Scientific Committee on Consumer Safety

SCCS

Memorandum on use of Human Data in risk assessment of skin sensitisation

The SCCS adopted this memorandum at its 12th Plenary meeting

on 15 December 2015

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MEMORANDUM

1. INTRODUCTION

Skin exposure of humans to contact allergens may cause contact allergy. Contact allergy, as defined by a positive patch test, is seen in 27% of the general population of Europe (Diepgen *et al.,* 2015) and may be caused by consumer as well as occupational exposures.
The development of contact allergy has two phases: an induction phase, also called the sensitisation phase, and the elicitation phase. In the induction phase, T-lymphocytes of the immune system are specifically activated by a contact allergen and generally circulated in the organism. In the induction phase, both effector and memory T lymphocytes are formed. In the elicitation phase upon re-exposure to the allergen, memory T lymphocytes will be activated and migrate to the allergen exposed skin area, where they will release cytokines and mediate cellular killing. This will lead to skin inflammation presented as allergic contact dermatitis, which is the disease (Martin S., 2015).

Contact allergy develops after months to years of exposure and is a chronic/repeat dose toxicity end-point, except for rare events, when exposure occurs to extreme doses of contact allergens (e.g. spills at the work place). In such cases, sensitisation may occur from a single exposure.

Contact allergy is diagnosed by patch testing (see 2.1). In the population only a fraction of all those sensitised know what they are allergic to, since only a part of the population has been diagnosed by patch testing (Schnuch *et al.,* 2002; Thyssen JP *et al.,* 2009). Further, most of those who have been patch tested have only been tested with a limited set of allergens, the baseline series, as only specialised clinics at universities perform testing with other substances. Information about the presence of ingredients in cosmetic products is of great help for the prevention of allergic contact dermatitis in those consumers who are informed, and for diagnosis. Restrictions in contents of allergens provide prevention, which is independent of the situation and abilities of the individual and therefore more likely to be of benefit for a wider group of sensitised individuals.

According to the EU Cosmetic Regulation[1] it will be necessary to initiate regulatory measures on substances identified by the SCCS as likely to cause allergic reactions and/or impose certain conditions concerning them. In order to ensure that the 'end user', meaning either a consumer or professional using the cosmetic product, is adequately informed, the presence of these substances should be mentioned in the list of ingredients and consumers' attention should be drawn to the presence of these ingredients. This information should improve the diagnosis of contact allergies among consumers and should enable them to avoid the use of cosmetic products which they do not tolerate. For substances which are likely to cause allergy to a significant part of the population, other restrictive measures such as a ban or a restriction of concentration should be considered.

This memorandum is an update of the SCCP/0919/05 Memorandum on Classification and categorisation of skin sensitisers and grading of test reactions concerning human data. For interpretation of animal data, SCCP/0919/05 should be considered.

The scope of this memorandum is to clarify issues essential for interpretation of human data and dossier results in risk assessment of contact allergens/contact sensitisation.

1 http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02009R1223-20150416&from=EN

2. TYPES OF HUMAN DATA

Human data concerning contact allergy consists of epidemiological studies e.g. in the general population, diagnostic patch test studies in eczema patients, case reports and experimental elicitation and induction studies, as outlined in Table 1.

Sensitisation vs. Elicitation

All these types of studies in humans concern sensitisation and elicitation. The patients have become sensitised, not in an experiment but by real-life exposures.
In the experimental induction studies, induction of sensitisation is made under controlled circumstances; however the result of the test depends on provocation of an elicitation response. In case the dose used for elicitation is too low, then the test will be false-negative.
The experimental elicitation studies (dose-response and repeated open application tests) are performed in already sensitised patients; the end-point in these studies is the dose of allergen and exposure conditions which gives an elicitation response i.e. the disease allergic contact dermatitis.

Table 1. Main types of studies in humans (modified/adopted from ECHA, June 2015)

Type	**Subjects**	**Methodology**	**Comments**
Epidemiological studies	General population, occupational groups or other selected groups.	Investigation with questionnaires or diagnostic patch tests in samples of individuals with and without symptoms.	General population studies are rare. See section 2.1
Clinical studies based on diagnostic patch test studies	Eczema patients attending dermatological clinics for diagnosis; reported from individual clinics or networks of dermatologists	Diagnostic patch testing. Aggregated data reported as numbers of contact allergy cases to a particular substance in relation to the whole group tested.	Primary source of information concerning occurrence of sensitisation, see section 2.1.1 and annex 2. May provide information on causal exposures, see section 2.1.1
Case reports	Eczema patients diagnosed with contact allergy to a particular substance	Individual cases reported. Usually in more detail than in larger data-sets.	Reports on individual cases are often the first reports made. Useful in early detection of skin sensitisers and classification, see annex 1.
Experimental dose-response elicitation studies.	Sensitised eczema patients proven by a positive diagnostic patch test.	Dose-response patch tests or repeated open application tests (ROAT)	Several protocols exist. Provides an indication of safe limits of exposure for induction as well as elicitation, see section 2.2
Experimental induction tests, such as the Human Repeated Insult Patch Test (HRIPT) and the Human Maximization Test (HMT)	Healthy volunteers	Induction of sensitisation is performed by repeated applications of a skin sensitiser. Proof of sensitisation is made by an elicitation response.	No longer performed for EU regulations due to ethical reasons, but historical data may exist. See section 2.3.

2.1 Epidemiological and clinical studies based on diagnostic patch testing

Diagnostic patch testing
Diagnostic patch testing is the procedure used for the detection of contact allergy to substances in humans. Patch testing is performed in patients with dermatitis suspected of having contact allergy. It may also be used for epidemiological studies to examine

certain groups for skin sensitisation e.g. occupational groups or samples of the general population, whereof some may or may not have symptoms of allergic contact dermatitis.

The test procedure is standardised. Test substances in the European baseline series for patch testing (Johansen JD *et al*., 2015) are well established concerning concentration and vehicle. Other test substances used may include commercially available screening series, other appropriately diluted substances and formulations, solid materials and products. Patch testing by a dermatologist requires experience.
Exposure: 2 days
Reading: recommended on day 2 and 3 or 4 and 5 to 7 after application of the test patches.
The grading scale and criteria are shown in Table 2.

Table 2: Grading scale for the evaluation of diagnostic patch test reactions*

Symbol	**Morphology**	**Assessment**
-	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

*Johansen JD *et al*., 2015

A reaction fulfilling the criteria of +, ++ or +++ is regarded as positive and the patient is diagnosed with contact allergy. A positive patch test should result in investigation of the patients' environment for exposures to the substance in question. In case exposures to the allergen are identified and have caused or contribute to the current disease, patients are diagnosed with allergic contact dermatitis.

Basic quality criteria
A number of basic quality criteria in clinical patch testing have been developed as part of a previous Opinion of the SCCS (SCCS/1459/11), which should be considered in assessment of data:
- Adherence to international patch test guidelines.
- Material(s) tested should be characterised.
- Total number of patients tested must be given.
- Patient selection should be described.
- Relevance may be demonstrated either on a case-by-case basis, following pertinent guidelines, or in terms of a significant epidemiological association between sensitisation and exposure or valid markers of exposure.

Concerning relevance, it is ideally based on comprehensive knowledge of exposures.
Only cosmetic products have full ingredient labelling. An exception is for fragrances, where only 26 allergens out of the total 2600 fragrance compounds potentially used in cosmetics have to be declared.
The cosmetic ingredient labelling is of immense support in diagnosis.
However, exposure to substances not listed on a product ingredient label is difficult to trace, except in rare cases where elaborate chemical analyses are feasible. Thus, even though relevance is not reported in studies, the patch test data can be useful in assessing the impact of the substance in relation to contact sensitisation.

Use of epidemiological and clinical diagnostic patch test data

Identification of contact allergens

The data from diagnostic patch testing can be used to identify a substance as a contact allergen (skin sensitiser) (Basketter DA *et al.,* 2015). Minimum criteria have been developed for this as part of the SCCS Opinion on Fragrance allergens in cosmetic products (SCCS/1459/11). The criteria for established and likely contact allergens in humans is included in this memorandum as Annex 1, and also published as a scientific publication (Uter W *et al.,* 2013).

Frequency of sensitisation

Clinical data from diagnostic patch testing in patients may provide information concerning the size of problems of contact allergy to a substance (Basketter DA *et al.*, 2015). In the SCCS Opinion on fragrance allergens in cosmetic products (SCCS/1459/11), the substances were divided into 4 groups according to the absolute number of published cases. Substances with equal to or more than 100 published cases[2] were identified as 'allergens of special concern'. In the ECHA Guidance on the Application of the CLP Criteria (ECHA November 2013, updated June 2015) this was adopted as one of the criteria for 'high frequency of sensitisation' and a subcategory 1A sensitiser (ECHA November 2013, updated June 2015).

Results from clinical investigations are often presented as percent of patients with a positive patch test reaction out of all patients tested to the substance within a certain time frame. A substance causing reactions in 0.5%-1% or more of consecutively patients is regarded a significant sensitiser and qualifies for inclusion in the baseline series (Bruze M *et al.,* 1999).
In the ECHA Guidance on the Application of the CLP Criteria (ECHA November 2013, updated June 2015) if more than 1% of consecutively patch-tested patients are diagnosed with contact allergy to a substance, this is considered of high concern (Table 3).
General population studies are rare. A sensitisation rate of ≥ 0.2% to a substance in the general population is considered high frequency by ECHA (Table 3).

Table 3: Relatively high or low frequency of occurrence of sensitisation to chemicals* (ECHA, 2015)

Human diagnostic patch test data	High frequency	Low/moderate frequency
General population studies	≥ 0.2 %	< 0.2 %
Dermatitis patients (unselected, consecutive)	≥ 1.0 %	< 1.0 %
Selected dermatitis patients (aimed testing, usually special test series)	≥ 2.0 %	< 2.0 %
Work place studies:		
1: all or randomly selected workers	≥ 0.4 %	< 0.4 %
2: selected workers with known exposure or dermatitis	≥ 1.0 %	< 1.0 %
Number of published cases	≥ 100 cases	< 100 cases

* Only one or two types of information may be sufficient for sub-categorisation.

2 The number of published cases is highly likely to underestimate the size of a problem due to underreporting, as it is difficult to publish such observations when a problem is already described.

The frequency is seen in relation to the degree of exposure to categorise sensitisers into subcategory 1A/1B or category 1 (see Annex 2 of this memorandum) (ECHA, June 2015).

It is also possible to estimate from patch-test data the number of people in the general population who are sensitised to a substance by back-calculations and based on the annual sales of patch tests in a country as well as a number of correction factors, e.g. spill, previously tested patients etc. (Thyssen JP *et al.,* 2009).

Causal exposures
A positive patch test leads to investigation of the patient's environment for exposures to the substance in question. Exposures which have caused or contributed to the patient's eczema disease are recorded, as part of the standard investigation (Johansen JD *et al.,* 2015). These data can provide important information on exposure/product types involved in allergic contact dermatitis e.g. Uter W *et al.,* 2007; Aerts O *et al.,* 2015.
This is information that has been used in risk management of several allergens and formed the basis of restrictions of skin sensitisers for prevention of disease (such as nickel in prolonged contact with the skin (REACH Regulation 1907/2006: restrictions, entry 27), chromium VI in cement (REACH Regulation 1907/2006: restrictions, entry 47) and leather products (REACH Regulation 1907/2006: restrictions, entry 47), dimethyl fumarate in articles (REACH Regulation 1907/2006: restrictions, entry 61) and methyldibromo glutaronitrile (SCCP/0863/05) see also section 3.1).

2.2 Experimental elicitation in human dose-response and repeated open application tests

Dose-response patch test
Patients sensitised to a substance, demonstrated by a positive patch test, may be retested with a serial dilution (2, 3 or 10 fold dilution step) of the substance.
The substance is applied in dilution in patch test chambers. Exposure time is 2 days. The vehicle is usually water or ethanol, sometimes petrolatum and should be included as control. A reading can be done for the diagnostic patch test (see 2.1), but a more fine-tuned scale may be used (Hindsén M and Bruze M, 1998; Fischer LA *et al.,* 2007). Between 10 and 30 individuals are included in the study. The data is used to define effective concentrations that elicit a reaction in 10% (ED10), 50% (ED50) or 90% (ED90) of the subjects based on the dose-response curve.

The ED10 values have been used as the point of departure to set safe levels of exposure to allergens that have caused a high frequency of sensitisation (see Annex 3), e.g. fragrance allergens of special concern (SCCS/1459/11).
Based on experience, limitations in exposure based on elicitation thresholds will, apart from helping the sensitised consumer/worker, also significantly reduce the risk of induction. This is the case for nickel allergy, where the restrictions in the EU nickel directive are based on elicitation threshold (ED10), leading to a significant reduction in new cases of sensitisation in young women (Thyssen *et al.,* 2009; Garg S *et al.,* 2011) and in a reduction in morbidity (Thyssen JP *et al.* 2009). Another example is the restriction of chromium VI in cement (Zachariae C *et al.,* 1996; Geier J *et al.,* 2011).

Repeated Open Application Test (ROAT)
In patch testing the exposure is made under occlusion for 2 days. These exposure conditions are not comparable to actual exposures occurring in the daily life or working environment of the patient, which often involve long-term, repeated and low-dose contact with the allergen. However, procedures such as the repeated open application test (ROAT) or provocative use test much better reflect actual exposure by daily repeated open applications at relevant skin areas with solutions/product matrices of allergens in

realistic concentrations (Johansen JD *et al*., 2015). Depending on the product type and allergen studied, the exposure can be 1-5 times daily usually for 2-3 weeks (Yazar K *et al.,* 2015; Jorgensen PH *et al.,* 2007; Nielsen NH *et al.,* 1999). A standardised scale is used for assessing reactions (Johansen JD *et al*., 2015). The group size is 10-20 sensitised individuals (patch test positive eczema patients) and a similar number of non-sensitised control persons.
The dose per area per application required to elicit a reaction in the ROAT is lower than the dose per area required to elicit a reaction in the patch test. A factor of around 30 between the dose in the patch test and the ROAT giving a response has been identified for two non-volatile allergens (Fischer LA *et al.,* 2009).
Safe levels identified with this method are directly relevant to exposures and disease. A negative test is a strong indication that the dose will be safe for most individuals concerning both induction and elicitation.

2.3 Predictive tests in humans

Predictive human sensitisation tests involve attempts to induce sensitisation in healthy individuals, a permanent immunologic condition. Due to serious ethical considerations, the SCCS shares the opinion of the former SCCNFP that predictive human sensitisation tests of potentially cutaneous sensitising cosmetic ingredients or mixtures of ingredients should not be undertaken (SCCNFP/0120/99). Historical data may be considered.

A range of human test methods for predicting skin sensitisation potential has been developed (overview in Marzulli FN and Maibach HI,1976) and has been widely used by industry, while experience in academia with these tests is scarce. In brief, a suspected contact allergen is repeatedly applied to the skin of a group of healthy volunteers (a panel size 25 -200). In some test systems the skin is pre-irritated (eg. Human Maximization Test) and in others not (Human Repeated Insult Patch test) prior to repeat application of a known or suspected skin sensitiser. The substance is applied repeatedly to the arm, back or thigh over weeks, followed by a rest period of 1- 3 weeks, prior to challenge.

A variation of the HRIPT, a modification of the original Draize procedure, is named 'Confirmatory HRIPT' (Politano VT and Api AM, 2008) and is used to test the concentration that is thought to induce no dermal sensitisation in healthy human volunteers. This dose is usually based on animal data. There is no experience with this test outside industry: its sensitivity and predictive value is unclear. The concentrations/doses used in the test may cause sensitisation in the healthy volunteers.

The possible results of these predictive tests depend both on the concentration (dose) used in the inductions and in the challenge (elicitation) phase.

In the ECHA guidance on application of the CLP Criteria (ECHA, June 2015), historical data from HRIPTs or HMT classify a substance as a subcategory 1A skin sensitiser based on a positive response at ≤ 500 μg/cm^2 as the induction threshold.

3. QUANTITATIVE RISK ASSESSMENT FOR SKIN SENSITISATION (QRA)

A quantitative risk assessment approach for allergens in consumer products has been developed for fragrance ingredients to prevent induction. It follows the same four fundamental steps as identified for general toxicology risk assessment: a) hazard identification b) dose-response assessment or hazard quantification c) exposure

assessment and d) risk characterisation (Api AM *et al.,* 2008). The data to feed the QRA is animal data and/or results from predictive tests in humans (see 2.3).

The SCCP adopted an Opinion concerning Dermal Sensitisation Quantitative Risk Assessment (SCCP/1153/08). In this Opinion, a number of critical points were raised e.g. lack of consideration of aggregate exposures. A new version of the QRA has been developed and is under evaluation. The QRA for skin sensitisation is based on predictive tests and will be useful for substances that are new or where no or only little information exists concerning contact allergy in consumers.
However, in situations where the adverse health effects have already occurred in humans, it is appropriate to consider the epidemiological and diagnostic patch test data already available as these represent the relevant end-point at which preventive actions are to be directed.

4. USE OF HUMAN TEST RESULTS IN EUROPEAN LEGISLATION-OVERVIEW

A brief overview of the use of human data for assessing skin sensitisation risk in EU chemicals regulations, CLP regulation, REACH regulation, Biocidal products regulation (BPR), Plant protection products regulation, and Detergents regulation is given in Table 4 and more details can be found in Annex 3.

In these chemical regulations data from humans, when available and reliable, are taken into account and should be given priority over data derived from animal studies, when they demonstrate hazards not identified from animal studies.

Table 4. Information on human data or human health aspects on skin sensitisation in EU chemicals regulations on CLP, REACH (registration and restrictions), Biocidal products, Plant protection products, and Detergents.

Classification as skin sensitiser (H317) and subcat 1A, 1B	The human and animal criteria for classification of skin sensitisers are given in the CLP regulation and are further explained in Guidance on application of the CLP criteria. The different regulations i.e. REACH, Biocidal products regulation (BPR), Plant protection products regulation (PPPR) give reference to these. In the Detergents regulation, reference is given to the Dangerous Substances Directive, which preceded CLP.
Use of human data	It is generally stated that available human data concerning skin sensitisation shall be used for the regulation of concern.
Types of human data	Available data specified in the CLP regulation and in the guidance document on application of the CLP criteria: positive patch test data from clinics; epidemiological studies (eczema patients, occupational groups, general population); positive data from experimental studies (dose-response in sensitised individuals; see below concerning induction studies); episodes of allergic contact dermatitis; severity of reaction may also be considered.
Endpoints	It is generally explained that human data on skin sensitisation largely is elicitation data, and that induction data on skin sensitisation is scarce.
Testing in humans and ethical aspects	It is generally stated that human testing not shall be performed for the purpose of these regulations. It is also specified that new experimental testing for hazard identification in humans (induction studies), such as human repeat insult patch test (HRIPT) and human maximisation test (HMT), is not acceptable for ethical reasons. Historical data may be used.
Thresholds for induction and elicitation	It is explained that the dose required to induce sensitisation usually is greater than that required to elicit a reaction in a previously sensitised subject; therefore the dose-response relationship for the two phases differs.
Restrictions	Restrictions of skin sensitisers by REACH aim at prevention of induction (sensitisation) and elicitation (allergic contact dermatitis). Current restrictions cover chromium VI in cement, chromium VI in leather, dimethylfumarate in articles, and nickel in prolonged

	contact with the skin.
Information requirements for detergents	All preservatives need to be identified on the label, irrespective of concentration; and sensitising fragrances, according to the Cosmetics Regulation, need to be identified when above 0.01%.
Information requirements for mixtures (chemical products)	It is mandatory, according to CLP regulation (Annex II special rules for labelling and packaging of certain substances and mixtures to give labelling information on the presence of chromium (VI) in cement and cement products (EUH203); isocyanates (EUH204); epoxy resins (EUH205); and of all classified skin sensitisers (EUH208) in unclassified mixtures: 'Contains (the name). May produce an allergic reaction.'

5. CONCLUSION

Results from tests in humans are currently used in many types of chemical regulations for assessing skin sensitisation potential and risk assessment. Several types of data exist, but data from diagnostic patch testing is the most used in current regulations.
Criteria for established contact allergens in humans are available (annex 1).
Under CLP regulation criteria for identification of substances with 'a high frequency of sensitisation' is present (table 3), which is in accordance with criteria used to identify allergens of concern by SCCS (SCCS/1459/11). According to the Cosmetic Regulation, for substances which are likely to cause allergy to a significant part of the population, restrictive measures such as a ban or a restriction of concentration should be considered.

Restrictions of skin sensitisers by REACH aim at prevention of induction (sensitisation) and elicitation (allergic contact dermatitis). The data concerning induction thresholds in humans are scarce, and if available, circumstantial. Results on threshold responses in sensitised patients and exposures have formed the basis of decision-making concerning several restrictions under REACH. It has a direct relevance to the end-point: allergic contact dermatitis. It is generally accepted that levels of allergens that will protect (the majority of) sensitised individuals against allergic contact dermatitis (elicitation) will also be safe for induction.

The QRA for skin sensitisation is based on predictive tests and will, when finally developed and evaluated, be useful for substances, which are new or where no or only little information exists concerning contact allergy in consumers. In situations where a high frequency of contact allergy has already occurred in humans, it is appropriate to consider the epidemiological, diagnostic patch test and dose-response elicitation data already available as these represent the relevant end-point at which preventive actions are to be directed.

In the population, only a fraction of all those individuals sensitised know what they are allergic to, since very few have been diagnosed by patch testing. Information about content in cosmetic products is of great help for prevention of allergic contact dermatitis in those consumers who are informed, and for diagnosis. Restrictions of allergens of concern will be of benefit for a wider group of sensitised individuals, including those who have not been diagnosed.

In conclusion, available and reliable data and experience with regard to contact allergy to substances in humans, such as diagnostic patch test data and if relevant dose-response elicitation studies, should be taken into account for risk management. They should be given priority over data derived from animal studies, particularly when human data demonstrate hazards and risks not identified from animal studies.
The results of animal studies should be weighed against the results of data from humans and expert judgement should be used to ensure the best protection of human health when evaluating both the animal and human data. Guidance on interpretation of animal data for skin sensitisation can be found in SCCP/0919/05.

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7. ANNEX 1

CRITERIA FOR ESTABLISHED CONTACT ALLERGENS IN HUMANS. EXTRACT FROM (SCCS/1459/11):

Established contact allergen in humans

To qualify as an *established contact allergen*, the SCCS considers that *at least one* of the following two criteria must be met:

- At least two clinical series fulfilling the quality criteria from two different centres with cases of sensitisation, or at least three separate clinical series from different centres if a study, or studies, do not meet all quality criteria. (⟷ *sufficient human evidence present*)

or

- Case reports from at least two independent centres describing more than two patients altogether in whom clinically relevant contact sensitisation had unequivocally been proven (⟶ *sufficient human evidence present*)

or

- At least one clinical series fulfilling the quality criteria, together with at least one case report of clinically relevant contact sensitisation (⟶ *sufficient human evidence present*);

or

- Experimentally induced sensitisation (e.g. unequivocally positive human maximisation tests/repeated insult patch test) (⟶ *sufficient human evidence present*).

8. ANNEX 2

Classification of substances for skin sensitisation

Extract from ECHA, guidance on the application of the CLP criteria, version 4.1 June 2015

The information from table 3 (section 2.1.1) is in the CLP compared with exposure, as presented in table 3.4.2-c to arrive at a conclusion concerning sub-categorisation table 3.4.2.-d.

Table 3.4.2—c Relatively high or low exposure *

Exposure data	Relatively low exposure (weighting)	Relatively high exposure (weighting)
Concentration / dose	< 1.0% < 500µg/cm^2 (score 0)	≥ 1.0% ≥ 500µg/cm^2 (score 2)
Repeated exposure	< once/daily (score 1)	≥ once/daily (score 2)
Number of exposures (irrespective of concentration of sensitizer)	<100 exposures (score 0)	≥100 exposures (score 2)

* To achieve the exposure index (see text below) a response in each row is necessary.

The scores in Table 3.4.2—c represent weightings whose purpose is to enable an exposure index to be derived which best reflects our understanding of the relative importance of dose versus frequency of exposure. An additive exposure index of 1-4 equates to low exposure, whereas 5-6 reflects high exposure.
Careful consideration has to be given regarding the release (migration) of a sensitising substance from a solid object, and not the concentration. Ideally, skin exposure is best expressed in dose per unit area, but it is recognised that this data is often not available, hence concentration may be used as a surrogate indicator of exposure.

Table 3.4.2—d Sub-categorisation decision table

	Relatively low frequency of occurrence of skin sensitisation	Relatively high frequency of occurrence of skin sensitisation
Relatively high exposure (score 5-6)	Sub-category 1B	Category 1 or case by case evaluation
Relatively low exposure (score 1-4)	Category 1 or case by case evaluation	Sub-category 1A

9. ANNEX 3

Overview of the use of human data in EU chemicals regulations:

CLP, REACH regulation (registration and restrictions), Biocidal products regulation (BPR), Plant protection products regulation, and Detergents regulation.

Classification, Labelling and Packaging (CLP) Regulation 1272/2008

Purpose	**Type of human data**	**Ref.**
General	*Preamble (20):* "The manufacturer, importer or downstream user should also take into account historical human data, such as epidemiological studies on exposed populations, accidental or occupational exposure and effect data, and clinical studies. That information should be compared with the criteria for the different hazard classes and differentiations in order for that manufacturer, importer or downstream user to arrive at a conclusion as to whether or not the substance or mixture should be classified as hazardous." *Preamble (28):* "For the purposes of classification, data should not be generated by means of testing on humans. Available, reliable epidemiological data and experience with regard to the effects of substances and mixtures on humans (e.g. occupational data and data from accident databases) should be taken into account and may be given priority over data derived from animal studies when they demonstrate hazards not identified from those studies. The results of animal studies should be weighed against the results of data from humans and expert judgement should be used to ensure the best protection of human health when evaluating both the animal and human data." *Article 7, Animal and human testing:* "3. Tests on humans shall not be performed for the purposes of this Regulation. Data obtained from other sources, such as clinical studies, can however be used for the purposes of this Regulation."	1.
Classification as skin sensitiser (H317)	*3.4.2.2.4.1.:* "For classification of a substance, evidence shall include any or all of the following using a weight of evidence approach: a) positive data from patch testing, normally obtained in more than one dermatology clinic; b) epidemiological studies showing allergic contact dermatitis caused by the substance. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small; c) positive data from appropriate animal studies d) positive data from experimental studies in man (see section 1.3.2.4.7); e) well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic; f) severity of reaction may also be considered."	1.
Classification	*Table 3.4.2a - Types of Human Studies:* In summary: • Human repeated insult patch test (HRIPT) and Human maximization test (HMT); subjects: healthy volunteers; endpoint: induction of sensitisation; Not a clinical study and is only of historical relevance. New studies for this regulation are not permitted. • Diagnostic patch test; Eczema patients in dermatology clinics; Elicitation; Primary source of clinical information on the occurrence of skin sensitisation. • Dose response study (eg patch test serial dilution; repeated open application test); Sensitised individuals (usually from diagnostic patch tests); Elicitation; Not yet a standardised protocol, provides indication of the degree of sensitivity and safe limits of exposure. • Epidemiology study; Eczema patients, selected occupational groups, other selected groups, or general population; Elicitation; Large general population studies are scarce, focused studies in selected populations are more common, provide insights on frequency of sensitisation compared to exposure.	2.
Categorisation as 1, 1A, 1B	*3.4.2.2.2. Classification criteria for substances:* "For a newly identified skin sensitiser, which might also be a substance newly	2.

	introduced onto the market, or a substance not included in the baseline diagnostic patch test series, the high severity of responses might be used as an indication that classification as Category 1A is appropriate. For example, where the substance has caused: • Hospitalisation due to acute skin reaction • Chronic dermatitis (lasting > 6 months) • Generalised (systemic/whole body) dermatitis It should be noted that the severity/strength of diagnostic patch test reactions normally cannot be used for this purpose."	
Labelling for prevention of elicitation (allergic contact dermatitis)	*3.4.4.2. Additional labelling provisions:* EUH208 'Contains (name of sensitising substance). May produce an allergic reaction'.	2.
Labelling for prevention of elicitation (allergic contact dermatitis)	*Table 5. Obligatory supplemental labelling information pursuant to CLP Articles 25 and 32: EUH203 'Contains chromium (VI). May produce an allergic reaction' applies to cement and cement mixtures that contain, when they are hydrated, more than 0.0002% soluble chromium (VI) of the total dry weight of the cement.* EUH204 'Contains isocyanates. May produce an allergic reaction' applies to mixtures containing isocyanates, regardless of concentration. EUH205 'Contains epoxy constituents. May produce an allergic reaction' applies to mixtures containing epoxy constituents with an average molecular weight ≤ 700, regardless of concentration. EUH208 'Contains (name of sensitising substance). May produce an allergic reaction' applies when mixtures not are classified and the concentration is >1/10 of the concentration limit for classification.	3.

1. Regulation 1272/2008 - CLP Regulation http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1272-20150601&from=EN
2. Guidance on the Application of CLP Criteria. Version 4.1 June 2015. Part 3.4 http://echa.europa.eu/documents/10162/13562/clp_en.pdf
3. Guidance on labelling and packaging in accordance with the CLP Regulation http://echa.europa.eu/documents/10162/13562/clp_labelling_en.pdf

The REACH Regulation 1907/2006: registration

Area and purpose	Type of human data to be used	Ref.
Registration/Chemical safety report	*Annex I*: Reference is given to CLP for human health hazard assessment	4.
Classification as skin sensitiser	*R.7.3.3.2 Human data on skin sensitisation:* "Human data on cutaneous (allergic contact dermatitis and urticarial) reactions may come from a variety of sources: • consumer experience and comments, preferably followed up by professionals (e.g. diagnostic patch tests) • diagnostic clinical studies (e.g. patch tests, repeated open application tests) • records of workers' experience, accidents, and exposure studies including medical surveillance • case reports in the general scientific and medical literature • consumer tests (monitoring by questionnaire and/or medical surveillance) • epidemiological studies • human experimental studies such as the human repeat insult patch test (Stotts, 1980) and the human maximisation test (Kligman, 1966), although it should be noted that *new* experimental testing for hazard identification in humans, including HRIPT and HMT, is not acceptable for ethical reasons."	5.
Dose-response	*APPENDIX R. 8-10 Skin sensitisation p. 119-129* "Skin sensitisation is generally regarded as a threshold effect, although in practise it may be very difficult to derive a threshold and to set a DNEL." "…new experimental testing for hazard identification in humans, including HRIPT and HMT, is not acceptable for ethical reasons, therefore historical information from this type of studies will be available for a limited number of chemicals. Furthermore, the quality/reliability of the results from these studies should be carefully checked in particular in relation to the number of people tested (21)." "Potency of induction cannot be directly derived from human elicitation threshold data from diagnostic clinical studies (e.g. patch test dose-	6.

	response data, Repeated Open Application Test (ROAT)), however, a low elicitation threshold could indicate high potency and vice versa (21)." "If the DNEL exceeds the exposure, it can be assumed that at that specific exposure no induction in a non-sensitised person would occur. However it should be noted, that at this exposure level, a reaction in a previously sensitised person could still occur. "	

4. Regulation 1907/2006 – REACH Regulation http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1907-20150601&from=en
5. Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf
6. Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

The REACH Regulation 1907/2006: restrictions

Area and purpose	Restriction	Ref.
Chromium VI compounds /cement: Protection against induction and elicitation if already sensitised	*Entry 47* *Limit value:* Cr VI in cement 2 mg/kg (0.0002%)	7.
Chromium VI in leather articles: Protection against induction and elicitation in already sensitised	*Entry 47* *Limit value:* Cr VI in leather 3 mg/kg (0.0003%)	7. 8.
Dimethylfumarate (DMFu): Protection against induction and elicitation in already sensitised	*Entry 61* *Limit value:* DMFu in articles 0.1 mg/kg	7.
Nickel in prolonged contact with the skin: Protection against induction and elicitation in already sensitised	*Entry 27* *Limit values:* nickel release from post assemblies inserted into pierced parts of the human body: 0,2 µg/cm2/week; articles intended to come into direct and prolonged contact with the skin such as jewellery, wrist-watch, buttons, zippers etc: 0.5 µg/cm2/week	7.
Nickel in prolonged contact with the skin/Mobile telephones: Protection against induction and elicitation in already sensitised	*Entry 27 [663]:* Mobile telephones are covered by the restriction of nickel and shall comply with the conditions set in Entry 27 of Annex XVII to REACH, based on clinical case reports on allergic contact dermatitis.	9.
Nickel in prolonged contact with the skin/Definition of prolonged contact: Protection against induction and elicitation in already sensitised	*Entry 27 [935]:* The need for a definition of "prolonged contact" was identified based on clinical data showing continuously high prevalence of nickel allergy and nickel dermatitis. Human data used for the definition were patch test results from dose-response studies and testing with alloys, and skin exposure studies. Prolonged contact with the skin is defined as contact with the skin to articles containing nickel of potentially more than 10 minutes on three or more occasions within two weeks, or 30 minutes on one or more occasions within two weeks.	9. 10.

7. REACH list of restrictions http://echa.europa.eu/addressing-chemicals-of-concern/restrictions/list-of-restrictions
8. Regulation 301/201 on restriction of Cr VI in leather http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0301&from=EN
9. Questions and Answers http://echa.europa.eu/support/qas-support/qas
10. Prolonged contact with the skin - definition building for nickel http://echa.europa.eu/documents/10162/13641/nickel_restriction_prolonged_contact_skin_en.pdf

Biocidal Products Regulation (BPR) 528/2012

General	*Article 28:* Active substances give rise to concern where: (a) they meet the criteria for classification according to Regulation (EC) No 1272/2008 as: . . . skin sensitiser	11

BPR/human health/information	*8.3. Skin sensitisation*: The assessment of this endpoint shall comprise the following consecutive steps: 1. an assessment of the available human, animal and alternative data; 2. *in vivo* testing	11
BPR/human health/information	*Annex II, Information required, 8.3 Skin sensitisation:* Reference is given to Guidance on the Application of the CLP Criteria (ECHA) and Part B Human Health Effects Assessment (BPR guidance under development)	12
BPR/human health/risk assessment	*1.6 Sensitisation* *1.6.3.1 2 Human data for skin sensitisation:* "Evidence of skin sensitising activity derived from diagnostic testing may reflect the induction of skin sensitisation to that substance or cross-reaction with a chemically very similar substance. In both situations, the normal conclusion would be that this provides positive evidence of the skin sensitising activity of the chemical used in the diagnostic test." "Ultimately, where a very large number of individuals (e.g.10^5) have frequent (daily) skin exposure for at least two years and there is an active system in place to pick up complaints and adverse reaction reports (including via dermatology clinics), and where no or only a very few isolated cases of allergic contact dermatitis are observed then the substance is unlikely to be a significant skin sensitiser. However, information from other sources should also be considered in making a judgement on the substance's ability to induce skin sensitisation. It is emphasised that testing with human volunteers is strongly discouraged, but when there are good quality data already available they should be used as appropriate in well justified cases." *1.6.5. Concluding on suitability for Classification and Labelling* "In order to conclude on classification and labelling, all the available information needs to be taken into account, and consideration should be given also to the Guidance for the implementation of the CLP Regulation."	13

11. Regulation 528/2012 - biocidal products http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02012R0528-20140425&from=EN
12. Guidance on the Biocidal Products Regulation Volume III: Human health Part A: Information Requirements http://echa.europa.eu/documents/10162/15623299/bpr_guidance_ir_part_vol_iii_part_a_en.pdf
13. Guidance on the Biocidal Products Regulation Volume III: Human Health Part B: Risk Assessment http://echa.europa.eu/documents/10162/15623299/biocides_guidance_human_health_ra_iii_part_b_en.pdf

Plant Protection Products Regulation 1107/2009

Area and purpose	**Type of human data to be used**	**Ref.**
General	*Preamble (13)* "For ethical reasons, the assessment of an active substance or a plant protection product should not be based on tests or studies involving the deliberate administration of the active substance or plant protection product to humans with the purpose of determining a human 'no observed effect level' of an active substance. Similarly, toxicological studies carried out on humans should not be used to lower the safety margins for active substances or plant protection products."	14
Plant protection products/active substances: Protection against induction and elicitation	*Annex, introduction, 5.3.* "Tests involving the deliberate administration of the active substance or the plant protection product to humans and non-human primates shall not be performed for the purpose of this Regulation." *5.2.6. Skin sensitisation:* "The study shall provide sufficient information to assess the potential of the active substance to provoke skin sensitisation reactions."	15
Plant protection products/products: Protection against induction and elicitation	*7.1.6. Skin sensitisation* "The study shall provide information to assess the potential of the plant protection product to provoke skin sensitisation reactions."	16

14. Regulation 1107/2009 - plant protection products http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32009R1107
15. Regulation 283/2013 - data requirements for active substances http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:093:0001:0084:EN:PDF
16. Regulation 284/2013 – data requirements for plant protection products http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:093:0085:0152:EN:PDF

Detergents Regulation 648/2004

Purpose	Labelling requirement	Ref.
General/protection of human health: Protection against elicitation, and medical information	*Preamble (25):* "Specific labelling is introduced to inform consumers about fragrance substances and preservation agents that are present in detergents. Medical personnel should be able to obtain from the manufacturer upon request a full listing of all ingredients of a detergent to assist them investigate whether a causal link exists between the development of an allergic response and exposure to a particular chemical substance, and Member States should be able to require that such a listing is also made available to a specific public body designated to provide this information to medical personnel."	17
Labelling requirement	*Annex VII:* "If added, preservation agents shall be listed, irrespective of their concentration . . . If added at concentrations exceeding 0.01 % by weight, the allergenic fragrances that appear on the list of substances in Annex III, Part 1 to Directive 76/768/EEC, … by adaptation of that Annex to technical progress."	17

17. Regulation 648/2004 - detergents http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004R0648-20120419&from=EN