	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