



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

**Priority setting and Risk Management
Option under REACH for sensitizers**

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W. ter Burg | W.P. Jongeneel



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Abstract

Priority setting and Risk Management Option under REACH for sensitizers

A proper risk management option for sensitizers (substances that can cause allergy) is to qualify sensitizers as substances of very high (SVHC) concern, under REACH legislation (article 57f). Then an authorization process can be started. The authorization route in REACH aims at ensuring that the risks resulting from the use of SVHCs are controlled and that the substance is replaced where possible. In three case studies, several risk management options to control the possible risks of sensitizers were explored. Currently, possible risks of these sensitizing substances are not adequately controlled in existing legislation.

The substances selected for the case studies are based on a priority setting strategy for sensitizers set up in this report. Criteria are whether a substance can induce respiratory and/or skin sensitization or both, is used in high amounts leading to widespread use, and not already covered in other legislations.

Keywords: risk management options, sensitizers, REACH, priority setting

Rapport in het kort

Prioritering en risicomanagement van sensibiliserende stoffen in REACH wetgeving.

Sensibiliserende stoffen (stoffen die allergie kunnen veroorzaken) kunnen worden aangemerkt als zeer ernstige zorgstoffen (stoffen met hoog risico), volgens de REACH wetgeving (artikel 57f). Als gevolg hiervan kan een procedure, waarbij toestemming voor het gebruik van de stof moet worden aangevraagd, worden gestart. Op deze wijze kunnen de risico's van sensibiliserende stoffen worden beperkt. In dit rapport zijn voor drie stoffen de mogelijkheden die artikel 57(f) biedt en andere risicomaatregelen verkend. Op dit moment wordt in de huidige wetgeving onvoldoende rekening gehouden met risico's van allergene stoffen.

De drie stoffen zijn geselecteerd op basis van een prioriteringsstrategie die in dit rapport is opgesteld. Prioriteit wordt gegeven aan stoffen die zowel via de luchtwegen als via de huid allergene reacties kunnen geven, die worden gebruikt in grote hoeveelheden, vele verschillende toepassingen kennen en niet al worden gereguleerd door andere wetgeving dan REACH.

Trefwoorden: risicomanagement, sensibiliserende stoffen, REACH prioriteitstrategie

Contents

Summary—7

1 Introduction—8

2 Hazard, exposure and risk of sensitizing substances—10

- 2.1 Current numbers—10
- 2.1.1 Underreporting—11
- 2.1.2 Number of listed sensitizers—11
- 2.2 Health effects and effects to society related to sensitizers—11
- 2.3 Risk analysis of sensitizing substances – exposure and toxicology—12
- 2.3.1 Mechanism of sensitization—12
- 2.3.2 Known sensitizers—14
- 2.3.3 Identification of (new) sensitizing substances—15
- 2.4 Deriving safe limits for sensitizing substances in risk assessment—16
- 2.4.1 Risk assessment of respiratory sensitizers—16
- 2.4.2 Risk assessment of skin sensitizers—17
- 2.4.3 General remarks on risk assessment of sensitizing substances—17

3 Legislation—18

- 3.1 Classification and labelling—18
- 3.2 REACH—21
- 3.2.1 Authorisation—22
- 3.2.2 Restriction—24
- 3.2.3 Substance evaluation—24

4 Risk management option analysis – explanation—25

- 4.1 Background and aim—25
- 4.2 Timing—25
- 4.3 Information basis—26

5 Identification and ranking of non-CMR sensitizers—27

- 5.1 Introduction—27
- 5.2 Possible candidates for the REACH article 57f route (hazard based approach)—27
 - 5.2.1 The Trade Union Priority list for REACH Authorization—27
 - 5.2.2 Identification of possible candidates—29
- 5.3 Sensitizing substances with highest impact/risk for workers and/or consumers (effect based approach)—30
 - 5.3.1 Workers—30
 - 5.3.2 Consumers—35
- 5.4 Prioritised substances for further analysis—36
- 5.5 Preliminary conclusions from the RMOs—37

6 Discussion—38

7 References—39

Annex 1: Other legislative frameworks—41

- Occupational Safety and Health Decree (Arbeidsomstandighedenbesluit).—41
- General Product Safety Directive 2001/95/EC—41
- Biocide Directive—41

Cosmetics Directive 76/768/EEC—41
Examples of legislative measures—42
Workers—42
Consumers—42
In summary—42

Summary

The presence of sensitizing substances may form a large problem in society as it may cause allergic reactions in large numbers of subjects in the working and general population. The associated health effects of sensitizers are irreversible and can become very severe leading to clinical manifestation of allergic contact dermatitis (eczema), asthma, and chronic obstructive pulmonary disorder (COPD). Sensitizing substances and associated risks could be covered by REACH, but have not received special attention thus far. The aim of the report is to address the risk of sensitizers, set up a priority setting strategy for sensitizers and explore risk management options including article 57(f) under REACH.

Actual figures of the number of subjects that are sensitized to substances are high, but likely to be underestimates. Sensitizing substances are poorly recognized as causal relationships between a chemical agent and the clinical effects are difficult to establish. An explanation as to why the current situation persists is due to the complex mechanism of action of sensitizers and difficulties in identifying sensitizers, especially for respiratory sensitizers for which no appropriate animal test is available. Furthermore, most tests that are available provide input on identification only rendering a quantitative risk assessment impossible. As a result, most legislative measures taken so far were not based on a risk, but rather on the hazard.

The new classification and labelling legislation (CLP) places identified sensitizers in categories 1, 1A and 1B. Substances in category 1A are most important due to their high occurrence in humans (surrogate for exposure as well as potency), their high potency and possibly also the severity of the effects. REACH states that testing for skin sensitization is mandatory and known sensitizers should be addressed on safety data sheets and provides options to address the risks from sensitizers. The article 57(f) route of equivalent concern was therefore explored for sensitizers and possible non-CMR sensitizing candidates were identified and prioritised under REACH. Three substances were selected based on a priority setting strategy that considered criteria such as hazard, potency, the incidence and prevalence of health effects associated with the substance, the production in high amounts leading to widespread use and if the substance was not already covered in other legislations. The substances selected are hexahydrophthalic anhydride (HHPA), methylenediphenyl diisocyanate (MDI) and isoeugenol. The results of the risk management options were that the article 57(f) could be considered for the three substances, possibly complemented with other risk management options.

In conclusion, based on the three cases it has been shown that the article 57(f) route can be an appropriate route for risk management of sensitizers.

1 Introduction

The presence of sensitizing substances may form a large problem in society as it may cause allergic reactions in large numbers of subjects in the working and general population. The associated health effects of sensitizers can become very severe leading to clinical manifestation of allergic contact dermatitis (eczema), asthma, and chronic obstructive pulmonary disorder (COPD). The health effects are such that withdrawal from work processes, inability to work with certain substances or avoidance of consumer products may eventually follow from contact with such substances. At present, the use of sensitizing substances is very widespread and may concern high production volume substances. As a result, in daily life, avoidance of coming into contact with sensitizers can be difficult.

Under the chemicals legislation REACH (Registration, Evaluation, Authorisation and restriction of Chemicals) general focus lies on the safe use of substances by workers and consumers. Sensitizing substances and associated risks could be covered by REACH, but have not received special attention thus far. Substances of special interest under REACH are the CMR (carcinogenic, mutagenic and reproduction toxic substances), PBT (persistent, bioaccumulative and toxic) and vPvB (very persistent and very bioaccumulative) substances. At the moment activities are taking place to make Annex XV Substance of Very High Concern (SVHC) dossiers for the CMR, PBT and vPvB substances by Member States and the Commission. Some of the sensitizers may already be covered when the substances also have CMR, PBT or vPvB properties, but no 'program' exists for sensitizers.

The aim of this report is:

- To shortly describe the poor recognition of the risks of sensitizers;
- To explore the so-called REACH article 57(f) equivalent concern route for sensitizers and to identify and prioritise possible non-CMR sensitizing candidates for this route (hazard based approach);
- To identify and prioritise the non-CMR sensitizers causing a (possible) risk for workers or consumers (effect based approach);
- To describe the possibilities, effects and advantages of possible risk management measures for selected substances in a risk management options (RMO) analysis.

In chapter 2 of this report an insight in the extent of the current situation in the EU in relation to the hazard, exposure and risk of sensitizing substances is given. Chapter 3 provides an overview of EU legislation relevant for sensitizers for the protection of workers and consumers. The information in this chapter is needed because REACH is not the only community wide legislation, since possibly sensitizing substances are already covered by several other legislative measures. In paragraph 3.2.1.1 of chapter 3, the REACH article 57(f) route is further explained.

Chapter 4 gives a general explanation of the risk management option (RMO) analysis. The aim of a RMO analysis is to facilitate the identification and choice of the most appropriate measure (or combination of measures) for the case at hand. In chapter 5 non-CMR sensitizers are identified and the main applications

are shortly described. Furthermore, sensitizing substances are prioritised for both the hazard based approach (REACH article 57(f)) and the effect based approach. For three prioritised sensitizers a description of the possible risk management measures within or outside the scope of REACH is summarized in Chapter 5 based upon which conclusions are presented (Chapter 6).

2 Hazard, exposure and risk of sensitizing substances

This chapter provides an overview of sensitizing substances related issues, without going into much depth. Descriptions are given of the extent of the problems, which sensitizing substances may cause, including effects on the general and worker population and the risks that skin and respiratory sensitizers may pose, but moreover provide insight as to why dealing with sensitizers and their risk is subject to difficulties.

2.1 Current numbers

In developed countries, allergic diseases affecting up to 15-30% of the population are amongst the most common chronic diseases (European Allergy White Paper, 1997; as cited in Wijnhoven et al., 2008). According to Diel et al. 2006, the prevalence of those diseases in Europe amounts to 20% of the population and is still increasing. However, the contribution of chemical substances to the total of allergic reactions is not completely clear. It is important to realize that not only low molecular weight substances, such as chemical substances, can cause sensitization. Also pollen, proteins, and micro-organisms can cause sensitization in humans. Furthermore, one should be aware that the clinical health effects associated with allergies, like contact dermatitis and asthma, are not only caused by allergic reactions, but also by irritation.

The number of persons with allergies to sensitizing substances is thought to be very high, but no accurate estimates can be given. Registration of work-related chemical allergies is also not very exhaustive. Although health effects are carefully reported, the causative agents are not. Based on symptoms alone, no distinction can be made between irritation and allergic effects (Terwoert et al. 2009). If substances are known to which the worker was exposed, it may be possible to determine the cause, however workers are often exposed to various substances. The incidence of occupational asthma in the Netherlands is estimated to be around 500 to 2000 new cases per year (Baars et al., 2005), while occupational physicians reported to the Netherlands center for occupational diseases (NCvB) a mere number of 24 new cases in 2006 (Terwoert et al. 2009). It is unknown what percentage of the cases is caused by allergic reactions. NCvB estimated that yearly 13,000 new cases with contact eczema occur of which is assumed that 20% can be accounted for by allergic reactions.

No estimations of respiratory allergies in consumers were found. Estimates of contact eczema in the Dutch population, based on registrations by general practitioners, are around 330,000 subjects (VTV, 2010, www.vtv2010.nl access date 15 Nov. 2011), without making a distinction to causes of the illness. In contrast to the estimate above, nickel (skin) allergy in the general population is one of the most common allergies, which prevalence in the Netherlands has been estimated to be about 12.5% (2 million subjects) of the Dutch population (Schuur et al., 2008). It is unclear however, how these two estimates relate to each other. There are many other well known causative agent groups available to the general public, such as some metals (chromium and cobalt), fragrances, preservatives, dyes, resins and solvents, but prevalence number are not available. Only for textile (unknown what type of sensitizer), a prevalence figure was given for Germany where 1 to 2% of the allergies were related to textile.

2.1.1 *Underreporting*

A major issue in the registration of allergic reactions from exposure to substances (both for worker and the general public as for respiratory and skin allergies) is underreporting of effects. Possible reasons are:

- Workers are not aware of risk inventories and evaluations or do not comply with work instructions. Consequently, the workers do not know if they are exposed to allergens. Education and training of workers on possible risks of hazardous substances is considered to be minimal.
- Allergic responses may not be recognized if the symptoms are mild and furthermore do not hamper them in their work.
- Subjects may not go to see a practitioner if they do recognize allergic symptoms and take actions themselves. Many companies do not have access to a company practitioner.
- A lack in linking the data from (company) practitioners, dermatologists, lung specialists, and occupational hygienists makes it difficult to obtain the overview. In daily practice, the company doctor is replaced by general practitioners without specific training on work related issues. Therefore, often the specific problems and their causes are not recognised and practitioners will focus solely on treatment. Also interactions between company practitioners and occupational hygienists do not exist, which hampers any consequent preventive actions.
- Treatment often considered for workers is the replacement of the worker to other jobs, thereby covering up the problem. This type of ill recognition of the allergy issues is further strengthened by underreporting of mainly less severe effects by the workers themselves.

Increasing knowledge of a causal relationship between exposure and effect at the work place may contribute significantly to more realistic figures. For example, the automotive industry and spray painters haven't been looked at in the past, thereby missing a large population with relative high risks of respiratory sensitization. Special governmental programs to address such risks often immediately increase the number of registrations. Unfortunately the trend of reduced interference by the government on safety issues on the workplace as employers are expected to deal with the risks themselves, may lead to a reduced knowledge level on causal relations.

2.1.2 *Number of listed sensitizers*

Based on literature searches it can be concluded that many substances are able to cause sensitization in the skin, airways or both. Schlede et al. (2003) lists 244 substances known to cause skin allergy; Diel et al (2006) lists approximately 400 substances without specifying skin or respiratory allergens. Annex VI of EU Classification, Labelling and Packaging of substances and mixtures (CLP) lists approximately 1,000 substances that are classified either for skin or respiratory sensitization or both. Probably the actual number of allergenic substances is higher.

2.2

Health effects and effects to society related to sensitizers

The health effects of sensitizers range from relative mild to very severe effects and symptoms. Effects on the airways by respiratory sensitizers may result in coughing, shortness of breath, rhinitis, asthma, and COPD. The health effect of skin sensitization is allergic contact dermatitis showing symptoms of redness of the skin, rashes, itching or burning sensations, and boils on the skin. The

severity of the effects may differ significantly in the affected population, ranging from situations where subjects sometimes do not even notice any symptoms to situations where medical treatment is necessary. Effects, at first, may be hardly noticeable or even recognized as an allergic effect, since the symptoms do not occur immediately. There lies a danger in this lack of awareness in that the effects can progress to more severe effects if exposure is prolonged or repeated once the subject has become sensitive to the allergen. Although health effects may subside once exposure has ceased, the allergy remains and cannot be cured; possibly leading to health effects upon every next contact.

The effects of sensitizers go beyond health effects alone. The health effects of sensitizers may lead to socio-economic effects as well. Respiratory and/or skin allergens may hamper persons in their daily activities, cause inconveniences, and may also lead to absenteeism of work and change in jobs, because of the recurring effects. Unlike the worker situation, consumers can take actions to avoid contact with an agent provided that the agent is known. However, certain agents, like pollen, are difficult to avoid. Treatment related costs can become very high as the health effects are incurable and treatment is only palliative (symptom based). Costs to society, including implications for workers and consumers, were calculated to be around €29 billion in Europe in 1997 (Diel et al. 2006).

2.3 Risk analysis of sensitizing substances – exposure and toxicology

2.3.1 Mechanism of sensitization

To understand better certain aspects that are related to the interpretation of the reason and extent of the risks of sensitizing substances, one needs to understand the mechanism of sensitizing substances and how health effects are elicited. The mechanism of action for respiratory and skin sensitization shows similarity. The mechanism of action for respiratory sensitizers can be subdivided into sensitization to enzymes, proteins and pollens and to sensitization to low molecular weight substances. A major difference exists in that with respiratory sensitization to enzymes, proteins and pollen there is no need to form a hapten to initiate respiratory sensitization (Verstraelen et al. 2008). This mechanism is much better understood than is the case for the low molecular weight substances.

One should also note that although much effort has been made to understand the toxicological mechanism, some parts are still not understood:

- Developing an allergy may differ significantly between subjects: one exposure may suffice for one subject, while others may take many years of exposure to develop an allergy, if at all (Terwoert et al. 2009).
- Unknown relation between induction and elicitation 'threshold'.
- Co-exposure to other substances increases the risk of sensitization or cross-reactions (42% of substances which showed cross-reactions in patients; Schlede et al. 2003). In practice, especially workers are exposed to various substances and it is unknown whether the exposure to the different substances leads to accumulation of effects.
- Low molecular weight substances can intrinsically induce both type I (related to respiratory allergy) and type IV immune responses (related to skin allergy) (De Jong et al. 2009). Whether or not sensitizing occurs via both routes of exposure is likely dependent on the fact if a substance is able to contact a antigen presenting cell.

- Isocyanates, for example, may cause skin *and* respiratory sensitization after dermal contact.

2.3.1.1 Mechanism of respiratory sensitization

The mechanism of action is not yet completely understood for respiratory sensitizers to low molecular weight substances. The respiratory allergy is a type I hypersensitivity reaction where the response is immediate with clinical effects occurring within minutes to hours after exposure.

The mechanism of action with respect to proteins, pollen and enzymes is briefly as follows: in the induction phase, inhaled antigens are captured by antigen-presenting cells leading to T cell activation and release of proinflammatory cytokines. This leads to IgE production and the resulting IgE binds on mast cells and basophils. Antigen re-exposure leads to mast cell degranulation (early-phase asthmatic reaction). During the late-phase asthmatic reaction, various cell types are involved in ongoing inflammation, which can be followed by airway remodelling (Figure 1).

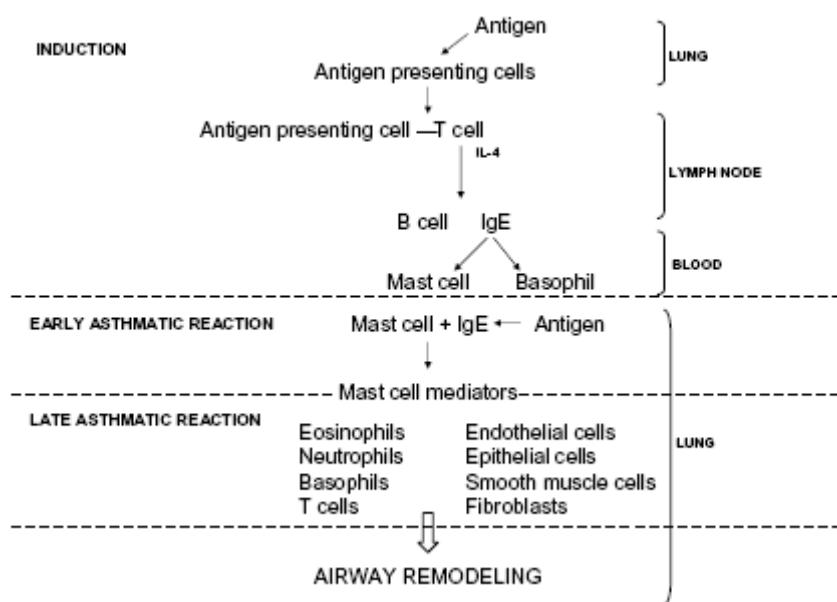


Figure 1 (adopted from Verstraelen et al. 2008). Overview of the allergic cascade.

2.3.1.2 Mechanism of skin sensitization

Briefly, allergic reactions to substances in the skin are generally type IV delayed hypersensitization reactions of the immune system. They are characterized by two steps, i.e. induction and elicitation (effect phase). In the induction phase, the immune system is activated after contact with the allergen, i.e. the subject is sensitized and thus called hypersensitive. To do so the allergen must form a hapten (reaction product of allergen and enzyme or protein), this is recognized by antigen presenting cells (APCs). Consequently, the APCs are recognized by lymphocytes (T-cells) by their antigens and the immune system is activated. The immune system will then build up a 'memory', which is shared over the lymphatic system. The time frame of becoming sensitized (induction phase) upon contact is difficult, if at all, to predict. In the elicitation phase upon the next exposure the allergen will trigger an immunoreaction leading to the health

effects. The reaction to an insult in a sensitized subject can be fast and fierce due to the memory that has been built up previously (Figure 2).

To cause skin sensitization a substance must be able to react or bind with enzymes or proteins. Important to realize is that the 'threshold' for the elicitation phase can be much lower than the induction phase (Kimber et al. 2002; Wijnhoven et al. 2008).

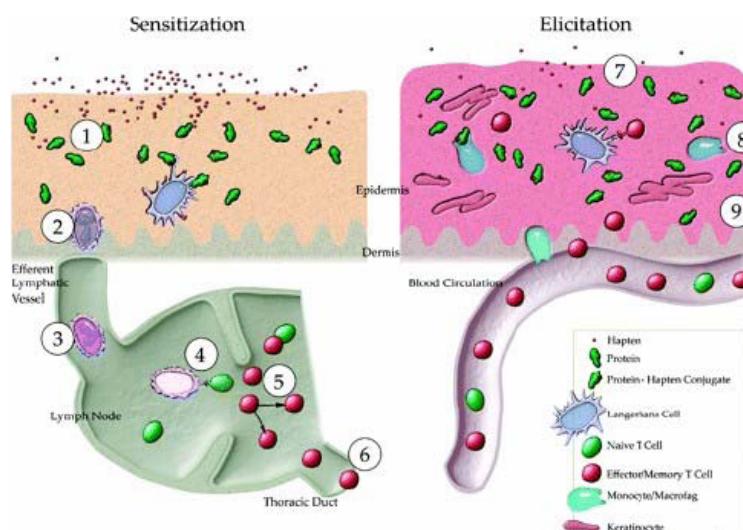


Figure 2: Mechanism of action of skin sensitizers.

2.3.2 Known sensitizers

2.3.2.1 Workers – respiratory

Occupational respiratory allergens that have received much attention are amylase (enzyme in bakers' flour), allergens from laboratory animals, latex, isocyanates and anhydrides (Baars et al., 2005). Risk factors are dusty environments and certain (spray) processes with high potential exposure to substances, particles and articles that become airborne.

2.3.2.2 Workers – skin

Workers at high risk of becoming sensitized to skin sensitizers often work with reactive substances in combination with circumstances that influence the integrity of the skin barrier. For example, hair dressers using hair dyes in wet or moist conditions or pavers working with binding material or preservatives in cement, while their skin is abraded by the rough materials. Well known skin sensitizers in the occupational setting are chromates, cobalt, nickel, hair dyes (PPD; para-phenylenediamine), rubber products such as latex, epoxy resins, fragrance materials, and preservatives amongst other. As mentioned above, contact dermatitis is a large contributing disease in the total burden of disease amongst workers, however up till now the distinction between irritative (orthokeratotic) or allergic contact dermatitis has not been fully characterized. Possibly, both irritative and allergic contact dermatitis occurs at the same time as co-exposure to multiple substances is likely (Baars et al., 2005). Therefore, the list of skin sensitizers in the occupational setting is believed to be far from complete.

2.3.2.3 Consumers – respiratory

Information on respiratory sensitization in the general population resulting from the use of consumer products is hardly available. In principle, subjects could be exposed to the same substances that cause respiratory sensitization in workers, for example isocyanates in do-it-yourself products, but as far as we know no evidence exists of a causal relationship between respiratory sensitization and the use of such consumer products. This might be explained that a different way of exposure (more frequent and higher exposures) is needed to become sensitized. Nevertheless, there still may be a risk that consumers may be sensitized by inhaling those substances.

2.3.2.4 Consumers - skin

The best known skin sensitizer for the general public is nickel. It was estimated that approximately 12.5% of the population is allergic to nickel (Schuur et al., 2008). Nickel is used in cheap jewellery (earrings), belt-buckles, alloys, and in coins, which is often unknown to the public. Fragrance materials, hair dyes and some preservatives, used in many cosmetic products, may also induce sensitization. Consumer products known to be related with sensitizer substances are textiles and leathers, cosmetics, cleaning products and detergents, toys, scented products, do-it-yourself products and rubber. Other possible risks are those substances used in consumer products known to cause skin sensitization in workers, such as paints, lacquers, PU foams, and epoxy resins.

2.3.3 *Identification of (new) sensitizing substances*

In general, the identification of sensitizing substances based on symptoms alone is difficult. Therefore, findings of symptoms must be supported by some sort of evidence, e.g. clinical history, exposure history, and testing to ensure one is sensitized to a substance. Evidence that a substance is a sensitizer may be based on human data such as case reports including diagnostics (patch tests) or epidemiological studies or otherwise based on animal studies. Overall, identification of allergens is difficult, especially for respiratory sensitizers. This might also significantly contribute to the underreporting of sensitizing effects in the (worker) population.

2.3.3.1 Human data

Respiratory sensitizers

The identification of respiratory sensitizers is based on epidemiological data or human cases where a causal relationship between exposure and effect was established. To determine whether an individual is sensitive for a respiratory sensitizer a subject is subcutaneously exposed in a patch test to a number of known respiratory sensitizers. Medical reports and exposure history can often aid in determining the cause for the effects, e.g. the recent use of a certain product or occupational history. However, identification of new respiratory sensitizers is very difficult as it will not be picked up in the standard line-up of the patch test and many cases are required to give sufficient statistical power in an epidemiological study. However, in case there is reasonable suspicion of a substance causing respiratory sensitisation a specific patch test can be performed.

Skin sensitizers

In case of skin sensitization, underlying the registration process (and thus also identification) lays the diagnosis of the effects. Patch test reactions are scored according to international standards (ICDRG grading scale), using the following gradations: negative, doubtful (+?), weakly positive (+), moderately positive

(++) and strongly positive (+++) (Wilkinson et al. 1970). In general, the results of the patch test should not be regarded as stand alone, but its relevance should be evaluated in the context of clinical history and physical examination. Specifically, testing of multiple chemicals at once might give rise to false-positives. The sensitivity and specificity of the patch test is strongly dependent on the sensitizer and on the severity of patch test reactions in the patients. Patients who respond with strong skin reactions (++) or (+++) will be detected more easily than those with a weak response (+? or +). In addition, the patch test reaction of substances with strong irritant properties is difficult to score because it is hard to distinguish between an irritant reaction and a skin sensitization reaction. For these substances only concentrations that do not induce skin irritation can be used and this concentration might be too low to elicit allergy reactions. It is estimated that the overall sensitivity of the patch test is approximately 70% (Nethercott 1990). There are some ethical issues with patch testing as the patch test itself may also lead to sensitization; therefore patch tests will generally be conducted using low concentrations.

2.3.3.2 Animal data

Respiratory sensitizers

Work is in progress to obtain reliable animal tests for respiratory sensitizers, but up till today they have not been accepted for hazard or risk characterisation. Some animal studies are under consideration such as the mouse IgE test, guinea pig test, Local Lymph Node Assay (LLNA) and cytokine profiling with respect to respiratory sensitization to low molecular weight substances, but lack validation at this moment.

Skin sensitizers

Currently, there are animal studies to identify if a substance is a skin sensitizer. In earlier days, it was only possible to determine whether or not a substance is a sensitizer with the guinea pig maximisation test (GPMT) or the Buehler Assay (BA). With the murine Local Lymph Node Assay (LLNA) it is made possible to determine potency as well, making a quantitative risk assessment possible. The studies are standardized under OECD guidelines 406 (BA and GPMT) and OECD 429 (LLNA). However, all animal studies currently available describe the induction phase and not the elicitation phase. Moreover, some substances will not give positive results in the animal test, where in humans they do or vice versa, e.g. metals such as nickel test negative in the GPMT, BA and LLNA tests, but are well known skin sensitizers in humans.

2.4

Deriving safe limits for sensitizing substances in risk assessment

Risk assessment of sensitising substances is reliant on the identification of those substances and furthermore on the assessment of their potencies to induce sensitization in so far this is possible. In turn, information from the risk assessment is important for policy measures.

2.4.1 Risk assessment of respiratory sensitizers

Up till now respiratory sensitizers are identified using human data (epidemiology studies) or based on case reports. Therefore, 'risk' assessment for respiratory sensitizers is mainly done in a qualitative way. If epidemiological data is available, quantitative risk assessments (QRAs) for respiratory sensitizers can therefore be prepared in case relative risks or attributable risks have been determined for such substances. Unfortunately, in epidemiological studies the exposure is not always quantified very accurately or are substance groups or work

conditions considered, instead of a single substance. Estimating safe levels at which subjects are not expected to be at risk is therefore very difficult to establish for respiratory sensitizers. For this reason, historically, policy measures were based mainly on the hazard characterization of the respiratory sensitizing substance instead of basing the measures on the risks.

2.4.2 Risk assessment of skin sensitizers

In the past, 'risk' assessment of skin sensitizers was performed qualitatively, since the animal data provided information on hazard identification only. Hence, similar to the case of respiratory sensitizers, it was difficult to estimate safe levels for skin sensitizers. With the introduction of the LLNA it is possible to allocate potencies to the tested substances, which makes it possible to set up a QRA. To date, QRA for skin sensitizers is neither common practice nor widely accepted, but methods for QRA of skin sensitizers have been suggested for fragrance materials in cosmetics (Api et al. 2008; Ter Burg et al. 2010) and could be used for other skin sensitizers as well. Starting point in the QRA is the derivation of a No Expected Sensitization Induction Level (NESIL), which can be based on results from the murine LLNA and/or the human patch test. As the LLNA test is not suitable for all types of substances (most metals are not recognized as being skin sensitizers, while based on human evidence they certainly are), performing a QRA will not be possible in all cases. Further it should be noted, that the QRA for skin sensitizers focuses on the induction of skin sensitization and thus only safe levels are derived for naïve subjects (not previously sensitized).

2.4.3 General remarks on risk assessment of sensitizing substances

Knowledge on the mechanisms of action of sensitizers is increasing and efforts are made to identify respiratory sensitizers easier. Once this is realized, better understanding of how exposure results in respiratory or skin sensitization under different circumstances is necessary to improve the risk assessment and scientifically based policy measures. Some issues that were identified in developing the QRA for skin sensitizers were for example the relevance of peak exposures or prolonged repeated exposures in the sensitizing process. Another exposure issue was compromised body defences, such as abraded skin which influences the level of contact with APCs and consequently initiation of the immune response (Api et al. 2008; Ter Burg et al. 2010).

Most importantly, as most hazard identification tests are based on the induction of (skin) sensitization, the resulting risk assessment will derive a safe level for induction and not elicitation, whereas the latter is expected to be much lower. Furthermore, the quantitative correlation between induction and elicitation is unknown and thus no estimates can be made to derive a safe level for elicitation. Hence, such 'safe' limits may give a false sense of protection. Due to all listed uncertainties in this section, the legislation in different frameworks and resulting legislative measures on sensitizers taken in the past were predominantly hazard-based. Thus it can be considered that legislative measure having been rather arbitrary as the reduction in exposure would not guarantee a reduction in the risk.

3

Legislation

Legislation is a tool to control the risks of sensitizers. Most frameworks mention sensitizers where the use of sensitizers is either restricted or in case of specific sensitizers restricted or banned (see annex 1). As indicated in section 2.4.3, the measures taken in the past were predominantly hazard-based and resulting from observations in the occupational sector or in the general public, e.g. diisocyanates exposure in the work place and nickel allergies in the general population (Annex 1). There was, however, no preset incentive to act against sensitizers in general. In this chapter is described how sensitizers are classified under the EU Classification, Labelling and Packaging of substances and mixtures (CLP) and how sensitizers can be addressed under REACH.

3.1

Classification and labelling

According to the Dangerous Substance Directive (67/548/EC) substances can be classified as respiratory sensitizer (R42) or skin sensitizer (R43). A substance is classified as a respiratory sensitizer, when there is evidence in humans that the substance can lead to specific respiratory hypersensitivity. R42 embraces all materials that are implicated as inducers of occupational asthma, elicited either by immunological or non-immunological mechanisms.

The Preparations Directive (1999/45/EC) states that preparations should be classified as sensitizing with R42, when they contain substances which are classified as skin or respiratory sensitizers. For nongaseous preparations, the preparation should be assigned Xn and R42 (inhalation) or R43 (skin), when the substance is classified with R42 or R43 respectively and present in the preparation in a concentration $\geq 1\%$. For gaseous preparations, the preparation should be assigned Xn and R42 or R43 when the concentration of the classified substance in the preparation is $\geq 0.2\%$.

According to Annex V: the packaging of preparations containing at least one substance classified as sensitizing and being present in a concentration equal to or greater than 0.1 % or in a concentration equal to or greater than that specified under a specific note for the substance in Annex I to Directive 67/548/EEC must bear the inscription: 'Contains (name of sensitizing substance). May produce an allergic reaction.'

The abovementioned animal tests (GPMT, LLNA, and BA) can be used to classify a substance as skin sensitizer according to the Dangerous Substances Directive (DSD) or the EU Classification, Labelling and Packaging of substances and mixtures (CLP). A substance is classified as a skin sensitizer (R43) when there is evidence in humans that the substance can induce sensitization by skin contact in a substantial number of persons, or if there are positive results from an appropriate animal test. A response is needed in more than 30% of the animals in a test with adjuvant (Guinea Pig Maximization Test (GPMT)), or more than 15% in a test without adjuvant (Buehler test). When the Local Lymph Node Assay (LLNA) is employed, a three-fold increase in proliferation in the draining lymph nodes compared to the control group (Stimulation Index (SI) ≥ 3) is used as a cut-off point to designate a chemical as a skin sensitizer (OECD, 2002).

The implemented new global harmonizing system (GHS) for classification and labelling of substances in the EU, the EU Classification, Labelling and Packaging

of substances and mixtures (CLP), will replace in time the Dangerous Substances Directive and the Preparations Directive. The CLP differs from the DSD in a sense that subcategories have been set up. See the following figures adopted from the CLP (Figure 3 to 7).

Hazard category and sub-categories for respiratory sensitizers	
Category	Criteria
Category 1	Substances shall be classified as respiratory sensitizers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: <ul style="list-style-type: none"> (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity; and/or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests ⁽¹⁾ . Severity of reaction may also be considered.
Sub-category 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 ⁽¹⁾ . Severity of reaction may also be considered.

⁽¹⁾ At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

Figure 3: Hazard categories for respiratory sensitizers under CLP.

Hazard category and sub-categories for skin sensitizers	
Category	Criteria
Category 1	Substances shall be classified as skin sensitizers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: <ul style="list-style-type: none"> (a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or (b) if there are positive results from an appropriate animal test (see specific criteria in section 3.4.2.2.4.1).
Sub-category 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-category 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.

Figure 4: Hazard categories for skin sensitizers under CLP.

If a substance is classified as a sensitizer according to the Dangerous Substance Directive or CLP, the general concentration limit for those substances is set at 1% for skin sensitizers in mixtures or lower limits under certain conditions (see figure 5 and 6).

Generic concentration limits of components of a mixture classified as either respiratory sensitisers or skin sensitisers that trigger classification of the mixture

Component classified as:	Generic concentration limits triggering classification of a mixture as:		
	Respiratory sensitiser Category 1		Skin sensitiser Category 1
	Solid/liquid	Gas	All physical states
Respiratory sensitiser Category 1	≥ 1,0 %	≥ 0,2 %	
Respiratory sensitiser Sub-category 1A	≥ 0,1 %	≥ 0,1 %	
Respiratory sensitiser Sub-category 1B	≥ 1,0 %	≥ 0,2 %	
Skin sensitiser Category 1			≥ 1,0 %
Skin sensitiser Sub-category 1A			≥ 0,1 %
Skin sensitiser Sub-category 1B			≥ 1,0 %

Figure 5: Concentration limits that trigger classification of sensitizers in mixtures under CLP.

Concentration limits for elicitation of components of a mixture

Component classified as:	Concentration limits for elicitation		
	Respiratory sensitiser Category 1		Skin sensitiser Category 1
	Solid/liquid	Gas	All physical states
Respiratory sensitiser Category 1	≥ 0,1 % (Note 1)	≥ 0,1 % (Note 1)	
Respiratory sensitiser Sub-category 1A	≥ 0,01 % (Note 1)	≥ 0,01 % (Note 1)	
Respiratory sensitiser Sub-category 1B	≥ 0,1 % (Note 1)	≥ 0,1 % (Note 1)	
Skin sensitiser Category 1			≥ 0,1 % (Note 1)
Skin sensitiser Sub-category 1A			≥ 0,01 % (Note 1)
Skin sensitiser Sub-category 1B			≥ 0,1 % (Note 1)

Note 1:

This concentration limit for elicitation is used for the application of the special labelling requirements of Annex II section 2.8 to protect already sensitised individuals. A SDS is required for the mixture containing a component above this concentration. For sensitising substances with specific concentration limit lower than 0,1 %, the concentration limit for elicitation should be set at one tenth of the specific concentration limit.²

Figure 6: Concentration limits for sensitizers of mixture that trigger labelling.

Respiratory or skin sensitisation label elements

Classification	Respiratory sensitisation	Skin sensitisation
	Category 1 and sub-categories 1A and 1B	Category 1 and sub-categories 1A and 1B
GHS pictograms		
Signal word	Danger	Warning
Hazard statement	H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled	H317: May cause an allergic skin reaction
Precautionary statement prevention	P261 P285	P261 P272 P280
Precautionary statement response	P304 + P341 P342 + P311	P302 + P352 P333 + P313 P321 P363
Precautionary statement storage		
Precautionary statement disposal	P501	P501'

Figure 7: Labelling of sensitizers under CLP. Please note that the classification of a substance with H334 does not implicitly mean that the substance is a sensitizer!

The new classification and labelling legislation (CLP) places sensitizers in categories 1, 1A and 1B. The category 1 is used when the criteria for categories 1A and 1B do not apply to a suspected sensitizer. Category 1A is used when the substance shows a high frequency of occurrence in humans and/or shows high potency in animal testing, leaving space to take severity into account as well. In case of respiratory sensitizers, obviously there will be human evidence only, due to the lack of an appropriate animal test, and thus it is stated that animal data can only be used in weight of evidence assessments of its sensitizing potential. Category B is used when the substance shows either lower frequency of occurrence in humans or has moderate to low potency in animal tests. The way of classification provides valuable input on which sensitizers to prioritize for RMOs, showing that substances in category 1A are most important due to their high occurrence in humans (surrogate for exposure as well as potency), their high potency and possibly also the severity of the effects.

3.2

REACH

In the REACH legislation, skin and respiratory sensitizers are mentioned in a few places. First of all, testing for skin sensitization is mandatory as standard information requirement for all registered substances that are imported or manufactured in quantities of one tonne or more per year (REACH Annex VII)

Furthermore, the sensitization properties of a substance should be mentioned in the Safety Data Sheets (REACH Annex II).

Within the REACH legal framework Member States have several options if a concern is identified on substances with sensitizing properties where risks are not controlled and need to be addressed. The key options are authorization, restriction or substance evaluation.

3.2.1 *Authorisation*

The aim of the authorisation process under REACH is to ensure the good functioning of the internal market while assuring that the risks from substances of very high concern (SVHC) are properly controlled and that these substances are progressively replaced by suitable alternatives where these are economically and technically viable.

Substances may be identified as SVHC's by ECHA's Member State Committee based on a proposal (an Annex XV dossier) prepared by a Member State or a proposal prepared by ECHA on request of the Commission. ECHA decides whether to include these substances in the so called "Candidate List" of substances for possible inclusion in the Authorisation List (Annex XIV of the REACH Regulation). ECHA recommends priority substances for inclusion in the Authorisation List. The European Commission takes the decision to include a substance in the Authorisation List through a regulatory committee procedure.

Substances on the Authorisation List cannot be placed on the market or used after the so called "sunset date". Unless specific exceptions apply, these substances may be placed on the market only if an authorisation has been granted for a specific use, or the use has been exempted from authorisation. The European Commission decides based on opinions from both the Risk Assessment Committee (RAC) and the Socio-Economic Assessment Committee (SEAC) on the granting or refusing of authorisations. Applications for authorisation can be prepared by manufacturers, importers or downstream users of a substance on the Authorisation List. The Authorisation process is described in Title VII of the REACH regulation.

The identification of substances as SVHC's is described in article 57 of the REACH regulation:

Article 57

Substances to be included in Annex XIV

The following substances may be included in Annex XIV in accordance with the procedure laid down in Article 58:

- (a) substances meeting the criteria for classification as carcinogenic category 1 or 2 in accordance with Directive 67/548/EEC;
- (b) substances meeting the criteria for classification as mutagenic category 1 or 2 in accordance with Directive 67/548/EEC;
- (c) substances meeting the criteria for classification as toxic for reproduction category 1 or 2 in accordance with Directive 67/548/EEC;
- (d) substances which are persistent, bioaccumulative and toxic in accordance with the criteria set out in Annex XIII of this Regulation;

- (e) substances which are very persistent and very bioaccumulative in accordance with the criteria set out in Annex XIII of this Regulation;
- (f) substances – such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of points (d) or (e) – for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59.

As can be deducted from the legal text of article 57; sensitizers that are not classified as CMR category 1 or 2, PBT or vPvB can only be identified as SVHC if they fulfil the criteria as set out in 57(f).

3.2.1.1 The 57(f) route

Article 57(f) of the REACH Regulation states that substances, without the properties listed in 57(a) – (e), can be identified as SVHC if there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e). In the REACH guidance this level of equivalent concern is more specified as:

"The concerns for substances which exhibit carcinogenicity, mutagenicity and reproductive toxicity arise from a number of factors – the seriousness of the effects, the often irreversible nature of the effects, the consequences for society and the difficulty in performing concentration-based risk assessments - should be taken into account when considering whether a substance shows an equivalent level of concern to CMR (cat 1 or 2) substances"

For respiratory sensitizers, especially those classified 1A under CLP, the criteria described above to be identified as SVHC may be met, it might be more difficult for skin sensitizers to assign a SVHC status. For most of the respiratory sensitizers the criteria set out above are fitting as:

- occupational asthma is a serious, irreversible disease, with a substantial impact for the person involved.
- workers are not able to perform their original work anymore and have to be assigned other work.
- at the present time it is not possible to define reliable exposure-response relationships with regard to the risk of respiratory sensitization for most respiratory sensitizers.

When preparing a RMO analysis paper for a sensitizer these criteria must be discussed in the paper together with the argumentation why the selected substance could (not) be identified as SVHC. For a substance for which additional information on the use in articles would have value, inclusion on the candidate list could be an option, even without the aim of including the substance in Annex XIV. By inclusion of sensitizers in Annex XIV industry would be actively forced to look for substitutes and phase out use of the sensitizer. For sensitizers with a very widespread use, a total phase out might not be realistic, depending on the availability of alternatives. Without suitable alternatives, all major companies would likely apply for authorization ensuring safer use by workers. In the authorization request industry will have to demonstrate the appropriateness and effectiveness of risk management measures. It can be expected that the exposure of workers to sensitizers will be

reduced. If specific sensitizers are widely used in small and medium enterprises (SME) this could lead to major market disruption.

3.2.2 *Restriction*

REACH foresees a restriction process to regulate the manufacture, placing on the market or use of certain substances if they pose an unacceptable risk to health or the environment. The restriction is designed as a "safety net" to manage risks that are not addressed by the other REACH processes.

Any substance on its own, in a preparation or in an article may be subject to a restriction if it is demonstrated that risks need to be addressed on a Community-wide basis. A restriction dossier needs to justify that the proposed restriction is the most appropriate risk management measure to address these risks.

Proposals for restrictions can be prepared by Member States or by ECHA on request of the Commission. The Restriction process is described in Title VIII of the REACH regulation.

The main difference between the authorization and the restriction route is the approach. The authorization process is based on the intrinsic properties (hazard) of the substance, whereas in the restriction process a risk for the environment or the health of workers or consumers has to be identified. Also the administrative burden for industry or Member States differs between the two processes. For authorization, the industry has to show the safe use of these substances before an authorisation can be granted for the specific use. With restrictions, the Member States have to show there is an unacceptable risk for the environment or the health of workers or consumers associated with the intended use.

3.2.3 *Substance evaluation*

The REACH Regulation contains a specific process for substance evaluation. Its aim is to clarify whether the uses of a substance poses a risk to human health or the environment. Substance evaluation can be useful for substances triggering initial concerns for human health or the environment. Such substances will be prioritised for substance evaluation if it is expected that by requesting and receiving further information the initial concern will be confirmed, validated, eliminated or marginalised so that a conclusion can be drawn as to whether further action is necessary.

The selection and eventual prioritization of substances for evaluation is made according to risk-based criteria, which include: hazard information, exposure information regarding people and the environment and the tonnage. Member States can also propose substances based on other specific risk based concerns as they find appropriate and necessary. Prioritized substances will then be listed in a Community Rolling Action Plan (CoRAP).

Substance evaluation will normally result in a request for further information from the registrants of the substance. The registrants must submit the required information within the deadline specified in the final decision.

4 Risk management option analysis – explanation

4.1 Background and aim

In most cases where a concern related to a substance has been identified, there will be several options for addressing this concern. The different legislative measures that may be used, all have different strengths and weaknesses which will vary depending on the case. The aim of a systematic analysis of the risk management options (RMOs) is to facilitate the identification and choice of the most appropriate measure (or combination of measures) for the case at hand.

Documenting the RMO analysis and sharing it with other MSs and the Commission will promote early discussion and should ultimately lead to a common understanding on the need for action and the type of action needed. By giving the possibility for other MSs and the Commission/ECHA to provide further information the identification of the most appropriate RMO can be facilitated. Consideration of the views, concerns and special features of different MSs early enough can facilitate and speed up the actual process to establish the new legal provision.

The decision to prepare and submit either type of Annex XV dossier under REACH will always be based on the submitter's considerations and reasons for why an action under REACH is needed and why exactly one type of action is considered better than another. In essence, using the RMO format is only meant to help documenting these reasons and sharing them with others. Preparing and discussing this analysis is not a legally required step in REACH but is a voluntary action. Submission of the RMO analysis does not automatically initiate any process. The actual restriction or authorisation process under REACH (or another process under other legislation) only starts when a MS or the Commission/ECHA submits an Annex XV dossier (or uses the procedure defined under other legislation).

4.2 Timing

It can be very useful to make a systematic RMO analysis well before the process which may lead to new legal requirements is formally initiated. This is because implementing one process may affect or even block the possibility to use another process. Secondly initiating any process requires resources from all Member States, the Commission and ECHA and will furthermore, affect industry and other actors. Therefore the RMO analysis should preferably be made and circulated before a MS/the Commission initiates the preparation of an Annex XV dossier under REACH, but in any case (well) before the dossier is submitted. The submitter can decide to update his RMO analysis when comments or new information have arrived and where further/other measures seem to be necessary.

Furthermore, it should be noted that in case the chosen RMO is a restriction under REACH, the Annex XV restriction report needs to contain a justification that the suggested restriction (including the exact scope and conditions) is the most appropriate Community wide measure. It is expected that the preceding RMO analysis can be used as a basis for preparing this justification. However,

the justification in the Annex XV restriction report will in most cases be more targeted but also more extensive and thorough.

4.3 Information basis

The RMO analysis should be done on the basis of available information. Depending on the case and point in time the analysis is prepared there may be fairly little information available for the MS which may hamper drawing firm conclusions on the most appropriate RMO. However, one of the aims of documenting and sharing the RMO analysis is to gather available further information from other MSs and the Commission/ECHA. In those cases it would be useful to note in the analysis which type of information would be most valuable to improve the decision basis.

5 Identification and ranking of non-CMR sensitizers

5.1 Introduction

Within this project, non-CMR skin or respiratory sensitizers need to be identified and ranked according to their hazard or risk for both worker and consumer. Starting point of the identification of potential substances is the Trade Union Priority list for REACH Authorization (Santos et al. 2010) and their note with a proposal of sensitizers for SVHC identification under 57f (Santos et al. 2011). The ETUI approach is based on the hazard (skin or respiratory sensitizer) of the substance and its wide spread use or production tonnage. All sensitizers also classified as CMR category 1A or 1B should be de-selected because CMR substances are already covered by several other activities.

Another approach is to identify those substances that still pose a risk to workers and consumers in the Netherlands based on incidence reports on allergic contact dermatitis or asthma. The yearly reported incidence of allergic contact dermatitis or asthma due to exposure to chemicals in the Netherlands is known. For workers, figures from the Occupational Dermatoses Surveillance (ADS) registration project of Netherlands Centre for Occupational Diseases (NCvB) in collaboration with the Netherlands Expertise Centre of Occupational Dermatoses (NECOD) will be studied. Also various epidemiological data available for contact allergy in Europe has been summarized in RIVM reports and will be used to identify the most frequent encountered sensitizing substances in consumer products.

5.2 Possible candidates for the REACH article 57f route (hazard based approach)

Starting point of the identification of potential substances is the Trade Union Priority list for REACH Authorization (Santos et al. 2010) and their note with a proposal of sensitizers for SVHC identification under 57f (Santos et al. 2011). This note is basically a follow-up of the Trade Union Priority List but focussed on sensitizers. As this note uses the same priority list of the Trade Union as the basis for selection, it is not discussed in detail here.

5.2.1 *The Trade Union Priority list for REACH Authorization*

The Trade Union Priority list for REACH Authorization contains in total 568 substances. This list is composed to contribute to the practical implementation of REACH. In particular the authorisation procedure by proposing Substances of Very High Concern (SVHC) which from a union perspective should have priority for inclusion in the Candidate List and potentially in the Authorisation List. These substances are selected through a methodology displayed in Figure 8. The substances are subsequently scored according to their intrinsic properties (see Table 1) in a similar way as was done in the European Union Risk Ranking Method (EURAM). The substances are then ranked according to the sum of the scores obtained from the scoring of their intrinsic properties.

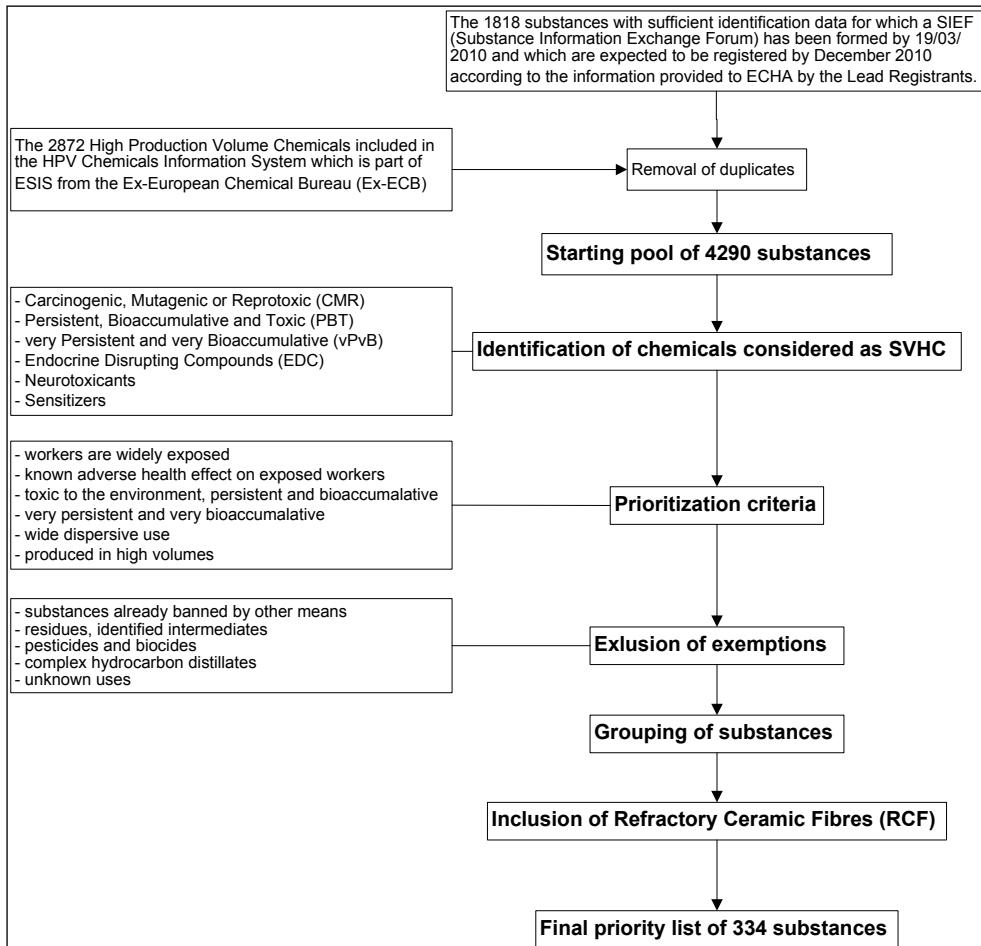


Figure 8: The selection of substances in the Trade Union Priority List.

Table 1: Scoring of the substances in the Trade Union Priority List

Substances	EURAM score	Trade Union List score
EU Carcinogens Cat 1A or 1B	10	10
IARC Carcinogens 1 or 2A group		10
EU Mutagens cat.1A or 1B	10	10
EU Reprotoxicants cat.1A or 1B	10	10
EU known Endocrine Disrupters		9
PBT		9
EU Carcinogens cat.2	9	9
IARC Carcinogens 2B group		9
EU Mutagens cat. 2	9	9
EU Reprotoxicants cat.2	9	9
Sensitizers by skin contact	6	7
Sensitizers by inhalation	7	7
EU suspected Endocrine Disrupters		7

5.2.2 *Identification of possible candidates*

A list of possible candidates was selected similar to the methodology used in the Trade Union Priority List and their following note (see figure 9). Starting point was the Trade Union Priority List. Substances classified as sensitizers in the Trade Union Priority list were selected and subsequently those classified as CMR category 1A or 1B were de-selected. In our list 90 substances remained (in contrast with the note by (Santos et al. 2011), which consisted of 89 substances after the same selection steps, the cause of this discrepancy was not found). It is anticipated that only respiratory sensitizers will have serious human health effects of an equivalent level of concern to the category 1A and 1B CMR substances (see paragraph x). Therefore, from the 90 substances those classified as respiratory sensitizers were selected. This led to a total of 11 substances. Those substances only used in cosmetics, as pesticides or as preservatives were also de-selected because they are exempted from the REACH legal framework. Finally, substances with high structural similarities have been grouped (for instance, a group of diisocyanates is made).

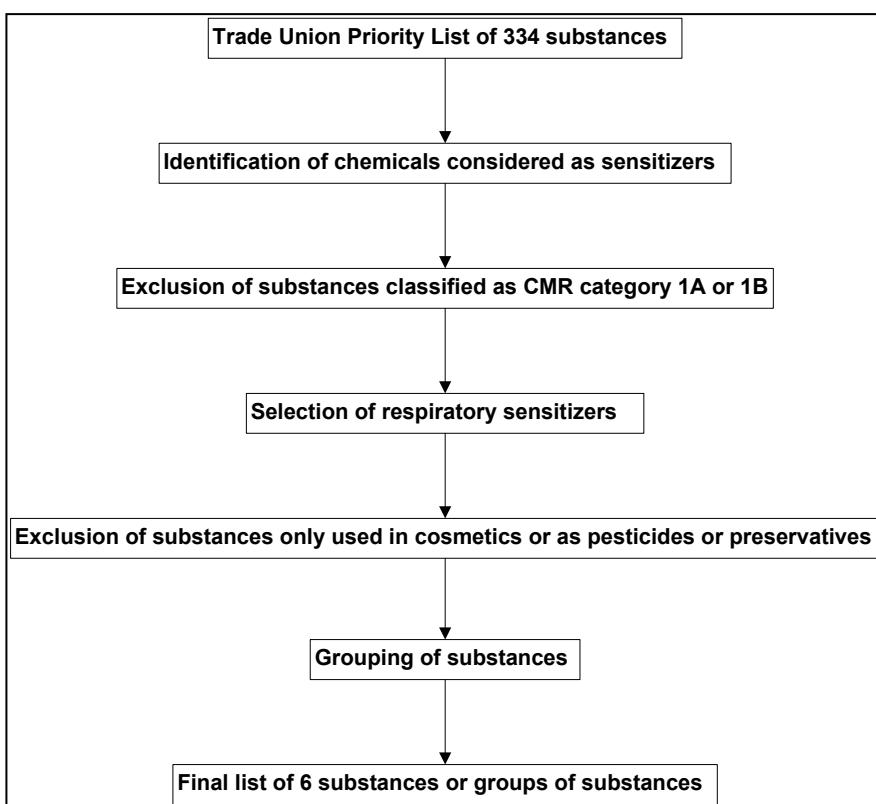


Figure 9: methodology used in the Trade Union Priority List

In table 2 the substances are mentioned that remained after the final selection step with their CAS number and short description on the use.

Table 2: List of substances based on priority setting by Trade Union

Name	CAS number	Usage
Ethylenediamine	107-15-3	pesticide, solvent, emulsifier, stabilizer, inhibitor, pharma, reagent, intermediate, process regulator, paints, surface treatment, corrosion inhibitor, lubricant, additive, adhesive, reprographic agent, construction material, electroplating agent, colouring agent, photochemical, filler, hardener, curing agent, oils, caulking compound
Cobalt	7440-48-4	paints
Piperazine	110-85-0	scruber, hardener, intermediate, pharma, corrosion inhibitor, surface-active agent, pesticide, accelerator, adhesive, photochemical, process regulator, reagent
(di)isocyanates	584-84-9 26471-62-5 5124-30-1 822-06-0 4098-71-9	additive, solvent, hardener, paints, construction material, adhesive, surface treatment, casting material, colouring agent
Anhydrides (phthalic and maleic)	85-44-9 108-31-6	curing agent, rubber retarder, scorch inhibitor, plasticizer, hardener, intermediate, pesticide, reagent, softener, tanning agent, light- and heat-stabilizer, construction material, paints, adhesive, corrosion inhibitor, impregnation material, colouring agent, surface treatment, reprographic agent, vulcanizing agent, filler, preservative, stopping material, binder
Subtilisin	9014-01-1	cleaner, food agent, process regulator, softener, pesticide, surface-active agent, catalyst, spot (stain) remover, detergent, disinfectant, reagent, pharma

5.3 Sensitizing substances with highest impact/risk for workers and/or consumers (effect based approach)

In the effect based approach substances need to be identified that are expected to elicit effects in workers and consumers in the Netherlands based on incidence reports on allergic contact dermatitis or asthma. A distinction is made between workers and consumers.

5.3.1 *Workers*

5.3.1.1 Contact Dermatitis

For workers incidence numbers for occupational contact dermatitis are known from the ADS project. In the Netherlands around 25 dermatologists around the country participate in this project. In table 3 the most mentioned causes of occupational contact dermatitis between 2002 and 2010 are reported. No distinction is made between allergic or irritant contact dermatitis.

Table 3: Most mentioned causes of occupational contact dermatitis reported in the framework of the ADS project (2002-2010). The main chemical substance categories are highlighted (NCvB 2007; NECOD 2008; NECOD 2011).

Agent	Number of times mentioned (n)								
	2010	2009	2008	2007	2006	2005	2004	2003	2002
Wet work	63	100	128	103	161	154	183	269	266
Irritating substances	18	17	31	41	56	70	78	88	60
Mechanical factors	*	*	*	10	25	23	39	33	23
Rubber chemicals	9	19	26	16	17	21	22	24	27
Plants	9	5	6	14	16	10	17	23	30
Hair (dye) products	15	20	11	7	13	14	23	29	34
Preservatives	20	22	11	15	13	17	39	25	16
Metalworking fluids and oil	*	*	*	*	11	10	15	13	17
Climate	*	*	*	*	11	8	9	13	11
Soaps and detergents	13	4	13	12	9	16	27	29	20
Acrylates	5	2	10	*	9	16	7	15	21
Protective clothing	6		6	*	9	4	9	19	11
Fragrances	16	18	15	6	7	6	17	14	16
Epoxy substances	12	14	8	*	7	6	12	13	17
Nickel	7	8	9	*	4	8	18	31	20

* Due to differences between years and institutions not all agent categories are available for all years

Although these numbers are an underestimation of the total cases of occupational contact dermatitis, they do indicate what group of substances are mainly responsible for the reported contact dermatitis. For the agents wet work and irritating substances the reported contact dermatitis is assumed to be due to irritant contact dermatitis. These agents are therefore excluded for further analyses. As indicated in table x, the other agents mainly responsible for contact dermatitis in recent years are:

- rubber chemicals
- hair (dye) products
- preservatives
- metalworking fluids and oil
- soaps and detergents
- acrylates
- fragrances
- epoxy substances

From these, preservatives are excluded from this exercise as they are biocides and therefore are regulated by the biocide legislation and do not fall under the REACH framework. Within the agents leading to occupational contact dermatitis we need to identify the main individual substances responsible for sensitization. However, the identified agents can contain complex mixtures of substances. In an attempt to identify individual substances, literature on patch tests used for each specific agent is searched and reviewed.

Rubber chemicals

Rubber chemicals are substances used in the vulcanization process to give rubber the desired elasticity and firmness. Most people are allergic for the so-called accelerators, which support the vulcanization process and the anti-oxidants, which are added to prevent aging and dehydration of the rubber. There are several patch tests available for the determination of a rubber allergy;

- black rubber mix: N-isopropyl-N'-phenyl paraphenylenediamine (IPPD), N-cyclohexyl-N'-phenyl paraphenylenediamine (CPPD) and N, N'- diphenyl paraphenylenediamine (DPPD).
- thiuram mix: Tetramethylthiuram monosulphide (TMTD), Tetramethylthiuram disulphide (TMTM), Tetraethylthiuram disulphide (TETD) and dipentamethylthiuram disulphide (PTD).
- mercapto mix: N-cyclohexylbenzothiazylsulphenamide (CBS), mercaptobenzothiazole (MBT), dibenzothiazyl disulphide (MBTS) and morpholinylmercaptobenzothiazole (MOR).
- carba mix: (1,3-diphenylguanidine (DPG), Bis(diethyldithiocarbamate)zinc (ZBC) and Bis(dibutylidithiocarbamate)zinc (ZDC).

In a study by Bendewald et al. (2010) results from 773 patch tests (2000-2007) with rubber allergens are reviewed. The allergens that most commonly yielded positive reactions were 4,4-dithiodimorpholine (28/286 [9.8%]), thiuram mix (56/739 [7.6%]), and diphenylguanidine (57/759 [7.5%]).

Hair (dye) products

Sensitization due to the use hair dyes is mainly caused by p-phenylene diamine (PPD), a potent skin sensitizer.

Metalworking fluids and oil.

Geier et al. (2004) published results of the German Contact Dermatitis Research Group (DKG) on patch test results with metalworking fluid. They tested 251 metalworkers because of suspected metalworking fluid dermatitis.

Monoethanolamine (MEA) was identified as the substance leading to the most positive reaction in the patch test. However, MEA is lightly irritating and not sensitizing in animal studies, so the results could be false positives. A later comparison study by Lessmann et al. (2009) on MEA, diethanolamine (DEA) and triethanolamine (TEA) concluded:

- For MEA and DEA, results of animal studies indicate a very low sensitization potential.
- The low overall frequency of positive reactions in diagnostic patch testing with MEA and DEA is also indicative of a weak sensitization potential.
- Nevertheless, the industrial use of MEA (and DEA in the past) in water-based metalworking fluids, and the regular, even daily exposure to these fluids is regarded as a cause of occupational sensitization to this (these) substance(s). Wet work or chemical irritation by solvents or the alkaline cutting fluid itself, and possibly mechanical irritation, seem to be important cofactors contributing to sensitization in this special occupational group.

Besides MEA, formaldehyde and formaldehyde releasing products are believed to be an important component of metalworking fluids causing sensitization. The formaldehyde is added as a preservative. However, formaldehyde as preservative in metalworking fluids has been already restricted (Commission Decision 2008/681/EC).

Soaps and detergents

No information was found on standardized patch tests for soaps and detergents. Sensitizing due to soaps of detergents is almost always caused by an additive like perfume, ionaline, turpentine, preservatives and enzymes.

Acrylates

Acrylates are common monomers and belong to the class of synthetic plastics and resins. They have acrylic acid as common basis, forming the acrylate polymers. Acrylates easily form polymers because the double bonds are very reactive. Uncured acrylates are known as potent skin sensitizers. The most common sources of acrylates are nail polish, paints and dental implants. In Sweden some specific patch tests for acrylate allergy has been performed. 2-hydroxyethyl methacrylate (2-HEMA) was the most common allergen among acrylate-allergic dental patients and dental personnel (Goon et al. 2006). The most common allergens in the industrial acrylate setting were triethyleneglycol diacrylate (TREGDA), diethyleneglycol diacrylate (DEGDA), and 1,4-butanediol diacrylate (BUDA) (Teik-Jin Goon et al. 2007).

Fragrances

Fragrances are known sensitizers, the standard fragrance mix used in patch test are fragrance mix I¹ and II². No information was found on which of these individual fragrances has the highest prevalence. This is because patch tests for fragrances contain the fragrance mix and no single fragrances. Instead, information is available on the potency of the different individual fragrances that make up the fragrance mixes (see table 4).

¹ Fragrance mix I contains cinnamyl alcohol, cinnamaldehyde, eugenol, alpha-amyl-cinnamaldehyde, hydroxycitronellal, geraniol, isoeugenol and oak moss absolute

² Fragrance mix II contains alpha-Hexyl cinnamaldehyde, Citral, Citronellol, Farnesol, Coumarin and Hydroxymethylpentylcyclohexenecarboxaldehyde

Table 4: Potency of some common allergens (data source: Wijnhoven et al. 2008)

Fragrance	LLNA EC3 value*	Category	Human category**
Amyl cinnamal	10.6	+	Extremely weak
Amylcinnamyl alcohol	25	+	Weak
Anisyl alcohol	5.9	+	Weak
Benzyl alcohol	>50	+	Weak
Benzyl benzoate	>50	+	Extremely weak
Benzyl cinnamate	18.4	+	Weak
Benzyl salicylate	1.5	++	Weak
Cinnamyl alcohol	20.1	+	Weak
Cinnamal	2.0	++	Moderate
Citral	5.6	+	Weak
Citronellol	43.5	+	Extremely weak
Coumarin	Negative	Non-sensitizer	Non-sensitizer
Eugenol	10.1	+	Weak
Farnesol	4.8	+	Weak
Geraniol	22.4	+	Weak
Hexyl cinnamaldehyde	9.9	+	Moderate
Hydroxycitronellal	33	+	Weak
Hydroxymethylpentylcyclohexenecarbonylaldehyde	17.1	+	Weak
(Lyral)			
Isoeugenol	1.5	++	Strong
Lilial®	18.7	+	Weak
d-Limonene	69	+	Weak
Linalool	46.2	+	Extremely weak
Methyl heptine carbonate	0.5	++	Strong
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	21.8	+	Weak
Oak moss	3.9	+	Moderate
Tree moss	>20	+	Moderate
Peru balsam	NA	--	NA

* EC3 values determined in the LLNA were used to categorize potency of allergens: EC3 ≤ 2%: stronger sensitizer (++) and EC3 > 2%: other sensitizer (+)

** Chemicals are classified into five categories: strong, moderate, weak, extremely weak, nonsensitizing. These data are based on human data and expert judgment.

Abbreviations: LLNA: local lymph node assay; NA: not available

Epoxy substances

The uncured epoxy resin (the reaction of bisphenol A or other hardeners with epichlorhydrine) is known as a strong sensitizer.

5.3.1.2 Respiratory sensitizers

For workers there is only limited information on the incidence of occupational asthma due to respiratory sensitizers. Occupational asthma incidence figures from the NCvB show that in the period 2000-2010 only a few cases (1-6) of occupational asthma a year are contributed to chemical agents (Dekkers et al. 2006; NCvB 2011). Although not further specified, diisocyanates and anhydrides are regarded as the main causal agents. These numbers are believed to be an underestimation of the real number of cases.

5.3.2 Consumers

5.3.2.1 Contact dermatitis

The RIVM report *Allergens in consumer products* by Wijnhoven et al. 2008 gives an overview with respect to the prevalence of contact dermatitis; sensitization potency of the allergens and the frequency of allergens found in products. The underlying data comes from epidemiological studies in Europe; scientific reviews on sensitization potency and market research in the Netherlands and Europe. This report is used as primary source of information as it was published recently (2008) and focuses on consumers in the Netherlands.

Consumers are exposed to allergenic compounds via various consumer products such as cosmetics, toys and detergents. A lot of consumer products like cosmetics, toys, clothing and textile, and scented products contain chemical allergens that have the potential to induce either contact dermatitis or respiratory allergy in consumers (Wijnhoven et al. 2008). Also products that are known to cause allergy in an occupational setting, such as cleaning products and detergents, do-it-yourself and hair-dye products are frequently used in a domestic setting where they may also induce or elicit allergic reactions.

Several international epidemiological studies have estimated the frequency of contact dermatitis and the contribution of allergens present in consumer products (summarized in Wijnhoven et al. 2008). Allergic patients or the general population can be tested for allergies with patch tests containing several known wide spread allergens. The multitude of these studies was focused on sensitization in a selected population of patients with contact dermatitis. The number of studies that have estimated prevalence in the general population is limited. Studies in patients cannot be used to extrapolate the prevalence data to the general population, but they provide insight in which allergens are the most frequent sensitizers. In addition, these studies can give information on the impact of regulatory and preventive decisions by assessing time trends of sensitization to allergens in consumer products.

Wijnhoven et al. (2008) identified five main categories of allergic substances in consumer products:

- metals
- fragrances
- (hair)dyes
- preservatives
- resin/solvents

Again, preservatives are excluded from this exercise as they are biocides and therefore are regulated by the biocide legislation and do not fall under the REACH framework.

Metals

When all data are put together, contact dermatitis due to metals show the highest prevalence. Metals can be present for consumers in metallic accessories. Metals like nickel (positive reactions up to 17.9% in allergic patients and 10% in the general population), cobalt (6% in patients and 2% in general population) and potassium dichromate (4.6% in patients) give the highest positive reactions (Wijnhoven et al. 2008).

Fragrances

Looking at substances, various fragrances present in cosmetic and household products result in high prevalence of contact dermatitis. Prevalence of contact dermatitis after testing with fragrance mix I vary from 10% in patients and 1-11% in the general population, for Peru Balsam this is 6% in patients and 1% in the general population (Wijnhoven et al. 2008).

Hair dyes

The use of the hair dye para-phenylene diamine results in a high prevalence of contact dermatitis in patients (3.9%) (Wijnhoven et al. 2008).

Resins and solvents

One of the allergens mentioned is colophonium, a natural product made from resin from conifers. It has a variety of applications such as in paints, glues, printing inks and is used in paper and cardboard. Figures from Sweden and Lithuania indicate a prevalence of 3.4-5.0% among dermatitis patients (Beliauskienė et al. 2011; Isaksson et al. 2011).

Uncured epoxy resin is also mentioned as contact allergen for consumers. From prevalence studies it is difficult to distinguish between contact dermatitis due to occupational exposure or due to consumer exposure. In Europe about 1.2-1.8% of contact allergy patients tested positive for the uncured bisphenol A epoxy resin (Uter et al. 2005; Geier 2010). Another allergen is turpentine oil, it is used as a solvent and diluting agent in varnishes, paints, shoe polishes, resins and building materials. According to a European multicentre study around 1.1-1.9% of the patients reacted positive to turpentine oil (Uter et al. 2005).

5.3.2.2 Respiratory sensitizers

There is no information available on the prevalence of respiratory allergy induced by chemicals present in consumer products. It is thought that respiratory allergy induced by chemicals occurs less frequently than contact dermatitis.

5.4 Prioritised substances for further analysis

Based on the information above in paragraphs 5.2 and 5.3 individual substances need to be selected for further analysis in a risk management options (RMO) paper. The selection of the substances was discussed during an expert meeting at RIVM. Through consensus the substances (or substance groups) were selected. Via the hazard based approach the following substances were selected for further analysis:

- diisocyanates (TDI, MDI or HDI)
- anhydrides (phthalic or maleic)

The main rationale for these substances was the wide spread use and their known respiratory sensitizing properties. A further selection within these substance categories was performed taken into account the total tonnage used or manufactured; the wide dispersive use and differences in potency and exposure. Eventually, methylenediphenyl diisocyanate (MDI) is chosen from the diisocyanates group and hexahydrophthalic anhydride (HHPA) from the anhydrides group to perform the RMO analysis for.

Via the effect based approach isoeugenol is selected for further analysis. The categories fragrances, (hair)dyes and epoxy resins are both present by consumers and workers. The category fragrances is selected based on the prevalence figures for both workers as consumers. Within this category, isoeugenol is chosen based on its sensitizing potency and occurrence in consumers products.

5.5

Preliminary conclusions from the RMOs

Therefore, for three sensitizing substances (hexahydrophthalic anhydride (HHPA), methylenediphenyl diisocyanate (MDI) and isoeugenol) the risk management options were explored. The RMO analysis are not shown in this report due to confidentiality issues. The analysis have been made available to and discussed with competent authorities of the EU Member States. A very short summary of the RMOs is given below. More information is available on request.

For HHPA several options were considered as good risk management options. Setting an OEL at community level would seem a good risk management option to reduce the number of workers at risk for respiratory sensitization. However, such an OEL would not fully protect the workers, but rather a considered 'acceptable' residual risk of developing occupational asthma due to HHPA would be taken. The authorization route could also be considered for HHPA. The effectiveness of the authorization route is dependent on the type of uses of HHPA by small and medium enterprises (SME) and the availability of alternatives. Furthermore, the number of workers still exposed to HHPA during processes in which HHPA is considered to be an intermediate (intermediate use is not covered by authorization processes). From the registration dossiers the use of HHPA as intermediate is limited, only 3-8% of the annual production is used as intermediate. However, the use of HHPA as intermediate is not without exposure of workers. To cover all phases in which workers are exposed to HHPA a restriction targeted at the intermediate use of HHPA together with an authorization for all other uses could be considered. Therefore, a combination of authorization and restriction through article 57f could be followed best to reduce risks to HHPA exposure.

For control of the health risks by the use of MDI several options seem useful. Setting an OEL could reduce the exposure to MDI. However, it is questionable whether an OEL would protect downstream users in SME and on construction sites as monitoring and the enforcement of such OEL would be very time consuming and difficult. A restriction dossier could be considered to restrict the use of MDI for processes or use where there is a clear risk. It would be difficult and complex to specify the exact conditions and applications for which the highest unacceptable risks for workers would occur. Furthermore, a restriction dossier might be difficult to compile due to the lack of suitable alternatives as generally other isocyanates will be used. Identifying MDI and preferably other isocyanates as well as a SVHC and subsequent inclusion of MDI on Annex XIV would force the industry to search for alternatives and would give the best incentive to tackle the risk posed by MDI. Therefore, an Annex XV dossier for the identification of a substance as a substance of equivalent concern according to article 57f is considered the best option.

Several instruments can be utilized to control the health risks related to the use of isoeugenol. Especially in the case that the substance will qualify as potent sensitizer, as we expect, harmonized C&L may prove a good RMO. Placing isoeugenol on the candidate list for authorization is considered useful as an example for the exploration of the 57(f) route for a potent skin sensitizer with widespread use and a known cause of an increasing incidence in cases of contact dermatitis. In addition, restrictions are also deemed rightful as a way to formalize and extend the voluntary industry measures and existing labelling regulations.

6

Discussion

The risk analysis of sensitizing substances showed that both workers and consumers are exposed to a large number of sensitizing substances on a daily basis. The risks of becoming skin or respiratory sensitized are considered to be high with possibly severe health effects, such as contact dermatitis and occupational asthma. The registration of the health effects in workers does not seem to underline this observation, which is most likely due to poor recognition of the causal relation between exposure to sensitizers and the observed effects. In addition, the toxicological mechanisms of sensitization are complex and identification of sensitizing substances can be troublesome. A reliable and sufficiently protective QRA for naïve subjects is therefore difficult to establish, possibly resulting in rather arbitrary protective measures.

REACH and other current legislation do not provide clear instructions on how to deal with sensitizers. However, under REACH article 57(f) it was considered by us that possibly respiratory and skin sensitizers could fall under the description of that article. Other risk management options were taken into account as well when performing the risk management options analyses. Firstly, a selection of the most prudent substances had to be made, to say being prioritized, according to set criteria. As CMR substances categories 1A and 1B are already covered under REACH and thus sensitizers also having CMR properties were left out for consideration. It is noted however, that any legislation resulting from its CMR properties do not necessarily cover the risks of becoming sensitized.

Therefore, for three sensitizing substances (hexahydrophthalic anhydride (HHPA), methylenediphenyl diisocyanate (MDI) and isoeugenol) the risk management options were explored (RMO not shown due to confidentiality issues). The identification of the substances as sensitizers and their use in processes are crucial for the RMO. Risks have to be identified for several worker populations and in case of isoeugenol also for the general public. Setting OELs or using classification and labelling as tools to manage the risk might suffice for part of the population, but do not possibly reach all populations one desires to protect as exposure up to certain limits (OEL) remain possible, which does not necessarily protect all workers. This can be explained by the fact that risk based limits for sensitizers are difficult to derive. Identification of sensitizers as substance of equal concern according to the article 57(f) route makes it possible to follow the authorization or restriction routes, or both to cover intermediate uses, under REACH. This makes it possible to really address the identified risks of sensitizers for the processes and uses in the professional, industrial and consumer sector.

In conclusion, based on the three cases it has been shown that the article 57(f) route can be an appropriate route for risk management of sensitizers.

7

References

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA and Safford B (2008). Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. *Regul. Toxicol. Pharmacol.* 52, 3-23.

Baars AJ, Pelgrom SMGJ, Hoeymans N, Van Raaij, MTM (2005). Health effects and burden of disease due to exposure to chemicals at the workplace - an exploratory study [in Dutch]. RIVM report 320100001.

Beliauskienė A, S. Valiukeviciene, W. Uter and A. Schnuch (2011). "The European baseline series in Lithuania: Results of patch testing in consecutive adult patients." 25(1): 59-63.

Bendewald MJ, SA Farmer and MD Davis (2010). "An 8-year retrospective review of patch testing with rubber allergens: the Mayo Clinic experience." *Dermatitis* 21(1): 33-40.

De Jong WH, Arts JH, De Klerk A, Schijf MA, Ezendam J, Kuper CF, Van Loveren H. (2009). Contact and respiratory sensitizers can be identified by cytokine profiles following inhalation exposure. *Toxicology*. Volume 261, Issue 3, 10 July 2009, 103-111.

Dekkers S, EA Preller, AJ Baars, J. Marquart and MTM van Raaij (2006). Identificatie van belangrijke beroepsgroepen en stoffen bij het ontstaan van gezondheidseffecten en ziektelast door blootstelling aan stoffen onder arbeidsomstandigheden Bilthoven, Rijkstinstituut voor Volksgezondheid en Milieu. RIVM rapport 320506002.

Diel F, Fischer M, Kamsteeg J, Schubert H, Weber K-M. (AVE e.V./KEAC Working Group) (2006) List of REACH allergens. *Umwelt & Gesundheit* 2.

Geier J. (2010). "Contact allergy due to epoxy resins from the perspective of the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG) Kontaktallergie gegen Epoxidharze aus der Perspektive des Informationsverbundes Dermatologischer Kliniken (IVDK) und der Deutschen Kontaktallergie-Gruppe (DKG)." 70(1-2): 7-9.

Geier J, H Lessmann, H Dickel, PJ Frosch, P Koch, D Becker, U Jappe, W Aberer, A Schnuch and W Uter (2004). "Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG)." *Contact Dermatitis* 51(3): 118-130.

Goon AT, M Isaksson, E Zimerson, CL Goh and M Bruze (2006). "Contact allergy to (meth)acrylates in the dental series in southern Sweden: simultaneous positive patch test reaction patterns and possible screening allergens." *Contact Dermatitis* 55(4): 219-226.

Isaksson M, A Inerot, C Lidén, M Matura, B Stenberg, H Möller and M Bruze (2011). "Multicentre patch testing with a resol resin based on phenol and formaldehyde." 65(1): 34-37.

Kimber I, Basketter DA, Gerberick GF, Dearman RJ. (2002). Allergic contact dermatitis. *International Immunopharmacology* 2, 201-211.

Lessmann H, W Uter, A Schnuch and J Geier (2009). "Skin sensitizing properties of the ethanolamines mono-, di-, and triethanolamine. Data analysis of a multicentre surveillance network (IVDK) and review of the literature." *Contact Dermatitis* 60(5): 243-255.

NCvB (2007). Signaleringsrapport Beroepsziekten '07. Amsterdam, Netherlands Centre for Occupational Diseases

NCvB. (2011). "Nieuwsbrief Peilstation Arbeidsgebonden Longaandoeningen juli 2011." 2011, from <http://www.beroepsziekten.nl/node/1556>.

NECOD. (2008). "Nieuwsbrief ADS juli 2008 ", 2011, from <http://www.necod.nl/content/recentste-nieuwsbrief-ads-pdf>.

NECOD. (2011). "Nieuwsbrief ADS april 2011 ", 2011, from <http://www.necod.nl/content/recentste-nieuwsbrief-ads-pdf>.

Nethercott JR. (1990). "Practical problems in the use of patch testing in the evaluation of patients with contact dermatitis." *Curr Probl Dermatol* 2: 4.

Santos T, R Gadea and T Musu. (2011). "Proposal of Sensitizers for SVHCidentification under 57f: Contribution to the practical` implementation of REACH, in particular by proposing sensitizers as Substances of Very High Concern (SVHC) which, from a union perspective, should have priority for inclusion in the Candidate List and potentially in the Authorisation or Restriction Lists.", 2011, from <http://www.istas.net/web/abreenlace.asp?idenlace=8685>.

Santos T, D Romano and R Gadea. (2010). "Trade Union Priority List for REACH Authorisation." Version 2.0. 2011, from <http://www.etuc.org/IMG/pdf/TUListREACH.pdf>.

Schlede E, Aberer W, Fuchs T, Gerner I, Lessmann H, Maurer T, Rossbacher R, Stropp G, Wagner E, Kayser D. (2003) Chemical substances and contact allergy--244 substances ranked according to allergenic potency. *Toxicology*. 2003 Dec 1;193(3):219-59.

Schuur AG, Preller L, ter Burg W, Kroese D, van Engelen JGM, Goldbohm-Bausch S, van Kranen H, Kramers PGN, Van Raaij MTM (2008). Health impact assessment of chemicals in consumer products. The effect of mitigation measures. RIVM report 320015001.

Teik-Jin Goon A, M Bruze, E Zimerson, CL Goh and M Isaksson (2007). "Contact allergy to acrylates/methacrylates in the acrylate and nail acrylics series in southern Sweden: Simultaneous positive patch test reaction patterns and possible screening allergens." 57(1): 21-27.

Ter Burg W, Wijnhoven SWP, Schuur AG. (2010). Observations on the methodology for quantitative risk assessment of dermal allergens. RIVM report 320015003.

Terwoert J, Maas J, Siegert H, Wieland P. (2009). Dossier Irriterende en sensibiliserende stoffen.

Uter W, J Hegewald, W Aberer, F Ayala, AJ Bircher, J Brasch, PJ Coenraads, MLA Schuttelaar, P Elsner, M Fartasch, V Mahler, A Belloni Fortina, PJ Frosch, T Fuchs, JD Johansen, T Menné, R Jolanki, B Krêcisz, M Kiec-Swierczynska, F Larese, D Orton, A Peserico, T Rantanen and A Schnuch (2005). "The European standard series in 9 European countries, 2002/2003 - First results of the European Surveillance System on Contact Allergies." 53(3): 136-145.

Verstraelen S, Bloemen K, Nelissen I, Witters H, Schoeters G, Van Den Heuvel R. (2008). Cell types involved in allergic asthma and their use in in vitro models to assess respiratory sensitization. *Toxicol In Vitro*. Sep;22(6):1419-31.

VTv, 2010. www.vtv2010.nl (access date 15 Nov 2011).

Wijnhoven SWP, J Ezendam, AG Schuur, H van Loveren and JGM. van Engelen (2008). Allergens in consumer products. Bilthoven, Rijksinstituut voor Volksgezondheid en Milieu RIVM rapport 320025001/2008.

Wilkinson DS, S Fregert and B Magnusson (1970). "Terminology of contact dermatitis " *Acta Dermato-Venereol* 50(287-292).

Annex 1: Other legislative frameworks

In this paragraph legal texts, with respect to sensitizers and relevance to workers and consumers, from a number of legal frameworks will be given. The different frameworks are described briefly as the focus lies on RMO under REACH following the 57(f) route.

Occupational Safety and Health Decree (Arbeidsomstandighedenbesluit).

In general, the legislative framework is set to protect the workers against any type of (chemical) risk and does not specifically mention sensitizers. However in case of young employees, the Occupational Safety and Health Decree does state that young employee must not be exposed to sensitizers, according to the criteria described in the Environmental Management Act (milieubeheer), article 9.2.3.1.

General Product Safety Directive 2001/95/EC

Sensitizers are implicitly included in the General Product Safety Directive 2001/95/EC where it is stated that it is prohibited to sell products of which might be anticipated that they are a danger to the safety of or health of humans.

The list with classified chemicals (Annex I of Directive 67/548/EEC) is used by some other Directives, resulting in a ban or a specific concentration limit of the use of substances classified. It is included in e.g. the Biocides Directive, the Preparations Directive (1999/45/EC), the Limitations Directive (76/769/EEC) (now REACH annex XVII), the Cosmetics Directive (76/768/EEC) and the Toys Directive (88/378/EC) of which a new legal text will be implemented in 2013. The Biocides Directive, Preparations Directive and Cosmetics Directive are discussed below.

Biocide Directive

Toxicological information regarding sensitization should be considered in biocide dossiers. Active ingredients cannot be listed on annex IA (biocides with low-risks) of the Biocide Directive in case the ingredient is considered a sensitizer according to the Dangerous Substances Directive 67/548/EC. Annex VI, article 29 of the Biocide Directive further states that "With respect to skin sensitization and respiratory sensitization, in so far as there is no consensus on the possibility of identifying a dose/concentration below which adverse effects are unlikely to occur in a subject already sensitised to a given substance, it shall be sufficient to evaluate whether the active substance or substance of concern has an inherent capacity to cause such effects during use of the biocidal product." The Biocide Directive is aimed to protect both professionals and consumers.

Cosmetics Directive 76/768/EEC

Cosmetic products are exempted from the General Products Safety Directive in a sense that these products are regulated in the Cosmetics Directive. A substance must be allowed to be used in cosmetics (given certain conditions). Annex II of this Directive lists substances which are not allowed in cosmetics, with the exception of certain substances in natural extracts. In Annex III of this Directive, substances which use is restricted in cosmetic products, are listed. On this list are mentioned for example 26 registered fragrance materials known to

have skin sensitizing potential. The restriction, however, involves the labelling of the product above certain concentration limits. It does not restrict the use of the materials.

Examples of legislative measures

Workers

In the workplace efforts must be taken by employers to provide a safe working environment according to the Occupational Safety and Health Decree. In practice, this often means that substances are mentioned in safety data sheets and wearing personal protection is advised or mandatory. The effectiveness of such measures is sometimes questionable. Protective equipment for skin sensitization, i.e. gloves, can worsen skin effects instead of providing protection. The skin is hydrated and softened when wearing gloves. Incorrect use of gloves or unsuitable gloves (substances can penetrate the glove) will not protect the skin in those cases. Moreover, compliance with work regulations is often low when health effects do not immediately occur as may be the case for sensitization effects.

In the occupational setting many work agreements or guidance on how to work safely with sensitizers have been drawn up in branch organisations such as working agreements amongst bakers, hair dressers, health care (for cleaners and disinfectants), in the residential sector (house design, furniture), and in the construction sector. Substance specific restrictions are also applicable to the occupational sector, where, for example, the use of chromates in cement was reduced. This measure proved to be successful to reduce the sensitization due to chromates in cement. Nevertheless, recently sensitization to chromates has increased again due to its use as tanners of leather fabric. This is possibly caused by poor communications between the different industries and the lack of a widely accepted toxicological level based concentration limits (Beroepsziekten in cijfer 2010). Because toxicological thresholds are difficult to establish, most legislative measures are therefore predominantly driven by the reduction of exposure as much as possible. A similar approach, i.e. reduction of exposure, was followed to reduce isocyanates related respiratory sensitization, but till today no ban on these substances have been proposed.

Consumers

Most measures to protect the consumers have been implemented as annexes in existing legislation, mostly in the general products safety directive, or will be implemented under REACH. Some specific directives exist such as the Nickel Directive. The migration limit for nickel is set in such way that naïve subjects are protected and reduce the number of new cases of allergic contact dermatitis as much as possible. It was estimated that the reduction of causes would amount to 30%. The Nickel Directive, however, does not necessarily protect previously sensitized subjects (Schuur et al. 2008).

In summary

Classification and labelling and legislation are reliant on the identification of sensitizers. As discussed previously, identification of (new) sensitizers is difficult.

Furthermore, establishing threshold values and sensitizing potency is even more difficult. As these keystones are often lacking it is very difficult to take legislative measures. In practice, 'standard' legislation may not suffice and substance specific measures are required, e.g. isocyanate use in the occupational sector and the Nickel Directive, amongst other substance specific measures.

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