ANNEX I

Potential of sensitisers to be identified as SVHCs under the 'equivalent level of concern' route (Article 57(f))
–
Factors for case-by-case assessment

1. Introduction

This paper considers factors, which might be pertinent for assessing whether substances with sensitising properties could be identified as substances of very high concern (SVHCs), under the 'equivalent level of concern' route set out in Article 57(f) of REACH. A similar approach, amended as necessary, can be used when assessing whether substances with other properties relevant for human health could be identified as SVHCs based on Article 57(f).

The assessment is based on the consideration that in certain cases it can be demonstrated that the impacts caused by substances with sensitising properties, on the health of the affected individuals and on the society as a whole, are comparable to those elicited by carcinogens, mutagens and/or reproductive toxicants (CMRs). In such cases it might be justified to conclude, on a case by case basis, that such a sensitiser is of equivalent level of concern in accordance with REACH Article 57(f).

To support this, this document attempts to identify, characterise and compare the level of concern that exists for CMRs and respiratory and skin sensitisers.

This document provides generic considerations related to respiratory and skin sensitisers. It is noted that to identify a substance as SVHC based on Article 57(f) requires a case by case:

i. Assessment of the hazard properties of the substance and comparison of their potential impact on health and other factors and additional considerations with the impacts potentially elicited by carcinogenic, mutagenic or reprotoxic substances meeting the criteria of Article 57 (a-c)
ii. Evidence that the substance is of equivalent level of concern by concluding on the results of the comparison of hazard properties and potential impacts described under (i).

Therefore, classification of a substance as a sensitiser in itself is not enough in order to identify it as a SVHC under article 57(f). The substance must also be of 'equivalent level of concern'. It is recommended that any SVHC identification of sensitisers under article 57(f) should only be undertaken for substances already classified as sensitisers however. In this case any hazard assessment as to whether the substance indeed is a respiratory and/or skin sensitiser and to which CLP category it may belong is not necessary anymore. It will suffice to compare the potential impacts arising from the sensitising properties of the substance with those elicited by CMR substances.

For potential new sensitisers, the assessment of the hazardous properties needs to be based on classification and labelling rules. For respiratory sensitisers harmonised classification and labelling in Annex VI should be foreseen before work on possible identification as SVHC is initiated. This is the same approach as applied for CMR substances.

2. 'Level of Concern' comparison

In order to compare the level of concern that exists between CMR and sensitising substances, the potential adverse effects of carcinogens, mutagens, developmental reproductive toxicants[1], respiratory sensitiser and skin sensitisers will be compared under the following headings:

- Health effects (**Section 2.1**)
  - Type of possible health effects
  - Irreversibility of health effects
  - Delay of health effects
- Other factors (**Section 2.2**)
  - Quality of life affected
  - Societal concern
  - Is derivation of a 'safe concentration' possible?

In principle, the above comparison factors could be used to justify 'equivalent level of concern' for any substance, if required.

There are some further additional considerations included in **Section 3**. These considerations are specific to sensitisers and may be pertinent to this 'equivalent level of concern' comparison.

We consider it necessary to consider these 'level of concern' factors together in one package for each endpoint, rather than making comparisons one factor at a time. This comparison exercise is summarised in **Table 1** below and a full description is presented in **Section 2** and **3**. The **Appendix** provides some reference information on the topic of sensitisation.

[1] For reproductive toxicants, adverse effects on development of the offspring have been taken as an example of the hazard categories for reproductive toxicants in this paper. The hazard categories for reproductive toxicants include the adverse effects on sexual function and fertility, and adverse effects on development of the offspring. Considerations related to developmental toxicity are considered to generally cover also the concerns regarding to sexual function and fertility the main exception being potential fatal outcome of developmental toxicity.

Table 1 – 'Level of Concern' comparison between CMRs and sensitisers [Health effects] [Other factors]

	C & M	R (developmental)	Resp. Sens.	Skin Sens.
Possible serious health effects?	**YES -** ▪ Serious & permanent organ dysfunction ▪ Inheritable defects ▪ Could lead to death	**YES -** ▪ Serious & permanent organ dysfunction ▪ Malformations or death in (unborn) children	**YES -** ▪ Serious & permanent organ dysfunction ▪ Permanent impairment of lung functions ▪ Could lead to death	**POSSIBLY YES** – ▪ If response is severe **NORMALLY NO** – ▪ As organ dysfunction is reversible
Irreversibility of health effects?	**YES** ▪ Irreversible effects	**YES** ▪ Irreversible effects	**YES** ▪ Induction phase of sensitisation **YES** ▪ Elicitation phase of sensitisation - can lead to irreversible lung dysfunction	**NORMALLY NO –** ▪ Induction phase of sensitisation is irreversible however, ▪ The effects on skin (elicitation phase) generally reversible
Delay of health effects?	**YES** – ▪ Long delay until effects manifest	**YES** – ▪ Medium delay until effects manifest	**YES** – ▪ Long/medium delay between start of the induction phase and appearance of clinical symptoms	**YES** – ▪ Long/medium delay between start of the induction phase and appearance of clinical symptoms
Quality of life impaired?	**YES** – ▪ Long term illness limiting possibility of living a normal working and private life ▪ Possible mental/ psychological impacts	**YES** – ▪ Children with developmental effects may need life-long medication/ support in their daily life ▪ Life of parents also affected (emotional investment, care, financial costs)	**YES** – ▪ Long term illness limiting the possibility of living a normal working and private life ▪ Require long-term medication ▪ Re-training of affected staff	**POSSIBLY YES** – ▪ Possibility of long term illness limiting the possibility of living a normal working and private life ▪ Re-training of allergic staff ▪ Possible mental/ psychological impacts
Societal concern?	**YES** – ▪ Widespread concern about cancer ▪ Cost implications for society in terms of healthcare	**YES** – ▪ Widespread concern about adverse effects in children ▪ Cost implications for society in terms of healthcare ▪ Disability	**YES** – ▪ Cost implications for society in terms of healthcare and retraining ▪ Associated with disability	**YES** – ▪ Cost implications for society in terms of healthcare and retraining
Is derivation of a 'safe concentration' possible?	**NORMALLY NO** - ▪ 'Zero risk' only possible where no exposure	**NORMALLY YES** - ▪ Possible to determine a safe concentration	**NO –** ▪ Difficult to establish the threshold dose for induction and elicitation ▪ Derivation of safe concentration is not routinely possible	**NO –** ▪ Difficult to establish the threshold dose for induction and elicitation ▪ Derivation of safe concentration is not routinely possible

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2.1 Health Effects

2.1.1 Type of possible health effects

The chemical properties of certain substances can possibly lead to adverse health effects, in a proportion of individuals who have been exposed to these substances. The extent of these adverse health effects can range from mild to serious[2], depending on e.g. the properties of the chemical, the extent of the exposure (concentration and duration) and a number of other factors.

- In the case of carcinogens and mutagens, exposure to these substances has the potential to cause serious adverse health effects in a proportion of the population i.e. serious and permanent organ dysfunction, inheritable defects and/or death.

- In the case of reproductive toxicants (development), exposure has the potential to cause serious adverse health effects in a proportion of the population i.e. serious and permanent organ dysfunction, defects and/or death.

- In the case of respiratory sensitisers, the effects can initially result in mild damage however progression towards occupational respiratory illness can very often lead to severe damage, which can include permanent impairment of lung function (see **Note 1**). Such permanent damage to lung function can occur before the problem can even be appreciated. In addition, exposure to the allergen can cause severe asthma attacks, which can lead to death in serious cases.

- In the case of skin sensitisers, the adverse health effects can range from being mild to severe, with severe effects being less common (see **Note 2**). Severe allergic skin reactions (e.g. large lesions on the skin, leaving permanent scars and/or discoloration of the skin) can be considered serious effects due to the fact that they cause significant local skin dysfunctions and significant impairment of the person concerned depending on the location of the skin reactions. Severe reactions could lead to skin damage so severe that the affected person could experience a psychological impact, which could be considered as a serious health effect. Occasionally skin sensitising agents can have a lethal effect, but this type of severity of effect is rare.

[2] In the context of the '*Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC'* the term 'serious' means a hazard that could result in death, could be life-threatening, could result in patient hospitalisation or prolongation of existing hospitalisation, could result in persistent or significant disability or incapacity, or could be a congenital anomaly/birth defect or permanent or prolonged signs in exposed humans.

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Note 1 on immunological[3] respiratory effects:

Mild damage In this period improvement of the symptoms (e.g. asthmatic symptoms) occur when away from work, i.e. the symptoms are still reversible. Latency period can be several months. When removed from exposure at this point, full recovery may be possible.

Severe damage e.g. the removal from exposure does not improve the symptoms (e.g. asthmatic symptoms) within a significant period of recovery after the stopping of exposure. Long-term medication may be needed, a permanent impairment of the lung-function may occur.

Note 2 on skin effects:

Sensitisers may cause a range of effects on skin, depending inter alia on potency and other characteristics of the agent, the number of previous exposures to the agent (and development of the immune response), and the responsiveness of the individual. Skin damage may range from mild to severe.

Mild damage e.g. a rash that can heal quickly, when exposure to the sensitising agent is stopped.

Severe damage e.g. blistering that can burst. Skin function (integrity) is impaired, possibly leading to infection. Ongoing exposure can lead to chronic inflammation and scar formation. Minimal or a single small focus of scarring does not normally constitute "severe organ damage or major permanent functional change" in the skin as an organ.

2.1.2 Irreversibility of health effects

An irreversible health effect is a permanent change in the structure and/or function of an organ system or a permanently increased risk of suffering from a disease or some other threat to health[4].

- In the case of carcinogens and mutagens, adverse health effects e.g. development of cancer may lead to death or irreversible ill health.

- In the case of reproductive toxicants (development), adverse health effect may present in the form of irreversible malformations in children.

- In the case of sensitisers when discussing irreversibility, a clear distinction must be made between the induction and elicitation phases of sensitisation. The induction phase in itself may be

[3] In general there are two types of mechanisms: 1) immunological i.e. respiratory sensitiser with latency period, response to same chemical (may also be cross-reactivity to similar chemicals) and only low concentrations needed to give symptoms; 2) non-immunological i.e. irritant asthma. No latency period necessary; single, high intensity exposure.

[4] P. H. Brodish. The Irreversible Health Effects of Cigarette Smoking, *The American Council on Science and Health* (1998).

considered an irreversible health effect however one could say that this is not an adverse effect per se. It is only when the sensitised individual shows signs e.g. asthma (respiratory) or contact dermatitis (skin) that the adverse effect (elicitation) is seen. On the other hand, one could argue that the irreversible sensitisation induction is in fact an adverse effect, as it leads to a disposition of the sensitised individuals.

- In the case of respiratory sensitisers, the induction phase of sensitisation is irreversible and the elicitation phase can lead to irreversible impairment of lung function in a proportion of individuals exposed to certain respiratory sensitisers. In very severe cases this could also lead to death.

- In the case of skin sensitisers, the induction phase of sensitisation is irreversible, however the organ dysfunction resulting from elicitation is generally seen to be reversible i.e. the allergic reaction by the skin disappears when exposure to the sensitising agent is eliminated. In some instances, skin sensitisers can induce irreversible lesions (e.g. large lesions on the skin, leaving permanent scars and/or discoloration of the skin). However it is unusual to see irreversible damage at an early stage.

2.1.3 Delay of health effects

Delay of effects does not necessarily affect the seriousness of the effect. However considering the delay of effects (i.e. the time between exposure and effect), is of interest from a risk management point of view, particularly for substances where the hazardous properties (e.g. carcinogens, mutagens, reproductive toxicants and sensitisers) are not already known. For the purposes of this point, 'long delay' can mean decades, 'medium delay' can mean years and months and 'short delay' can mean weeks and days.

It is noted that risk management does not play a role in identifying a substance as an SVHC, however in the context of the 'equivalent level of concern' debate it is felt that a significant delay between exposure and effect warrants a higher 'level of concern' being associated with the substance in question.

As is the case for any chemical hazard, risk management measures can be put in place to avoid/reduce exposure, as soon as a risk associated with that hazard has been identified. It is likely to be easier to show the connection between the exposure and the effect, where the delay between the exposure and effect is not long. If the delay is long: 1) a long period of time can go by without appropriate RMMs being in place or 2) it is difficult to put risk management measures in place that will mitigate the exact risk.

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Whether the avoidance/reduction of exposure resulting from RMMs comes early enough for the affected individual, depends on the seriousness and irreversibility of the effects. If the effect appears only after several years, the affected person (and potentially other persons) could have continued to be exposed throughout the intervening period, in the absence of the necessary risk management measures to mitigate the risk, leading to an accumulation of T-cells capable of recognising and responding to the chemicals (elicitation) i.e. allergic response (see **Appendix Section A.1** for further details).

- In the case of carcinogens and mutagens, there are usually long delays before adverse effects manifest themselves.

- In the case of reproductive toxicants (development) there can be some delay before adverse effects manifest themselves.

- In the case of both respiratory and skin sensitisers, there may be long/medium delays between the start of the induction phase and the appearance of clinical symptoms. It is possible for a potent sensitiser to induce allergy resulting from very few exposures.

In the case of CMRs and sensitisers, adverse health effects will only be observed after a long/medium period of time.

2.2 Other factors

2.2.1 Quality of life impaired

A person's quality of life can be compromised as a direct result of the adverse health effects brought on by exposure to hazardous chemicals such as CMRs and sensitisers. Again, serious impairment of a person's quality of life does not play a role in identifying a substance as an SVHC, however in the context of the 'equivalent level of concern' debate it is felt that such impairment warrants a higher 'level of concern' being associated with the substance in question.

- In the case of carcinogens and mutagens, possible side-effects such as organ dysfunction can result in the person having to live with a long term illness, limiting the possibility of living a normal working and private life. Regardless of the prognosis, the negative health effects caused by exposure to carcinogens and mutagens is generally considered to be a 'serious' consequence, as it always has the potential to be fatal.

- In the case of developmental toxicants, depending on the effect manifested, the long-term consequences for the infants/person may be very severe and impair the quality of life. Children having developmental effects may need life-long medication and/or support during their daily life. There is also an indirect effect on the quality of life of such children's parents in terms of emotional investment, care and financial resources needed.

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- In the case of respiratory sensitisers, permanent impairment of lung function can lead to a decreased quality of life and a requirement for long-term medication. Long term illness limiting the possibility of living a normal working and private life.

- In the case of both respiratory sensitisers and skin sensitisers, once a person is sensitised to an allergen in the workplace (e.g. hairdressers who become sensitised to hair dye ingredients), the person's exposure to that substance needs to be eliminated. In most cases, this means that the person cannot work in their chosen profession any more. Re-training may then be needed, which can lead to a significant impact on that person's quality of life.

- In the case of skin sensitisation, the allergic reaction by the skin tends to disappear when exposure to the sensitising agent is eliminated. Severe reactions (e.g. large lesions on the skin, leaving permanent scars and/or discoloration of the skin) could lead to skin damage so severe that the affected person could experience a psychological impact, which could negatively impact that person's quality of life. Occasionally skin sensitising agents can have a lethal effect, but this type of severity of effect is rare.

2.2.2 Societal concern

Nowadays, society is more aware of the possible detrimental effects certain hazardous chemicals can have on human health and the environment. This generates a certain level of concern in society when it comes to chemicals, especially in terms of where they end up and what type of effect they can have on a person's health. Again, societal concern does not play a role in identifying a substance as an SVHC, however in the context of the 'equivalent level of concern' debate it is felt that significant societal concern may warrant a higher 'level of concern' being associated with the substance in question.

- In the case of carcinogens and mutagens, there is widespread concern in society, due to the high prevalence of cancer in the worldwide population and the uncertainty surrounding future effects that may arise e.g. development of cancer and potential death. There can be a high cost of treating affected individuals in society.

- In the case of developmental toxicants, the potential adverse health effects on children e.g. severe malformations or restrained intellectual capabilities are of high concern for the society. There can also be a high cost of treating affected individuals in society.

- Health effects caused by respiratory sensitisers can lead to permanent disability, which can be viewed as a concern within society. There can also be a significant cost of treating affected

individuals in society, in addition to retraining and unemployment support.

- In the case of skin sensitisers, society is generally aware of the health effects caused by skin sensitisation, in particular allergic contact dermatitis. However the extent of this 'level of concern' in society may differ depending on whether the resulting skin damage is deemed mild (e.g. rash that heals quickly when exposure to the sensitising agent is stopped) or severe (e.g. large lesions on the skin, leaving permanent scars and/or discoloration of the skin e.g. in the face etc.). In general, skin sensitisation could lead to significant costs for society due to the fact that the world's population encounters very many skin sensitising agents in everyday life. The re-training of many people working in more vulnerable professions (e.g. hairdressers) and the cost of supporting unemployed sensitised individuals may also increase the overall cost for society.

2.2.3 Is derivation of a 'safe concentration' possible?

CMRs may be non-threshold (i.e. it is not possible to define a Derived No-Effect Level (DNEL)) or threshold (i.e. it is possible to define a DNEL). Where such hazards have threshold effects; no-effect 'safe' levels can be determined. These levels can then be compared to the predicted (e.g. worker) exposure level. For some hazard classes, especially germ cell mutagenicity and carcinogenicity, the available information may not enable a toxicological threshold to be established. While derivation of a safe concentration does not play a role in identifying a substance as an SVHC, in the context of the 'equivalent level of concern' debate it is felt that an inability to derive a safe concentration may warrant a higher 'level of concern' being associated with the substance in question.

- In the case of non-threshold carcinogens and mutagens, it is only possible to conclude 'zero risk' if there is no exposure. In certain cases, even very small doses of such substances can cause adverse effects, which may only manifest after several years of exposure. Consequently, derivation of a safe concentration is normally not possible. By contrast for non-genotoxic carcinogens it is normally possible to derive a threshold.

- In the case of developmental toxicants, it is normally possible to determine a toxicological threshold and consequently a safe concentration.

- In the case of both respiratory and skin sensitisers, the derivation of a safe concentration may not be routinely possible and any figure derived would be associated with large uncertainty (see **Appendix Section A.3** for further details). This means that safe conditions of use can be quite difficult to foresee and regulate.

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3. Additional considerations

There are some additional elements, unique to sensitisers which may need to be considered as part of this 'equivalent level of concern' debate. Supplementary information on each additional consideration can be found in the **Appendix** on the topic of sensitisation.

3.1 Classification & Labelling

Respiratory sensitisers can be subject to harmonised classification under the CLP Regulation, whereas this is not explicitly the case for skin sensitisers. The label elements associated with these two hazards are communicated differently under CLP ('Danger' and 'Health hazard' pictogram for respiratory; 'Warning' and 'Exclamation mark' pictogram for skin sensitisers). This more severe regulatory approach under CLP Regulation could support the view that respiratory sensitisers are of higher concern compared with skin sensitisers.

The second Amendment to Technical Progress (ATP) amending the CLP Regulation[5] includes 2 different sub-categories for both respiratory and skin sensitisation. This allows for discrimination between strong sensitisers and other sensitisers. Perhaps it could be said that strong sensitisers classified as sub-category 1A are more likely candidates for identification as SVHCs under the 'equivalent level of concern' route.

Further information on the topic of classification can be found in **Appendix Section A.2**.

3.2 Potency

Potent sensitisers are those which can sensitise people at very low doses and also with shorter and less frequent exposure.

The second Amendment to Technical Progress (ATP) amending the CLP Regulation includes 2 different sub-categories for skin sensitisation i.e. sub-category 1A for strong skin sensitisers (high frequency of occurrence with humans and/or high potency in laboratory animals), and sub-category 1B for other skin sensitisers. Using this categorisation, the CLP Guidance[6] indicates a degree of potency (extreme/strong/moderate) based on the Local Lymph Node Assay (LLNA) test for skin sensitisers as follows:

Extreme: EC3 value <0.2%
Strong: EC3 value 0.2 to <2%

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[5] Commission Regulation (EU) No 286/2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures

[6] Guidance on the Application of the CLP Regulation (EC) No. 1272/2008.

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Moderate: EC3 value >2%

Extreme and strong skin sensitisers would be categorised into CLP 1A sub-category. The Guinea Pig Maximisation Test (GPMT) and Buehler guinea pig test (Buehler assay) could also be used as above (similar cut off points developed depending on the induction and challenge concentrations). It is likely that the majority of substances with skin sensitising properties would fit in the CLP 1B sub-category. Perhaps it could be justified that certain skin sensitising substances in the CLP 1A sub-category (i.e. extreme and/or strong skin sensitisers) would more likely candidates for identification as SVHCs under the 'equivalent level of concern' route in accordance with article 57(f).

Having said this, it should be borne in mind that the relationship between sensitising potency and elicitation is not well characterised and even if a sensitiser is very potent, this does not necessary mean that there is a higher severity of effect. Therefore determining whether a potent skin sensitiser is of 'equivalent level of concern' would have to be investigated on a case-by-case basis.

This consideration of degree of potency is applicable to skin sensitisers due to availability of reliable animal testing models, which is not the case for respiratory sensitisers).

For further information on this topic, please refer to **Appendix Section A.2**.

3.3 Dose-response relationship

The difficulty in identifying clear quantitative dose-response relationships for sensitisers is a feature that sensitisers have in common with CMRs. This means that for both CMRs and sensitisers safe conditions of use can be quite difficult to foresee and regulate. This could support the opinion that it is justified to identify certain sensitisers as SVHCs under the 'equivalent level of concern' route in accordance with article 57(f).

For further information on this topic, please refer to **Appendix Section A.3**.

3.4 Reactivity

There is a known link between skin and respiratory sensitisation. Most if not all known respiratory sensitisers are also skin sensitisers, while the converse is not necessarily true. On the other hand, a large number of skin sensitisers is known, for which there is simply no knowledge about a possible potential for respiratory sensitisation (due to lack of an appropriate, harmonised test protocol).

In addition, certain individuals who become sensitised to one particular substance can also show allergic symptoms when exposed to other similar

substances i.e. cross-reactivity. This can often occur with substances which are not very similar but the tendency is that when the immune system has started to overreact, the sensitisation spreads to other factors/agents.

It is also known that sensitisation to substances via the skin can also lead to generalised inflammatory reactions, or even anaphylactic shock, e.g. when the same allergen is taken up systemically via other routes.

Again, this can mean that safe conditions of use can be quite difficult to foresee and regulate. This could support the opinion that it is justified to identify certain sensitisers as SVHCs under the 'equivalent level of concern' route in accordance with article 57(f).

For further information on this topic, please refer to **Appendix Section A.4**.

4. Conclusions

Based on several factors and additional considerations used to compare the level of concern that exists between CMRs and sensitisers, it appears to be possible to demonstrate that equivalent level of concern can exist and that certain sensitisers could meet the SVHC criteria under the equivalent level of concern route (Article 57(f)).

However, the justification for a substance to be identified as a SVHC based on Article 57(f) requires case by case:

i. An assessment of the hazard properties of the substance and comparison of their potential impact on health and other factors and additional considerations with the impacts potentially elicited by carcinogenic, mutagenic or reprotoxic substances meeting the criteria of Article 57 (a-c)
ii. Evidence that the substance is of equivalent level of concern by concluding on the results of the comparison of hazard properties and potential impacts described under (i).

In general, it appears to be easier to justify equivalent level of concern for respiratory sensitisers when compared with skin sensitisers. Nevertheless, this should not be considered as a general rule to be applied in all cases. There may be certain circumstances which may warrant skin sensitisers becoming identified as SVHCs under the 'equivalent level of concern' route, particularly in cases where the factors and additional considerations described in this document are taken into account, particularly in cases where factors and additional considerations described in this document apply.

It would be preferable that any SVHC identification under article 57(f) should only be undertaken for substances already classified as sensitisers. For potential new sensitisers, the assessment of the hazardous properties should be based on classification and labelling rules. For respiratory

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sensitisers harmonised classification and labelling in Annex VI should be foreseen before work on possible identification as SVHC is initiated. This is the same approach as applied for CMR substances.

It is stressed that for sensitisers, the same need applies as for CMRs i.e. to consider whether further regulatory action is needed and, if yes, is identification as SVHC and inclusion in the Candidate List the most appropriate option.

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Appendix: Sensitisation

A.1 Introduction

According to the EU Classification, Labelling and Packaging (CLP) Regulation[7], a respiratory sensitiser is a substance that will lead to hypersensitivity of the airways following inhalation of the substance. A skin sensitiser is a substance that will lead to an allergic response following skin contact.

The CLP Regulation describes the two phases involved in sensitisation:

1. **Induction** of specialised immunological memory in an individual by exposure to an allergen and
2. **Elicitation** i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitised individual to an allergen

Usually, for both skin and respiratory sensitisation, lower levels are necessary for elicitation than are required for induction.

Chilcot et al., 2008 described the main type of adverse skin reaction associated with repeated exposure to chemicals as follows[8]:

1. **Induction phase:** the immune system develops a heightened propensity to react to a specific chemical penetrating the skin. The development of sensitisation may take from days to years of exposure to develop, depending on the frequency and duration of exposure, the chemical and the individual. During this time, the immune system is developing an expanded population of T lymphocytes (T-cells) capable of recognising and responding to the chemical.

2. **Elicitation phase:** exposure to the chemical evokes the classical inflammatory reaction, for example in allergic contact dermatitis (ACD) or chronic inflammation of the lungs.

An RIVM report[9] states that chemical allergens are mostly low molecular weight compounds that can only induce sensitization when they are capable of penetrating the skin and binding to proteins in the epidermis. After penetrating the skin, the chemical binds to proteins and hapten-carrier complexes are formed, which are recognized and processed by the dendritic cells of the skin i.e. Langerhans cells that migrate to the draining lymph nodes. In the lymph nodes, Langerhans cells present the hapten-carrier complex to T cells, which in turn are activated and start to proliferate and generate so-called memory T cells. These T cells re-

[7] CLP Regulation (EC) No. 1272/2008
[8] Robert P. Chilcott, Shirley Price, *Principles and Practise of Skin Toxicology*, John Wiley & Sons, Ltd., 2008, Chapter 9, pp. 152
[9] RIVM Report 320025001/2008, Allergens in Consumer Products.

circulate and gain access to the skin. After a second encounter with the substance, the hapten complex is processed again by Langerhans cells and presented to these circulating memory T cells present in the skin. The activation of these T cells causes a rapid release of cytokines and other inflammatory mediators, leading to a dermal inflammatory response[10].

Although such explanations are given, general uncertainty exists regarding the important biological and biochemical processes through which sensitisation is achieved. This is particularly the case for chemical respiratory sensitisers. For instance, although it is well established that sensitisation of the respiratory tract by protein allergens (high molecular weight) is dependent upon IgE antibody responses, there is no general consensus about the requirement for IgE antibody for respiratory sensitisation by chemicals (normally low molecular weight)[11 12 13].

The immune response is a complex reaction. Different allergens elicit different immune responses and their mechanisms can differ significantly. Some compounds react directly, while others require activation. Some allergens predominantly induce skin sensitisation, whereas others cause sensitisation of the respiratory tract.

Skin sensitisation resulting in allergic contact dermatitis represents the most common manifestation of immunotoxicity in humans, and many hundreds of chemicals have been implicated as skin sensitisers. There are far fewer chemicals that have been shown to cause sensitisation of the respiratory tract and asthma, but the issue is no less important because occupational asthma can be fatal (Kimber et al. 2011[14]).

A.2 Classification and Potency

A.2.1 Skin sensitisers

The CLP Regulation includes a hazard category for skin sensitisers. The recent 2nd ATP to the CLP Regulation introduces sub-categories for respiratory and skin sensitisers, discriminating between strong sensitisers and other sensitisers. The following table outlines the CLP hazard category for skin sensitisers (see CLP Table 3.4.2)

Category	**Criteria**
Category 1	Substances are classified as category 1 sensitisers where data are not sufficient for sub-categorisation in accordance with the following criteria:

[10] Kimber, I., Basketter, D. A., Gerberick, G. F., Dearman, R. J. (2002). Allergic contact dermatitis. *International Immunopharmacology* 2, 201-211.
[11] D.A. Basketter, I. Kimber. *Regulatory Toxicology and Pharmacology* 61 (2011) 365–372)
[12] Lalko J.F., Kimber I., Dearman R.J., Gerberick G.F., Sarlo K., Api A. *Toxicology in Vitro* 25: 433-445, 2011.
[13] Tallini D., Novelli E., Bacci E., Dente F.L., De santis M., Di Franco A., Melosini L., Vagaggini B. and Paggiaro P.L. *Journal of Allergy*, ID781470, 2011.
[14] Kimber I., Basketter D.A., Gerberick G.F., Ryan C.A. and Dearman R. *Toxicological Sciences* 120 (S1), S238-S268, 2011.

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	(i) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or (ii) if there are positive results from an appropriate animal test
Sub-cat 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.
Sub-cat 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered.

For skin sensitisation, an induction phase is required in which the immune system learns to react; clinical symptoms can then arise when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardised elicitation phase, typically involving a patch test. Evidence of skin sensitisation in humans normally is assessed by a diagnostic patch test.

There are three different in vivo tests for assessing skin sensitisation available. The Local Lymph node Assay (LLNA) (OECD Guideline 429) can be used for potency measurements. The LLNA directly measures the induction response, therefore the lower the induction dose the more potent the sensitiser is. Guinea Pig Maximisation test (GPMT) and the Buehler guinea pig test (OECD Guideline 406 for both guinea pig tests) can also be used for potency estimations, but there is often a degree of uncertainty associated with the derivation of allergic potencies.

The following table details the criteria for the animal test results for sub-category 1A (see CLP Table 3.4.3):

Assay	**Criteria**
Local lymph node assay	EC3[15] value ≤ 2%
Guinea pig maximisation test (GPMT):	≥ 30 % responding at ≤0.1% intradermal induction dose or ≥ 60% responding at > 0.1% to ≤ 1% intradermal induction dose.
Buehler assay:	≥ 15 % responding at ≤ 0.2% topical induction dose or ≥ 60% responding at > 0.2% to ≤ 20% topical induction dose.

The following table details the criteria for the animal test results for sub-category 1B (see CLP Table 3.4.4):

[15] The EC3 value is an estimate of the concentration of a sensitizer required to generate a threefold stimulation of proliferation in draining lymph nodes (D.A. Basketter, L.J. Lea, A. Dickens, D. Briggs, I. Pate, R.J. Dearman, I. Kimber. A comparison of statistical approaches to the derivation of EC3 values from local lymph node assay dose responses. *J. Appl. Toxicol.,* 19 (1999), pp. 261–266).

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Assay	Criteria
Local lymph node assay	EC3 value > 2%
Guinea pig maximisation test (GPMT):	≥ 30 % to < 60% responding at > 0.1% to ≤ 1% intradermal induction dose or ≥ 30 % responding at > 1% intradermal induction dose.
Buehler assay:	≥ 15 % to < 60% responding at > 0.2% to ≤ 20% topical induction dose or ≥ 15 % responding at > 20% topical induction dose.

Positive effects seen in either humans or animals will normally justify classification as a skin sensitiser. Evidence from animal studies is usually much more reliable than evidence from human exposure.

The Guidance on the Application of the CLP Regulation[16] indicates that an inverse relationship exists between EC3-value and potency meaning that extremely potent sensitisers have extremely low EC3-values. The relevance of potency derives from an appreciation that skin sensitisers vary by up to four or five orders of magnitude with respect to the minimum concentration required inducing skin sensitisation. Potency is graded on the basis of these minimum concentrations each grade reflecting a concentration range of approximately one order of magnitude.

The CLP Guidance indicates that the following scheme could be used for determination of potency categories for sensitisers. However, classification into potency categories is currently not a requirement in the classification of sensitisers.

Skin Sensitisation Potency in the Mouse Local Lymph Node Assay

EC3-value (% w/v)	Potency
≤ 0.2	Extreme
> 0.2 - ≤ 2	Strong
> 2	Moderate

A.2.2 Respiratory sensitisers

The CLP Regulation includes a hazard category for respiratory sensitisers and the recent 2nd ATP also introduced sub-categories for respiratory sensitisers, discriminating between strong sensitisers and other sensitisers. The following table outlines the hazard category for respiratory sensitisers (see CLP Table 3.4.1)

Category	Criteria
Category 1	Substances shall be classified as respiratory sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or

[16] Guidance on the Application of the CLP Regulation (EC) No. 1272/2008.

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	(b) if there are positive results from an appropriate animal test.
Sub-cat 1A:	Substances showing a high frequency of occurrence in humans; or a probability of a high sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered.
Sub-cat 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered.

For respiratory sensitisation, the pattern of induction followed by elicitation phases is shared in common with skin sensitisation. However there are currently no recognised animal models available at present for the testing of respiratory hypersensitivity. Evidence that a substance can induce 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[17].

Arts et al., 2008[18] reported that respiratory sensitisers can be identified with the LLNA. However if human data is not available the positive results obtained from LLNA does not distinguish whether the substance is a respiratory sensitiser in addition to the skin sensitisation.

Arts et al., 2007[19] suggested that a chemical which fails to induce a positive response in the LLNA at appropriate test concentrations most probably lacks the potential for respiratory allergy.

A.3 Dose-response relationship

A single exposure can induce skin sensitisation, and repeated exposure can lead to an accumulation of T-cells capable of recognising and responding to the chemicals (elicitation) i.e. allergic response (see **Section A.1** for further details). There is evidence that for both skin sensitisation and respiratory hypersensitivity dose-response relationships exist, although these are frequently less well defined in the case of respiratory hypersensitivity.

The severity of symptoms may be directly related to exposure levels (frequency, duration and route of exposure) and genetic differences in susceptibility to sensitisation via skin or the respiratory tract (Arts and Mommers et al. 2006[20]). Bernstein et al., 1997[21] demonstrated that such a concentration-dependency was found in humans exposed to trimellitic anhydride. Arts et al., 2007 concluded that assays that utilise an induction

[17] Section 3.4.2.1.2.1 CLP Regulation (EC) No. 1272/2008.
[18] Arts, J.H.E, et al, 2008. *Toxicological sciences* 106 (2).
[19] Arts J.H.E, Kuper C.F. 2007. *Methods* 41, 61-71.
[20] Arts J.H.F., Mommers C. and de Heer C. *Critical Reviews in Toxicology* 36: 219-251, 2006.
[21] J.A. Bernstein, D.I. Bernstein, I.L. Bernstein, in: I. Kimber, R.J. Dearman (Eds.), Toxicology of Chemical Respiratory Hfypersensitivity,Taylor & Francis Ltd., London, UK, 1997, pp. 29–59.

phase seem to serve best as indicators of respiratory sensitisation potential whereas assays in which both an induction and an elicitation or challenge phase are being used seem to provide more information on potency and presence of thresholds.

Cytokine fingerprinting can be used for dose responses (NOEL) for the induction phase, but not for the challenge phase, since in that experiment no challenge is given to the mouse. It should be noted that this method lacks also formal validation[22].

It is difficult to establish what the threshold dose is for the induction and elicitation phases of response, this dose can vary depending on the individual. Once someone becomes sensitised (induction) the allergic reactions occurs with much lower concentration (elicitation) than what was required for induction to occur.

A.4 Reactivity

The dermal route can also be very effective for airway sensitisation. Arts et al., 2007[19] reported that the efficacy of topical application for sensitisation with low molecular weight chemicals in both rats[23] and mice[24] suggests that skin exposure can be a significant risk factor in respiratory allergy in man and that induction of skin sensitisation may result in subsequent heightened respiratory responsiveness following inhalation exposure. There is some limited evidence in man that dermal exposure to some chemical respiratory allergens may induce immune responses of the type necessary to cause pulmonary sensitisation[25].

[22] D.A. Basketter, I. Kimber. Regulatory Toxicology and Pharmacology 61 (2011) 365–372).
[23] X. D. Zhang, J.S. Fedan, D.M. Lewis, P.D. Siegel, *J. Allergy Clin. Immunol*. 113 (2004) 320-326.
[24] E. Hamelmann, K. Takeda, A. Oshiba, E.W. Gelfand, *Allergy* 54 (1999) 297-305.
[25] L.A. Beck, D.Y. Leung, *J. Allergy Clin. Immunol*. 106 (2000) S258–S263.