Scientific Committee on Consumer Safety

SCCS

OPINION on Citral

(CAS No. 5392-40-5, EC No. 226-394-6)

sensitisation endpoint

The SCCS adopted this document
during the plenary meeting on 27 March 2024

ACKNOWLEDGMENTS

SCCS members listed below are acknowledged for their valuable contribution to the finalisation of this Opinion.

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1. ABSTRACT

The SCCS concludes the following:

1. *In light of the data provided and taking under consideration the derived upper safe levels using QRA2 methodology for the sensitisation endpoint, does the SCCS consider Citral safe when used as a fragrance ingredient in cosmetic products up to the maximum concentrations provided in the dossier submission?*

   The SCCS has noted some aspects of the QRA2 methodology that still need clarification and possible refinement. While some questions remain, the SCCS is of the opinion that the assessment based on QRA2 methodology has indicated that Citral can be considered safe in relation to the induction of sensitisation at the concentrations proposed for use in cosmetic products.

2. *Does the SCCS have any further scientific concerns with regard to the use of QRA2 to derive safe upper levels for Citral or for fragrance allergens in general?*

   Whilst the proposed QRA2 methodology is an improvement to QRA1 methodology, the SCCS recommendation is specific for the sensitisation potential of Citral at the proposed use concentrations. More case studies are needed to further confirm the applicability of this approach to other fragrances and other cosmetic ingredients. Until then, the SCCS will consider the suitability (for a population not already sensitised) of this methodology for other fragrances and other cosmetic ingredients on a case-by-case basis.

Keywords: SCCS, scientific opinion, fragrance, Citral, Regulation 1223/2009, CAS No. 5392-40-5, EC No. 226-394-6).

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on Citral (CAS No. 5392-40-5, EC No. 226-394-6) - sensitisation endpoint, preliminary version of 27 March 2024, SCCS/1666/24

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SCCS

The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background on Quantitative Risk Assessment (QRA)

Skin allergies may arise from exposure to certain chemicals and may lead to Allergic Contact Dermatitis (ACD). This adverse health effect, especially from fragrance ingredients is a common and relevant problem from exposure to cosmetic and other household products. Therefore, it is a topic of high interest for consumers, industry and Regulatory Authorities.

A model for dermal sensitisation quantitative risk assessment (QRA) was developed and implemented by the International Fragrance Association (IFRA). The methodology relied on thresholds (no effect or low effect levels) established in healthy human volunteers and/or in animal experiments. A set of safety factors were applied to derive 'acceptable exposure level'. The QRA methodology was evaluated by the Scientific Committee on Consumer Products (SCCP) in 2008 (SCCP/1153/08)[1] stating that there was no confidence that the levels of skin sensitisers identified by QRA are safe for the consumer. However, the committee added that models like the QRA approach may, after refinement and validation, be applicable in the future for risk assessment of new substances. In 2012, the SCCS reiterated this position in the context of the opinion on Fragrance Allergens (SCCS/1459/11)[2].

Following the SCCS opinion of 2012, the International Dialogue for the Evaluation of Allergens (IDEA) was established to improve the risk assessment of fragrance allergens. The IDEA project focused on reviewing the uncertainty factors, introducing dermal aggregate exposure for fragrance ingredients resulting in the QRA2 methodology which was reviewed by the SCCS in 2018 (SCCS/1589/17)[3]. In that Opinion, SCCS concluded that '*a lot of progress has been achieved since the initial publication of the QRA. However, it is not yet possible to use the QRA2 to establish a concentration at which induction of sensitisation of fragrance is unlikely to occur…A number of additional considerations and refinements have been incorporated to the proposed methodology. However, explanation of certain methodological approaches and assumptions, as well as a description of uncertainties is lacking, the provision of which would enhance understanding of the methodology. These aspects have been highlighted in the SCCS comments under each section with the aim to provide pointers for improvement. If shaped up properly, this could be a useful methodology not only for risk assessment of fragrance allergens, but potentially also for other cosmetic ingredients'.*

The IDEA project continued its work in order to further improve and refine the QRA2 methodology resulting in a peer-reviewed publication[4]. In December 2021, IFRA submitted a dossier on derived safe use levels for the fragrance ingredient Citral by applying the refined QRA2 methodology based on the induction of skin sensitisation.

Background on Citral

Citral (CAS No. 5392-40-5, EC No. 226-394-6) with the chemical name '3,7-Dimethyl-2,6-octadienal' is a mixture of neral and geranial, which are monoterpene aldehydes. It is widely used as both a fragrance and flavour ingredient in food, beverages and various cosmetic and household products due to its distinct, acceptable, and lemon-like pleasant odour. Citral is also a common constituent of many essential oils, such as lemongrass and *Litsea cubeba* oils.

Citral has been subject to a safety evaluation by SCCP in 2008 (SCCP/1153/08)[5] using the QRA methodology and by the SCCS in 2012 (SCCS/1459/11)[6] in the context of the opinion on Fragrance Allergens. Citral is currently regulated as a fragrance ingredient in cosmetic products in entry 70 of Annex III to the Cosmetics Regulation[7]. In particular, the presence of

[1] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_135.pdf
[2] https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf
[3] https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_211.pdf
[4] Api et. al., Updating exposure assessment for skin sensitisation quantitative risk assessment for fragrance materials, Regul. Toxicol. Pharmacol. 118 (2020) 1 - 12).
[5] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_135.pdf
[6] https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf
[7] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1223-20211001

the substance must be indicated in the list of ingredients referred to in Article 19(1)g of the Cosmetics Regulation when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

In light of the information provided, the Commission requests the SCCS to assess whether the derived safe use levels for Citral by application of the QRA2 based on the induction of skin sensitisation is adequate to protect consumers.

Terms of reference

1. *In light of the data provided and taking under consideration the derived upper safe levels using QRA2 methodology for the sensitisation endpoint, does the SCCS consider Citral safe when used as a fragrance ingredient in cosmetic products up to the maximum concentrations provided in the dossier submission?*

2. *Does the SCCS have any further scientific concerns with regard to the use of QRA2 to derive safe upper levels for Citral or for fragrance allergens in general?*

3. OPINION

Preamble:

The SCCS has reviewed the submission on Citral as a case study of the revised QRA2 methodology. In the former Opinion on QRA2 (SCCS/1589/17), the SCCS had concluded that '*a lot of progress has been achieved since the initial publication of the QRA. However, it is not yet possible to use the QRA2 to establish a concentration at which induction of sensitisation of fragrance is unlikely to occur'*. Several additional considerations for refinements were indicated in the proposed methodology. These aspects were highlighted in the SCCS comments under each section of the previous Opinion with the aim of providing points for improvement. The IDEA project has since continued work to further improve and refine the QRA2 methodology as reflected in a peer-reviewed publication (Api *et al.*, 2020a). In December 2021, IFRA submitted a dossier on derived safe use levels for the fragrance ingredient Citral by applying the refined QRA2 methodology based on the induction of skin sensitisation.

Assessment of the initial submission on Citral as a case study for QRA2 showed that clarification on a number of aspects of the methodology was still needed, and as a result, the SCCS was unable to form an opinion on the safety of Citral when used as a fragrance ingredient in cosmetic products up to the maximum concentrations provided in the dossier. As indicated in the previous SCCS Opinion on the QRA2 (SCCS/1589/17), the SCCS appreciates that a lot of progress has been made on the subject and, if further refined, the QRA2 could be a useful methodology not only for risk assessment of fragrance allergens, but potentially also for other cosmetic ingredients. Since more clarifications and adaptations were needed to be able to use this approach, the issues were notified to the Applicant in a letter. The information provided by the Applicant in response to the letter has been included and assessed as part of this Opinion.

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

INCI name: Citral
IUPAC name: (2E)-3,7-dimethylocta-2,6-dienal

Ref.: ECHA (https://echa.europa.eu/el/registration-dossier/-/registered-dossier/13515/11/, PubChem (https://pubchem.ncbi.nlm.nih.gov/compound/Citral)

3.1.1.2 Chemical names

3,7-dimethyl-2,6-octadienal
2,6-Octadienal, 3,7-dimethyl-
3,7- dimethylocta-2,6-dienal

SCCS comment
There are many synonyms (see https://pubchem.ncbi.nlm.nih.gov/compound/Citral)

3.1.1.3 Trade names and abbreviations

Lemarome
Citral Lemarome N
Citral E.Q.
Citral Extra
Citral N

3.1.1.4 CAS / EC number

CAS: 5392-40-5
EINECS: 226-394-6

3.1.1.5 Structural formula

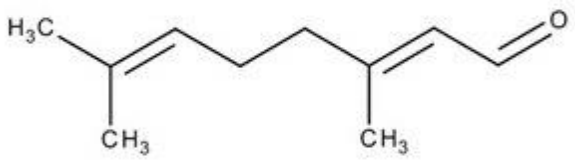

Figure 1: Structural formula of Citral

SCCS comment
According to the literature and the current mandate, Citral is a mixture of two isomeric acyclic monoterpene aldehydes, geranial (Z-isomer) and neral (E-isomer), with the following chemical structure:

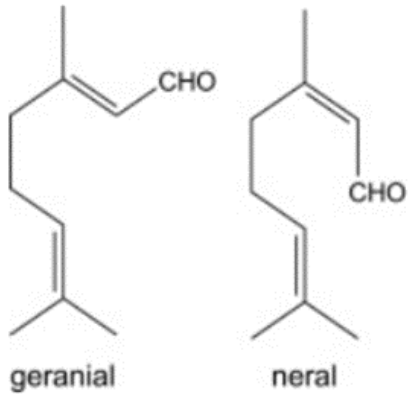

Figure 2: Chemical structure of Citral isomers

Ref: https://www.sciencedirect.com/topics/chemistry/Citral

3.1.1.6 Empirical formula

Formula: $C_{10}H_{16}O$

3.1.2 Physical form

Physical form: Light, oily, pale yellow liquid with strong lemon odour

3.1.3 Molecular weight

Molecular weight: 152.23

3.1.4 Purity, composition and substance codes

Degree of purity: >96% - 100%
According to the Applicant, Citral is composed of approximately equal amounts of the trans- and cis isomers (neral and geranial).

3.1.5 Impurities / accompanying contaminants

None noted by the Applicant.

SCCS comment
A full report of the chemical characterisation of Citral in terms of purity, identity and impurities in representative batches must be provided and the validity of the analytical methodologies used must be demonstrated. Identity and concentration of any impurities that may be present must also be stated.

3.1.6 Solubility

See section 3.1.8

3.1.7 Partition coefficient (Log Pow)

2.76 at 25°C

Ref.: ECHA (https://echa.europa.eu/el/registration-dossier/-/registered-dossier/13515/11/)

3.1.8 Additional physical and chemical specifications

pH value:	approx. 7
Freezing point:	<-20°C
Boiling point:	230°C (decomposes before boiling)
Temperature of decomposition:	180°C
Flash point:	98°C at 1013.25hPa
Ignition temperature:	225°C at 1013.25hPa
Vapour pressure:	0.046 hPa at 20°C
Density:	0.89 g/cm3 at 20°C
Relative density:	0.89 at 20°C
Solubility in water:	0.42 g/l at 25°C
Solubility in organic solvents:	soluble
Partition coefficient n-octanol/water:	2.76 at 25°C
Thermal decomposition:	not determined
Viscosity, dynamic:	2.15 mPa.s at 20°C
Viscosity, kinematic:	2.42 mPa.s at 20°C
Miscibility with water:	immiscible
pKA:	does not dissociate
Surface tension:	not expected based on chemical structure

Ref.: ECHA (https://echa.europa.eu/el/registration-dossier/-/registered-dossier/13515/11/)

SCCS comment
According to the literature, Citral is soluble in 5 volumes of 60% alcohol; soluble in all proportions of benzyl benzoate, diethyl phthalate, propylene glycol, mineral oil, fixed oils, and 95% alcohol. Solubility in alcohol is 1 ml in 7 ml 70% alcohol. Citral is very slightly soluble in water, 0.059 g/100ml at 25 °C (according to ILO-WHO International Chemical Safety Cards) and 0.42 g/l at 25°C (according to Applicant's dossier).

Ref.: ICSC database: ILO-WHO International Chemical Safety Cards (ICSCs)
https://pubchem.ncbi.nlm.nih.gov/compound/Citral

3.1.9 Homogeneity and Stability

Citral is reported in the literature as being unstable under certain conditions. Factors such as heat, oxygen, acid and light accelerate its degradation (Kimura *et al.*, 1983a and 1983b, Weerawatanakorn *et al.*, 2015, Ay *et al.*, 2019, Mercer *et al.*, 2021, Sandeep *et al.*, 2021).
In another study (Ay *et al.*, 2019), spectrum range simulating sunlight and artificial light irradiation close to realistic ambient storage conditions were used. ESR spectroscopy showed a new non-negligible degradation mechanism involving free-radical intermediates, in addition to cyclization, which appears to be the major degradation pathway.

3.2 EXPOSURE ASSESSMENT

3.2.1 Function and uses

According to the Applicant, Citral, with its strong citrus lemon odour, is widely used as both a fragrance and flavour ingredient. Citral is used as a fragrance ingredient in several cosmetics and, as an example, delivers an aroma which helps to provide reassurance concerning the functionality of a wide range of homecare products. Citral is also a common constituent of many essential oils such as lemon, lime, lemongrass, *Pistacia atlantica*, and *Litsea cubeba* oils.
Beyond its use as cosmetic ingredient, Citral is used in household products and other domestic as well as occupational products (De Groot *et al.*, 2019).

3.2.2 Calculation of the CEL

The QRA approach integrates exposure and risk assessment in an iterative manner. Therefore, in order not to disrupt the description of the methodology, the calculation and adjustment of CELs are described under step 3 of the QRA2 methodology (section 3.4.3.1) in the current Opinion.

3.3 TOXICOLOGICAL EVALUATION

3.3.1 Skin sensitisation

According to the Applicant, the body of information on Citral is more substantial than for any other fragrance because it is a long standing and widely used fragrance ingredient, but also because it has been deployed extensively in the validation process for the local lymph node assay (LLNA), the demonstration that the LLNA delivers information on dose response relationship and relative sensitising potency, and, most recently, in the development and

validation of a wide range of *in vitro* alternatives (Gerberick *et al.*, 2000; Basketter *et al.*, 2007; Tourneix *et al.*, 2020).

3.3.1.1 *In chemico* and *in vitro* data

According to the Applicant, Citral as a long-standing fragrance ingredient has been assessed extensively for its toxicological properties, including skin sensitisation, with this older body of information having been collated and published recently (Api *et al.*, 2020b). However, in recent years, non-animal methods for skin sensitisation have been developed (Rossi and Ezendam, 2018; Kleinstreuer *et al.*, 2018; Basketter *et al.*, 2019; Pistollato *et al.*, 2021). They have begun to predominate via their use for hazard identification, but deployment for the determination of potency is still evolving (Basketter *et al.*, 2020; Natsch *et al.*, 2020). Nevertheless, it is appropriate first to consider how Citral performs in methods representing the first three key events (KEs) in the adverse outcome pathway (AOP) for skin sensitisation (OECD, 2012). KE1, the covalent binding of a chemical to protein, is addressed via the Direct Peptide Reactivity Assay (DPRA). The KeratinoSens™ assay aligns with KE2, the activation of keratinocytes. KE3, the activation of dendritic cells, is assessed using the human Cell Line Activation Test (h-CLAT).

The results from the *in chemico* and *in vitro* assays as described in the Applicant's dossier are summarised in Annex I of this Opinion. The results have been included for completeness. According to the Applicant, the results demonstrate that Citral would be classified as highly reactive (in two Direct Peptide Reactivity Assays) and thus identified as skin sensitiser. Also, the results of the KeratinoSens™ assay as well as the Cell Line Activation Test (h-CLAT) demonstrate Citral to be classified as skin sensitising. Different published studies showed how the data can be combined quantitatively. Natsch and colleagues (Natsch *et al.* 2018) used regression models and predicted a relative LLNA EC3 value of 5.2 – 6.8% based on *in vitro* data which is close to the mean value (5.7%) reported below.

SCCS comments on *in chemico* and *in vitro* data
For Citral, all assays performed were positive, confirming that it has skin sensitising potential. The integration of *in vitro* data resulted in a potency value that is in line with the potency derived from the LLNA (paragraph 3.3.1.2). As pointed out in the publication from Lee *et al.* (2022) provided by the Applicant, it is still challenging to use *in vitro* data for potency determination. Much work in this area is still ongoing and progress is being made regarding the development of the Next-Generation-Risk-Assessment (NGRA) for skin sensitisation. More supporting frameworks are, however, still needed on how to use *in vitro* data, especially for potency assessment. At present, the integrated *in vitro* data for Citral can be used as a supportive element for derivation of the WoE NESIL.

3.3.1.2 *In vivo* data

This section details the historical *in vivo* studies, mouse and guinea pig, completed on Citral.

3.3.1.2.1 Local Lymph Node Assay (LLNA)

Data from a total of 15 LLNAs with Citral in various vehicles are summarized in Table 1 below. EC3 values are converted to a dose per unit area in µg/cm^2 using an applied volume of 25 µL and an ear surface area of 1 cm^2 (e.g., a 1% w/v solution delivers a dose of 250 µg/cm^2). Studies are presented in order of increasing EC3 values.

Results:
According to the Applicant, a concentration related increase in lymphocyte proliferation was observed under all testing conditions (where individual SIs were given) and the estimated concentrations for inducing a 3-fold increase (EC3) ranged from 1.2% (300 µg/cm^2) in EtOH:DEP (1:3) to 13.9% (3475 µg/cm2) in AOO. Lalko and Api (2008) reported a weighted mean EC3 value based on the vehicle used was 5.7% (1414 µg/cm^2).

Conclusion:
It was demonstrated that under the conditions investigated, Citral showed a potential to induce skin sensitisation in the murine local lymph node assay. In two of the 14 reported LLNAs had EC3 values < 2% (1.2 and 1.5%, respectively) indicating a strong sensitisation potency. In the majority of the studies, 12 out of 14, EC3 values ranging from 2.1-13%, and the calculated weighted mean of 5.7%, Citral would be classified as a moderate skin sensitiser (ECETOC 2003; Kimber *et al.*, 2003).

SCCS comments on murine LLNA studies
Citral has been tested in several LLNA studies, most of which were conducted according to OECD TG 429 under GLP conditions. Table 1 shows LLNA studies that used Citral that had aged for 90 days. It is known that ageing can lead to the formation of oxidation products that may be more or less potent in terms of toxicity than the compound itself. The purity of Citral is also lower in these studies, which can be expected because of degradation/transformation. Table 1 also includes LLNA studies in which an antioxidant was added to Citral. The LLNA studies with aged Citral, or with added antioxidants, resulted in the same potency range as the LLNA studies conducted with the pure ingredient. Overall, the potency of Citral in the LLNA does not seem to be affected by ageing or by the addition of antioxidants.

In different LLNA studies, EC3 values have ranged from 1.2%-13.9%. According to the Applicant, in QRA2 the calculated weighted mean is used to derive the NESIL. It is however not clear how the "weighting based on the vehicle used" have been calculated; this needs clarification. For Citral, additional data are available that support the value of the weighted mean from the LLNA. The NESIL derived from the human studies is 1400 µg/cm^2, which corresponds to the EC3 of 5.7% (1414 µg/cm^2). In addition, the EC3 value from the LLNA is supported by the integrated *in vitro* data that result in a relative LLNA EC3 value of 5.2 – 6.8%. Therefore, the SCCS agrees that the weighted mean can be used for Citral in the WoE NESIL derivation. For other less data-rich cosmetic ingredients, the SCCS would prefer the use of the lowest EC3 value in the WoE NESIL derivation in the absence of other data.

Table 1: Summary of 15 LLNA studies executed with Citral

Method Guideline	Species/Strain Sex, Group size	Test Substance Vehicle[1]	Concentration Stimulation Index (SI)	Results EC3% (µg/cm²)	Reference
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Female 4/group	Citral 1:3 EtOH:DEP	0.4% 1.68 2% 4.41 4% 13.92 8% 18.32 20% 19.01	1.2% (300 µg/cm²)	RIFM 2004a; cited in Lalko and Api, 2008
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Male 4/group	Citral 93.4% purity (aged 90 days) 0.1% α-tocopherol in 3:1 EtOH:DEP	0.3% 1.78 1% 2.45 3% 4.69 10% 23.84 30% 58.66	1.5% (375 µg/cm²)	RIFM 2003; cited in Lalko and Api, 2008
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Male 4/group	Citral 99.5% purity (fresh) 0.3% AO[2] in 3:1 EtOH:DEP	0.3% SIs 1% not 3% given 10% 30%	2.1% (525 µg/cm²)	RIFM 2003; cited in Lalko and Api, 2008
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Male 4/group	Citral 99.5% purity (fresh) 0.1% Trolox C in 3:1 EtOH:DEP	0.3% SIs 1% not 3% given 10% 30%	3.7% (925 µg/cm²)	RIFM 2003; cited in Lalko and Api, 2008

Method Guideline	Species/Strain Sex, Group size	Test Substance Vehicle[1]	Concentration Stimulation Index (SI)	Results EC3% (µg/cm^2)	Reference
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Male 4/group	Citral 92.6% purity (aged 90 days) 0.3% AO[2] in 3:1 EtOH:DEP	0.3% SIs 1% not 3% given 10% 30%	4.6% (1150 µg/cm^2)	RIFM 2003; cited in Lalko and Api, 2008
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Male 4/group	Citral 99.5% purity (fresh) 3:1 EtOH:DEP	0.3% SIs 1% not 3% given 10% 30%	4.6% (1150 µg/cm^2)	RIFM 2003; cited in Lalko and Api, 2008
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Male 4/group	Citral 85.5% purity (fresh) 3:1 EtOH:DEP	0.3% SIs 1% not 3% given 10% 30%	5.3% (1150 µg/cm^2)	RIFM 2003; cited in Lalko and Api, 2008
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Male 4/group	Citral 95.9% purity (aged 90 days) 0.1% Trolox C in 3:1 EtOH:DEP	0.3% SIs 1% not 3% given 10% 30%	5.8% (1400 µg/cm^2)	RIFM 2003; cited in Lalko and Api, 2008
OECD 429	Mice Female 4/group	Citral 1:3 EtOH:DEP	2.5% 2.8 5% 2.3 10% 5.1 25% 11.4 50% 22.1	6.3% (1575 µg/cm^2)	Lalko and Api, 2006
LLNA (pre-OECD TG)	Mice CBA/Ca Sex not specified 4/group	Citral AOO	5% 2.2 10% 5.1 25% 20.5	6.4% (1600 µg/cm^2)	Basketter et al., 1991

1

Method Guideline	Species/Strain Sex, Group size	Test Substance Vehicle[1]	Concentration Stimulation Index (SI)	Results EC3% (µg/cm²)	Reference
LLNA (pre-OECD TG)	Mice CBA/Ca Sex not specified 4/group	Citral AOO	5% 2.1 10% 5.0 25% 9.3	6.6% (1650 µg/cm²)	Basketter et al., 1991; Basketter and Scholes, 1992
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Male 4/group	Citral 99.5% purity (fresh) 0.1% α-tocopherol in 3:1 EtOH:DEP	0.3% 1% 3% 10% 30% SIs not given	6.8% (1700 µg/cm²)	RIFM 2003; cited in Lalko and Api, 2008
OECD 429 GLP	Mice CBA/Ca/Ola/Hsd Female 6/group	Citral AOO	5% 10% 25% SIs not given	12.6% (3150 µg/cm²)	Basketter et al., 2012
LLNA (pre-OECD TG)	Mice CBA/Ca Sex not specified 4/group	Citral AOO	5% 0.9 10% 2.2 25% 6.2	13.0% (3250 µg/cm²)	Basketter et al., 1991
LLNA (pre-OECD TG)	Mice CBA/Ca Sex not specified 4/group	Citral AOO	5% 0.9 10% 2.4 25% 4.7	13.9% (3475 µg/cm²)	Basketter et al., 1991

1 EtOH = ethanol; DEP = Diethylphthalate; AOO = Acetone: Olive oil, 3:1
2 AO = Antioxidant mix 1:1:1 BHT, tocopherol, eugenol

3.3.1.2.2 Guinea Pig Tests

In the Applicant's dossier, 6 different Guinea Pig Maximization tests and one Buehler test (1965) were described of which the results are summarized in Annex II. It was demonstrated from the GPMT studies that Citral has the potential to induce dermal sensitization in Guinea pigs when tested at 25% for the topical induction, 10% at challenge and 5% at rechallenge according to Magnusson and Klingman test conditions (Magnuson and Kligman, 1969).

In the Buehler test it was demonstrated that Citral has the potential to induce dermal sensitisation in Guinea pigs in the Buehler test when tested at 20% for both induction and challenge.

Overview of and conclusions from Guinea pig studies

According to the Applicant, Citral was consistently identified as a skin sensitiser in each of the Guinea Pig Maximisation Tests and the single Buehler test presented here. It is not possible

to draw a conclusion for the sensitisation potency of Citral from the guinea pig studies as these tests were not designed to predict potency classification.

3.3.1.2.3 Human studies

Human repeat insult patch tests (HRIPTs)

Five HRIPTs were performed, of which the detailed results are presented in Annex II. Table 2 below describes an overview of these studies, placed in order of induction dose expressed in µg/cm^2.
The first study presented in the text above (second in table), also the most recent and conducted fully according to the standard protocol with more than 100 volunteers, delivered the highest NOEL of 1417 µg/cm^2. The only greater level tested (almost 3-fold higher) gave positive results. Accordingly, the highest NOEL was rounded down to deliver a pragmatic NOEL of 1400 µg/cm^2.

Table 2: Overview of five HRIPT studies with Citral

Test Substance Concentration Vehicle	Dose Volume/Patch Area	Induction Dose (µg/cm^2)	Incidence of Positive Responses	References
5% in alcohol SDA 39C	0.5 mL / 6.45 cm^2	3876	63% (5/8)	Lalko and Api, 2008; RIFM 1964a
1.2% in 3:1 DEP:EtOH	0.3 mL / 2.45 cm^2	1417	0% (0/101)	Lalko and Api, 2008; RIFM 2004b
4% in petrolatum	0.2 mL / 6.45 cm^2	1240	0% (0/50)	Lalko and Api, 2008; RIFM 1971a
1.0% in alcohol SDA 39C	0.5 mL / 6.45 cm^2	775	0% (0/40)	Lalko and Api, 2008; RIFM 1965
0.5% in alcohol SDA 39C	0.5 mL / 6.45 cm^2	388	0% (0/41)	Lalko and Api, 2008; RIFM 1964b

SCCS comments on HRIPT studies
The SCCS has expressed ethical concerns several times about conducting human skin sensitisation tests, including the HRIPT (SCCP, 2008; SCCS, 2015; SCCS, 2018). One of the concerns is that exposure levels used in the test may themselves cause sensitisation in healthy volunteers.
Altogether in this dossier, five HRIPT studies have been performed, four of them are insufficiently sized according to the current standards. The result of the largest study suggests a NESIL of 1417 (or 1400, if rounded) µg/cm². It should be noted that the upper 95% confidence interval of 0% reactions, based on 0/101 volunteers, is around 3%. This means that given the standard biostatistical error rate of 5%, it cannot be excluded that actually 3 out of 100 volunteers may become sensitised under these conditions; for further explanation and discussion see Gefeller *et al.* (2013). The SCCS suggests to suitably incorporate the – limited – inherent uncertainty when deriving the NESIL. The impact of different vehicles ("alcohol SDA 39C" and petrolatum, respectively) used in the other HRIPT studies is not clear, in view of differences seen with petrolatum vs. butylene glycol in human maximization tests (see below). In any case, the results do not contradict the choice of 1417 µg/cm² as NESIL.

Ref: https://pubmed.ncbi.nlm.nih.gov/23848408/

Human maximization tests

Data from a total of 14 Human Maximization Tests (HMT) with Citral are summarized in Table A.3 in Annex II. The HMTs were conducted according to the method described in Kligman, (1966) and Kligman and Epstein (1975). Test material concentrations are converted from a percentage to a dose per unit area in µg/cm^2 using the reported applied volume and patch area in cm^2. Studies are presented ordered by decreasing induction concentration. In most of these HMTs, the induction patch sites were pre-treated with 5% aqueous sodium lauryl sulfate (SLS) for 24 hours, which greatly increases the sensitivity of the test (Kligman, 1966). However, as with adjuvant guinea pig studies, the use of SLS pre-treatment confounds interpretation with respect to relative sensitizing potency.

Under the conditions of the Human Maximization test, Citral in petrolatum induced skin sensitisation at concentrations ranging from 8% (5517 µg/cm^2) to 2% (1379 µg/cm^2). Only the study using Citral at 5% (3448 µg/cm^2) in butylene glycol failed to induce sensitisation in any of the 25 volunteers.

Conclusion

It was demonstrated that Citral has the potential to induce dermal sensitisation in humans. Except for the isolated study using butylene glycol as a vehicle, a NOEL was not demonstrated. There was only limited evidence of dose-response in the results, which, together with the intrinsic limitations of these assays already mentioned above, render it difficult to deduce information on potency. However, the trend of the data suggests a threshold around 0.5% - 1.0%, which, given the greater sensitivity of this assay compared to the HRIPT, but with the use of petrolatum as a vehicle (which was common at that time) suggests results consistent with the HRIPT.

SCCS comments on the Human Maximization tests

As stated in SCCS/1567/15, only historical human induction study results targeting the identification of induction levels can be considered (as contrasted to HRIPT studies targeting a NESIL, see above). Currently, such studies are considered unethical. In the present case, no (additional) information useful for the derivation of a NESIL can be taken from the historical HMT results, except the observation of a vehicle effect on induction.

3.4.2 Other toxicity endpoints

Other toxicological endpoints have not been assessed in this Opinion.

3.4.3 Special investigations

3.4.3.1 Introduction of the key steps of QRA2

According to the Applicant, toxicological safety evaluation often relies heavily on the application of expert judgment to biological test data that carry their own degrees of uncertainty. Against this background and prompted by the need to improve the safety profile of fragrance allergens in relation to skin sensitisation, QRA was developed (Gerberick *et al.*, 2001a; Api *et al.*, 2008). In principle, potency information, exposure information and the application of safety assessment factors to allow for uncertainties were combined, so that for each allergen, an acceptable level of consumer exposure could be defined for a range of products.

Due to continuing concern regarding the frequency of contact allergy (i.e., a positive patch or use test to a fragrance material, not necessarily the disease ACD) to fragrances, together with questions about the limitations of the original QRA, this led to a fundamental review, of

which the outcome was QRA2 (for comprehensive details see Api *et al.*, 2020a). Concerns surrounding QRA included the need for better individual exposure data, for inclusion of measures of aggregated exposure associated with multiple product use, as well as for a re-examination and appropriate refinement of SAFs. The review process that took place under project IDEA (ideaproject.info) which led to QRA2 was built upon two key foundations - a review of many aspects of the science (Basketter and Safford, 2016) and the development of an aggregate exposure model (Api *et al.*, 2020a). The review brought about, according to the Applicant, only modest changes to the SAFs, although it did increase their number, from three to four, so that they would clearly encompass aspects of interindividual variation, product composition, frequency/duration of exposure and the impact of skin condition at the exposure site(s).

A more fundamental change in the QRA2 involved, according to the Applicant, the application of newer individual product exposure data (Comiskey *et al.*, 2015, 2017). A further, and important, evolution was to aggregate the exposure from multiple products based on habits and practices data derived from extensive diary-based surveys (Safford *et al.*, 2017).

Aggregate exposure is determined with the Creme RIFM model which uses probabilistic (Monte Carlo) simulation to allow sampling from distributions of data sets providing a more realistic estimate of aggregate exposure to individuals across a population compared to the simplistic approach of adding or summing the exposures from all the individual product types (Comiskey *et al.*, 2015, 2017). The key data used in the Creme RIFM model are:

1) Concentration data on fragrance ingredients used in fragrance mixtures together with the concentrations of fragrance mixtures used in the final products that are collected in a systematic method by RIFM from all their member companies;

2) Detailed habits and practices data on product use patterns and body application sites from 42.000 panellists across Europe and the United States of America obtained from the Kantar World Panel Survey (https://www.kantarworldpanel.com/global) (Comiskey *et al.*, 2015, 2017; Safford *et al.*, 2015, 2017);

3) Statistical distributions of the quantities per use of each product (Tozer *et al.*, 2004; Loretz *et al.*, 2005, 2006, 2008; Hall *et al.*, 2007, 2011).

The key stages described in QRA2 are equivalent to those detailed in the original QRA (Api *et al.*, 2008) with the addition of incorporating aggregate exposure into defining an aggregate exposure adjusted upper concentration levels ($UCL_{product}$) (%) for each fragrance ingredient. The process of determining the maximum acceptable concentration level for a fragrance ingredient in each product is described in detail in Api *et al.* 2020a. Use of the Creme RIFM aggregate exposure model in the context of QRA2 is different from other uses of the model, such as for calculation of systemic exposure. For QRA2, the dermal route of exposure in the model is used to derive aggregate exposure factors which are used to set aggregate exposure adjusted UCLs for the product categories. The steps for deriving an aggregate exposure adjusted UCLs for the product categories are listed below and illustrated in Figure 3.

The following Figures (Figure 3 and 4) have been added to the dossier as response from the Applicant to the SCCS letter with the request of more clarification to the QRA2 methodology.

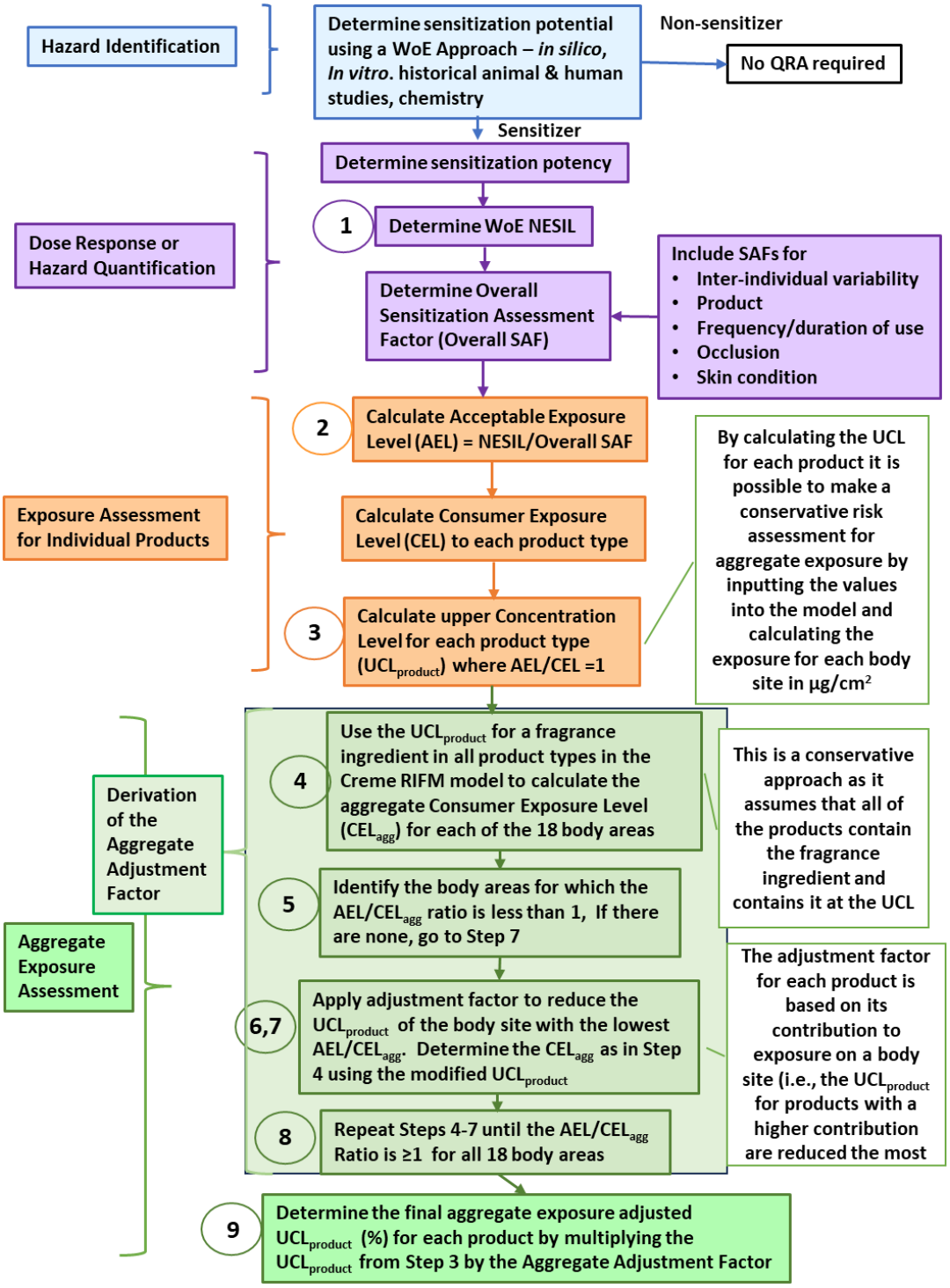

Figure 3: Overview of the QRA2 process

According to the Applicant, the main steps of the QRA2 process are:

Step 1. Determine the NESIL using a Weight of Evidence approach.

In deriving a NESIL, an overall WoE approach is utilized. This decision-making approach considers all available data which includes a strategic combination of data derived from NAMs along with historical animal and human data, when available, as well as data obtained through read-across on structurally and/or mechanistically related chemicals.

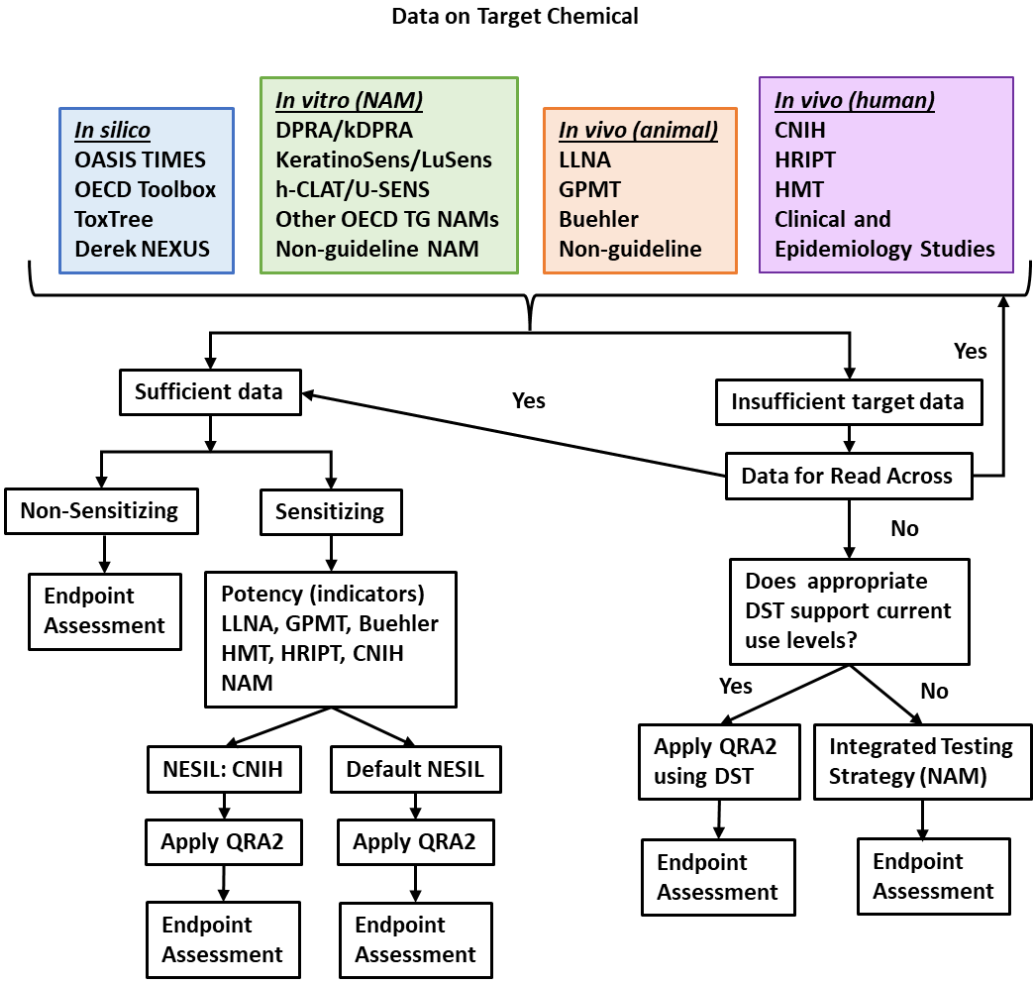

Figure 4: Hazard Identification and WoE NESIL derivation flowchart (Adapted from Lee *et al.*, 2022).
Note that this Figure describes the general process and not all parts are applicable defining the NESIL for Citral

According to the Applicant, the Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) is the point of departure used in the QRA approach. The WoE NESIL is an exposure, expressed as a dose per unit area of skin (i.e., µg/cm^2), which should not result in the induction of skin sensitization in humans. The process of deriving a WoE NESIL has evolved since the original QRA publication in 2008 (Api *et al.*, 2008) and an updated approach has been described in detail in a recent publication (Lee *et al.*, 2022) and is illustrated above (Figure 4).

The process of deriving of a WoE NESIL is described in the following sub steps:

- Hazard identification
- Dose response, determination of sensitization potency
- Determination of the WoE NESIL

According to the Applicant, it is important to note that the process and guidance for deriving WoE NESILs will continue to change over time as the available evidence will shift from historical *in vivo* data to information derived solely from New Approach Methods (NAMs).

Further details as provided by the Applicant on WoE NESIL derivation are described in Annex III of the current Opinion.

SCCS comment on WoE NESIL derivation

In the previous Opinion on QRA2, SCCS did raise several questions on the WoE guidelines for the NESIL derivation. Following this, a detailed clarification was provided by the Applicant and several articles were published. After carefully evaluating all the available information, the SCCS concludes that the information is still fragmented and that a practical guide for the WoE NESIL derivation is needed. For future submissions of a dossier based on QRA2, the SCCS will evaluate the WoE NESIL determination for a cosmetic ingredient on a case-by-case basis.

Step 2. Calculate the Acceptable Exposure Level (AEL) for use in each single product assessment using the NESIL and the appropriate product SAFs.

Once a NESIL has been derived, the next step is to determine the acceptable exposure level (AEL) for each product type. The AEL is essentially the NESIL divided by the overall Sensitization Assessment Factor (SAF) for the product type. SAFs are similar to extrapolation/uncertainty factors as they are applied in general toxicology risk assessment. The rationale for each of the individual SAFs has been described in detail (Basketter and Safford, 2016; Api *et al.*, 2020a). Briefly, for the QRA2 process the individual SAFs which comprise the overall SAF for each product type are:

- Interindividual variability which takes into consideration age, gender, pre-existing disease states (default value of 10).
- Product which considers the role of the ingredients of the product in the potential enhancement of induction; the predicted effect of product formulation versus the experimental conditions (0.3 for inert objects with no direct contact; 1 for most products; 3 for products with the potential to cause increased irritation).
- Frequency/duration of product use (1 if used intermittently; 3 if used frequently)
- Skin site condition which takes into consideration body areas that are specifically prone to increased level of inflammation (1, 3, or 10).

Overall product SAFs of 0.1, 0.3, 1, 3, 10, 30, 100 and 300 are calculated by multiplying the individual SAF values. In the calculation, 3 is treated as an integer when multiplied with 1, 10, 100 to give 3, 30, 300, respectively. When multiplied by itself it is taken as √10 (approx. 3.16) such that $3 \times 3 = 10$. In Annex IV of this Opinion, a supplementary table with the different SAFs per product type as previously published by Api *et al.* (2020a) has been included (Appendix 1 of the revised Applicant's dossier).

SCCS comments on SAFs

In Figure 3, the SAF for occlusion is still shown, while in the accompanying text,, SAF is not mentioned. In the previous Opinion on QRA2 (SCCS/1589/17), the Applicant explained that a SAF for conclusion was not needed, and the SCCS agreed.. This Figure should therefore be updated accordingly.

The sentence on the overall product SAF seems to contain a mistake. It is mentioned that the overall product SAF of 0.1, 0.3 etc are calculated by multiplying the individual SAFs. The SCCS does not understand how an overall SAF of 0.1 can be obtained, when the lowest individual SAF is 0.3.

In the previous Opinion on QRA2 (SCCS/1589/17), the SCCS raised several questions on the different SAFs. In the new submission, no further clarification on these questions was provided by the Applicant. While SAFs for interindividual variability and frequency of product use are plausible to use, the SAFs for skin site condition and product are still not clear to the SCCS.

According to the current dossier from the Applicant, the SAF for product is applied to cover the uncertainty of the potential enhancement of the induction of sensitisation caused by other ingredients in the product. It is noticeable that this explanation differs from the rationale provided for this SAF in the previous dossier that was submitted for the Opinion SCCS/1589/17. The relevance of this SAF for cosmetic ingredients seems to be low, since for most cosmetic products it is 1. There are no products mentioned in the supplementary Table

in Annex IV that have a SAF of 3. Furthermore, the SCCS does not agree with a SAF of 0.3, that is applied to products in category 11, such as facial tissues and napkins. This category is for products for which it is expected that there is minimal transfer of the fragrance from the inert product.
The Applicant explained that the SAFs are similar to an uncertainty factor. In risk assessment, uncertainty factors are always larger than 1, since they account for the uncertainty of the true value being larger, and thus support a conservative approach. Hence, SCCS does not agree with a SAF of 0.3 in QRA2 as being reflective of the uncertainty. It is more logical to take this into account in the exposure assessment, for example by including a characteristic moderating the availability of substance in a product-specific retention or release factor.
The skin condition SAF takes into consideration body areas that are specifically prone to increased level of inflammation and still raises some questions. Although this SAF is arbitrary, it makes the AEL calculation more conservative for certain product categories that are applied to specific body sites. In that sense, the SCCS agrees to include this SAF. A few questions on this SAF however remain. This SAF is body-site related and this poses a problem for product categories that are applied on different body sites (e.g. body lotion). If the SAF is product-related, is the SAF then adequate for the most sensitive body area to which it is applied? The methodology needs to be better explained.
It should be made clearer in the methodology description that the SAFs are associated with product categories and which assumptions are made. Some of the SAFs (e.g. skin condition SAF) seem to be related to body parts and not to products, and rely on assumptions about where on the body the products will be applied. These assumptions need to be made more transparent, e.g. by a table listing all assumptions in relation to the product categories.

Overall, although not all questions raised earlier by the SCCS have been answered, the overall rationale for the different SAFs is clearer and more acceptable. The exception is the product SAF of 0.3, which the SCCS still finds questionable.

Step 3. **Calculate the Upper Concentration Level (UCL)** of a fragrance in each individual product type using conservative deterministic **Consumer Exposure Levels (CEL)** based on reliable habits and practices data and the fragrance NESIL with the appropriate SAFs applied (e.g., NESIL/SAF), as previously done in the original QRA process. The UCL is the concentration at which the AEL = CEL.

According to the Applicant, estimation of the **consumer exposure levels (CEL)** is an essential element of the QRA. Using a deterministic approach, the consumer exposure level (CEL) to the fragrance ingredient is calculated on a 'per day' basis for each product type and is expressed in µg/cm^2. The CEL is the exposure that occurs under conditions of intended and foreseeable use but not deliberate misuse. Parameters for consumer habits and practices needed for the calculation include amount of product per use, number of uses per day and body site(s) exposed during product use. In cases where there are multiple habits and practices data sources for the same product, the highest (most conservative) value is used unless there is sound scientific rationale to use a different value (Api *et al.*, 2008). Body surface area in cm^2 of the exposed site(s) are taken from published data. If multiple data sources for the same body surface area (product application site) are available, preference is given conservatively to the smaller surface area (Api *et al.*, 2008).

The **CEL** for each product type is calculated according to the equations below:

CEL = Product Exposure (mg/cm^2) x Retention Factor x 1000 (µg/mg).

Exposure is the per day consumer exposure to the finished product in mg/cm^2.
Exposure = Amount of product per use (mg) x Frequency of use per day/Body Surface area (cm^2).

In alignment with the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients (SCCS 2023), a retention factor of 1 is used for a leave-on products, 0.01 for rinse-off products, and a factor of 0.1 for other products, except for toothpaste.

Prior to calculating the aggregate consumer exposure to the fragrance ingredient, upper concentration levels (**$UCL_{product}$**) are calculated deterministically for each product type, based on the NESIL for the fragrance ingredient, the overall SAF for each product and the consumer exposure level. The $UCL_{product}$ is the concentration of the fragrance ingredient in the finished product where the AEL/CEL = 1. Using the calculated $UCL_{product}$ for all product types as the initial concentration inputs in the Creme RIFM aggregate exposure model is a conservative approach as it assumes that the fragrance ingredient is present in all product types and that consumers use all product types on a daily basis.

Determination of the initial $UCL_{product}$ of a perfume ingredient not to be exceeded in a finished product is calculated using the product AEL and CEL using the following equation:

$$((\text{AEL } \mu g/cm^2 \times 0.001 \text{ mg}/\mu g) \div \text{CEL mg}/cm^2/\text{day}) \times 100 = UCL_{product} \%$$

SCCS comments on CEL

In the upper equation for CEL, the CEL is expressed in $\mu g/cm^2$, but in the bottom equation for UCL, it is expressed in mg/cm^2. Which deterministic parameters were used for the initial CEL in this approach was not explained. Since it concerns 71 product types, there have to be additional parameters beyond those included in the NoG and these have to be included in an Annex to the method, because the choice of initial CELs determines the outcome. Also, it is recommended that the equations are structured uniformly, i.e. that the variable being explained is always put to the left.

Step 4-7: **Derivation of the Aggregate Adjustment factor**

Aggregate adjustment factors are a function of the relative contribution of exposure from each product and are independent of the fragrance ingredient being assessed. Since the aggregate adjustment factors are derived using product exposure data, i.e., consumer habits and practices data, they are only calculated once as they do not depend on the skin sensitizer evaluated. However, if the underlying product exposure data change, then aggregate adjustment factors will need to be revised. The steps for deriving the aggregate adjustment factors are shown in Figure 5 below and described in the sections below. As mentioned previously, use of the Creme RIFM aggregate exposure model for QRA2 is unique in that aggregate dermal exposure is calculated for the purpose of deriving aggregate exposure factors. A detailed example of the process of deriving aggregate adjustment factors is provided in Appendix 2 of the revised Applicant's dossier and Annex V of the current Opinion.

According to the Applicant there are three important calculations in the process of determining QRA2 aggregate adjustment factors:

1) Determining the initial $UCL_{product}$. In the formula from Step 3, the terms Total SAF and Product Exposure are properties of the product types and are independent of the fragrance material in question. The only term that varies from one fragrance material to another is the NESIL and the AEL.

2) Checking exposure by comparing AEL/CEL_{agg} to 1. AEL is the NESIL/Total SAF. Again, note that the Total SAF term is a function of the product types and is independent of the fragrance material. Further, the CEL_{agg} reflects the concentration of fragrance material which, in turn, is related to the NESIL (while all other factors relevant to CEL_{agg} do not vary with fragrance material). This means that in the ratio AEL/CEL_{agg}, by being

included in both terms, the NESIL cancels itself out and the ratio is therefore independent of the fragrance material.

3) Adjusting the $UCL_{product}$. The Relative Contribution of each category, being a ratio of exposures, is a function of product exposure, and is independent of the concentration of the fragrance material in question. This being so, the Weighting Factors and any necessary Multiplication Factors are also independent of the fragrance material (Api *et al.*, 2020a).

According to the Applicant, the Aggregate Adjustment Factors do not change unless the key input habits and practices parameters for the Creme RIFM Exposure model require change. The habits and practices data from the Kantar World Survey are reviewed and updated, if necessary, every 6–8 years.

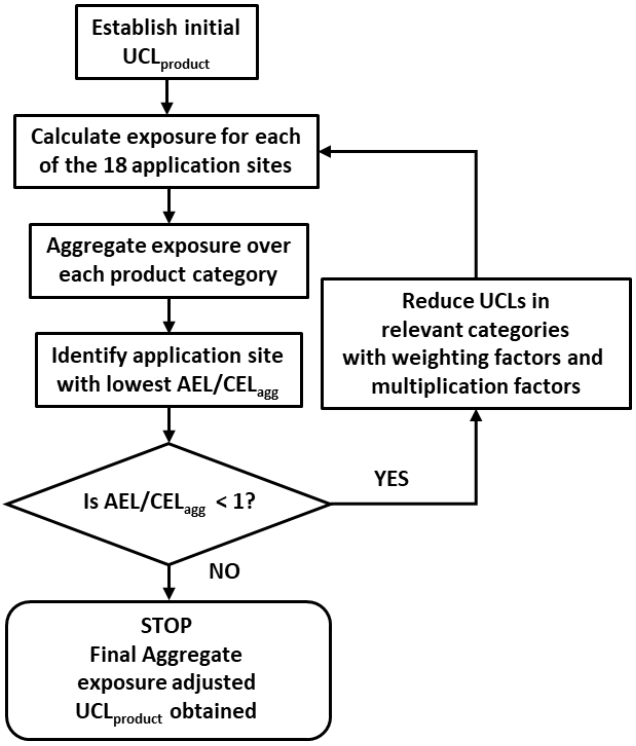

Figure 5. Derivation of the aggregate exposure adjusted $UCL_{product}$ (adapted from Api *et al.*, 2020a)

SCCS comments on aggregate adjustment factors

The term 'aggregate exposure factors' is used in the text. This seems to be a mistake. It should instead be 'aggregate adjustment factors'.

The detailed explanation provided by the Applicant in Appendix 2 of the dossier (Annex V of the current Opinion) is not sufficient to clarify how the aggregation was done and which SAFs were chosen.

The name of the box "aggregate exposure over each product category" in Figure 5 is unclear. The exposure should rather be aggregated over the body sites. It seems more logical to combine the two boxes and name the step "calculate aggregate exposure for each of the 18 application sites CEL_{agg}".

Step 4. Incorporate the Upper Concentration Levels into the Creme RIFM Exposure model and calculate aggregate consumer exposure level (CELagg) to the fragrance for each body area.

The aggregate Consumer Exposure Level (CEL_{agg}) is calculated with the Creme RIFM model, a Monte Carlo based probabilistic model which uses extensive consumer survey data from a number of countries (Comiskey *et al.*, 2015, 2017). The model uses declared habits and practices data from approximately 42,000 panellists across Europe and the United States of America (Kantar Database). Each Kantar panellist supplied diary data on which products were used during the day for seven consecutive days, as well as information on the application sites of most products.

According to the Applicant, a set of 18 non-overlapping skin sites is used in the Creme RIFM model and was adapted from the list of application sites recorded by participants in the Kantar survey (Table 3). The sites cover the entire body and are broad enough to describe usefully the behaviour of consumers, but specific enough that exposure in terms of quantity per unit area is not underestimated due to assigning too large a surface area. Therefore, the sites used to calculate aggregate exposure reflect relevant body sites based on consumer use patterns.

Table 3: Body sites used for aggregate exposure calculations (Adapted from Api *et al.*, al.,2020a)

Body Site	**Additional Definition**
Scalp	
Face	Does not include eyes, lips, mouth, behind the ears
Peri-ocular	The eyelid and surrounding skin around the eyes
Lips	
Inside mouth	Buccal/inside cheek; does not include lips
Neck	Does not include behind the ears
Behind ears	
Chest	Does not include the axillae or abdomen
Abdomen	Stomach region
Back	Does not include the axillae
Axillae	Underarm region
Arms	Includes the shoulder, forearm, and upper arm. Does not include the wrists, hands, palms, or axillae
Wrists	
Back of hands	Does not include the palms or wrists
Palms	
Anogenital	
Legs	Includes buttocks, thighs, and calves. Does not include feet
Feet	

In response to the queries of the SCCS, the Applicant provided the following additional information. Aggregate dermal exposure determined using the Creme RIFM model considers exposure to a fragrance ingredient in a total of 71 products. In addition to cosmetics, exposure to household care products (e.g., laundry, cleaning, dish care) and air care products, specifically aerosol sprays, are included in the calculation of aggregate exposure. All products in the model have habits and practices data from Kantar and/or other sources. These habits and practices data are updated every 6–8 years. A list of the individual products is provided in Annex VI of the current Opinion. The key parameters that are taken into consideration in the Creme RIFM aggregate exposure model are provided in Table 4.

Table 4: Key parameters considered in the Creme RIFM aggregate exposure model

Parameter type	**Parameter**	**Approach and justification**
Population	Assessed population	Exposed population
	Age group	Adults 18 years and over
	Geography	Presume EU and US as global standards
Product related	Concentration in product	Back calculation of max safe levels to set IFRA standards
	Occurrence	100% has been assumed at present.
	Retention Factor	Product type specific – consistent with SCCS 2023
Use related	Amount of product used	See Api *et al.*, 2008
	Frequency of use	Kantar diary
	Surface area of body sites	See Api *et al.*, 2008
	Skin sites of application of product types	Kantar diary information

The model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey *et al.*, 2015; Safford *et al.*, 2015). The model calculates the exposure for each product used by a subject derived from the highest product use day over the 7-day period, and it does this for all subjects. Taking the data from the highest product use day brings additional conservatism to the QRA2 process. Probabilistic modelling allows use of all data which enables assessment of the full variability in product uses. Calculations that make use of the variability in the input data provides variation in the output data. The output of the model is the estimated 95th percentile CEL_{agg} in µg/cm^2 for each of the 18 application sites (Api *et al.*, 2020a).

SCCS comments on body sites/ application sites

For the previous QRA Opinion, the Applicant had provided a rationale for the selection of the 18 body sites. This rationale was based on practicability: the 18 body sites represented the

most detailed partitioning provided by the Kantar database, which is used also by the Crème global model. However, the SCCS requested the scientific rationale for this, in addition to these practical considerations, so that these body sites could be considered appropriate for use in an assessment.
In Api *et al.* (2020a), some considerations and criteria were given for the selection of the body sites, namely that the whole body would be considered to be covered, that no sites would overlap, and that the sites would be broad enough to usefully describe consumer behaviour but also specific enough so that exposure in terms of quantity per unit area would not be underestimated due to assigning too large a surface area. Furthermore, body skin is divided into separate regions since regional (draining) lymph nodes critical for the acquisition of skin sensitisation function largely independently. Thus, where possible, aggregation of exposures to sites served by completely different draining lymph nodes has been avoided.

Still, the SCCS is of the opinion that the rationale provided for determining the body sites to be used as a basis for safety assessment, including by differentiation according to skin properties, occlusion levels, product types etc., has not been adequately explained.

Response from the Applicant
The paper by Api et al. (2020) states that, as indicated in Table 3 above, the set of 18 non-overlapping skin sites ''was adapted from the list of application sites recorded by participants in a survey of consumer habits and practices (Kantar Database).'' and that ''the criteria for selecting the application sites was that the whole body be covered, that no sites overlap, and that the sites be broad enough usefully to describe the behaviour of consumers, but specific enough that exposure in terms of quantity per unit area is not underestimated due to assigning too large a surface area.''
This approach ensures that the entire body surface is considered, but with no overlap between sites. Appendix 5, Section 13.5. "Product categorization and consideration of regional draining lymph nodes" has been added to the dossier to provide additional context to the statement made by Api et al. in the 2020 publication regarding skin site drainage to regional lymph nodes and to provide the rationale for not aggregating the body sites scalp, lips and head.

This information on the additional context has been added to the current Opinion in Annex VII.

Additional SCCS comment on aggregation over body sites
According to the explanation provided by the Applicant, one of the steps includes a safety assessment per body site and the most vulnerable site determines the safety. This is logical, but as such is not transparent where the SAF is considered in the above equations. From the example of Citral, it is clear that the SAF is included in the AEL. But it is not clear how the aggregate exposure for a specific body site can be related to the product-specific AEL. As different products may be used on a body site, they will then need to be related to one common AEL to determine a risk. It is not clear which AEL can be chosen for this comparison. This needs to be made clear in the methodology description.

Also, there is a "total SAF" and an "overall SAF". Are these the same or different? Given that SAFs are crucial to guarantee the conservatism of the method, it needs to be transparent how they are incorporated within the different steps of the method and how they are considered when there is aggregating exposure to different product types on one body site. Acceptance of this approach depends on this transparency, but unfortunately, the example of the bar soap and deodorant for Citral provided further on in this Opinion does not clarify this issue, because these product categories are not used on the same body sites.

Step 5. Identify body areas for which the AEL/CELagg ratio is less than 1. If there are none go to step 7.

The CEL_{agg} for all products at each application site derived with the Creme RIFM aggregate exposure model is compared to the AEL. The important consideration is that the CEL_{agg} must be less than the AEL, i.e., the AEL/CEL_{agg} ≥ 1 for all 18 application sites. Body sites with an AEL/CEL_{agg} less than 1 indicate which $UCL_{product}$ that must be lowered. The reduction process for the $UCL_{product}$ is described in detail below.

Step 6. **Apply an adjustment factor to reduce the acceptable levels for products** used on the body area with the lowest AEL/CELagg ratio. The adjustment factor for each product was calculated based on its contribution to exposure on that body area (i.e., products with a higher contribution were reduced the most).

According to the Applicant, for the practical implementation of QRA2, products were grouped into categories based on functional type, and major factors in habits and practices of consumers such as area of use (head, face, axillae, etc.), body sites exposed during product application, and whether they are rinse-off or leave-on applications (for the current product categories see Table 5). This represents a change from the categorization used previously in QRA1 (Api *et al.*, 2008) but was considered necessary to fully implement aggregate consumer exposure into the process. The individual product within a category that has the highest consumer exposure level drives the exposure for the category.

Table 5: QRA product categories (according to Api *et al.*, 2020a)

QRA2 category	Overall SAF[1]
1 – Products applied to the lips	100
2 – Products applied to the axillae	300
3 – Products applied to the face using finger tips	100
4 – Fine fragrance products	100
5 – Products applied to the face and body using the hands (palms), primarily leave-on	100
6 – Products with oral and lip exposure	100
7 – Products applied to the hair with some hand contact	30
8 – Products with significant anogenital exposure[2]	300
9 – Products with body and hand exposure, primarily rinse-off	300
10 – Household care products with mostly hand contact	100
11 – Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate[2]	300
12 – Products not intended for direct skin contact, minimal or insignificant transfer to skin (e.g. fragranced candles)	Not Restricted

SCCS comments on product types

It is not clear to the SCCS why product categories have been formed (see Table 5) instead of bundling products according to application site and then performing the QRA per application site. In addition, the rationale behind the construction of the product categories is not sufficiently clear. The Applicant seems to be inspired by exposure considerations, but then does not bundle products that create exposure at the same application site. Examining what influence the construction of categories with the same adjustment factors may have on the outcome might build confidence in the performance of the approach and ease doubts on associated uncertainties. For this, alternative categories could be created.

Response from the Applicant

Product categorization was conducted to facilitate implementation of QRA-based IFRA Standards as implementing maximum acceptable concentrations for >70 individual products (and potentially more product types likely to be added in the future) would be unwieldly and too complex to implement. Categorization was done by grouping consumer product types based on functional type, and major factors in habits and practices of consumers, such as area of use (head, face, axillae, etc.), body sites exposed during product application, and

whether they are rinse-off or leave-on applications. The current product categories are the same for all health effects. For systemic health effects an important consideration was to group products based on exposure route. For site-of-contact health effects, i.e., skin sensitization, which is the focus of the Citral dossier, the body sites exposed and application type (e.g., rinse-off or leave-on) were the most important considerations. This represents a change from the categorization used previously in QRA1 (Api et al., 2008) but was considered necessary to fully implement aggregate consumer exposure into the process. For example, category 6 assumes that the lips are exposed to oral care products such as mouth wash and toothpaste which, in turn, has an impact on the aggregate dermal exposure estimates.
Additional text has been added to Section 8.5 of the revised dossier to clarify the product categorization rationale.

Additional SCCS comment on product categories

The major concern of the SCCS regarding product categories and body sites is that all relevant exposures that occur at the same time are considered in the exposure calculation. It needs to be clarified if the broader product categories created in QRA2 are just a means to bundle according to recommended concentration levels or whether it is also assumed in the calculation that only one product per broad product category is used at the same time. The latter approach would not be acceptable to the SCCS.

Step 6. (continued)

According to the Applicant, the next step in the process is the identification of the product types used on the body sites with AEL/CEL_{agg} less than 1 and determine the contribution from those individual products categories. Since not all product categories will have an equal contribution to aggregate dermal exposure, it is necessary to approximate their relative contributions to the total body site exposure.

The reduction for the CEL_{agg} is determined as follows: for each product category the exposure at the application site to the fragrance ingredient is estimated over all products within the category. The sum of all category-level exposures is calculated as:

Category Sum = Exposure Category 1 + Exposure Category 2 + … + Exposure Category 12

Then for each product category, the exposure for the category is divided by the category sum above to obtain a Relative Contribution to the total skin application site exposure for the category. The relative contribution will have a value ranging from 0 to 1.

$$\text{Relative Contribution Category} = \frac{\text{Exposure Category}}{\text{Category Sum}}$$

A Weighting Factor is calculated for each product category by subtracting its relative contribution from 1.

Weighting Factor Category = 1 – Relative Contribution Category[1]

Use of the Weighting Factor allows the upper use level concentration to be reduced in proportion to the size of its relative contribution. In this way, the categories with exposures that have a higher potential to induce sensitization have the largest reduction in the $UCL_{product}$ (Api *et al.*, 2020a). The Weighting Factor is applied to the initial (or current as the process is iterative) category UCL to reduce it.

*Adjusted UCL Category = Initial UCL Category * Weighting Factor Category*

Weighting Factors are used to ensure that the UCLs are appropriate and do not exceed the AEL. The nature of the Weighting Factor is such that the UCLs of each product category are reduced in proportion to the size of its relative contribution, i.e., UCLs of product categories

with a low contribution to the body site exposure are reduced only a little while UCLs of categories with a high contribution are reduced to a greater degree.

The CEL_{agg} is recalculated using the new UCL values. If the adjusted UCL result in an AEL/CEL_{agg} that is still below 1 or greatly exceed 1, the Weighting Factor is adjusted by applying a Multiplication Factor to the Relative Contribution of all categories to derive refined UCLs ($AEL/CEL_{agg} \geq 1$).

Weighting Factor Category = 1 – (Relative Contribution Category x Multiplication Factor)

In cases where the adjustment of the Weighting Factor is too low, the Multiplication Factor is assigned a value to greater than 1 to amplify the effect of each category's Relative Contribution. When the adjustment of the Weighting Factor is too high, the Multiplication Factor is assigned a positive value less than 1 to reduce the effect. The Multiplication Factor assigned is established empirically using iterative calculations. No one product category is treated differently compared to other categories, maintaining the principle of applying the greatest reduction to the UCL of product categories with the highest exposures. As many products are applied to more than one body site several iterations of checking the AEL/CEL_{agg}, identifying the body site with the lowest AEL/CEL_{agg}, and adjusting UCLs may be required before the AEL/CEL_{agg} for all application sites is greater than 1 (Api *et al.*, 2020a). The ratio of the final category UCL divided by the initial category is the QRA2 aggregate adjustment factor for that product category.

Since the aggregate adjustment factors are a function of the relative contribution of exposure from each product, they are independent of the fragrance ingredient being assessed and are always the same for fragrance ingredients used in products within a category.

The Aggregate Adjustment Factors do not change unless the key input habits and practices parameters for the Creme RIFM Exposure model require change. The habits and practices data from the Kantar World Survey are reviewed and updated, if necessary, every 6–8 years.

Step 7. **Determine aggregate exposure** as in Step 2 using these modified acceptable levels.

Step 8. Follow steps 4-7 until the AEL/CEL_{agg} ratio for all body areas is equal or greater than 1 (in Step 3).

Step 9. Determine the final upper concentration levels for each product by applying the appropriate adjustment factor to the values determined in Step 1. The UCL for each product is the **maximum acceptable concentration level** for fragrance material in each product based on the potential for inducing dermal sensitization to the fragrance material.

Since the aggregate adjustment factors are a function of the relative contribution of exposure from each product, they are, according to the Applicant, independent of the fragrance ingredient being assessed. For the practical implementation of QRA2, products were grouped into categories based on the body sites exposed during application and use. The individual product within a category that had the highest consumer exposure level drives the exposure for the category. As such, the adjustment factors are always the same for fragrance ingredients used in products within a category (see also Table 6 for the case of Citral).

Additional SCCS comments to the key steps of the QRA2 methodology

The SCCS appreciates the additional clarifications, including the Figures, that have been provided by the Applicant on the different steps of the QRA2 methodology in response to the

SCCS letter. However, although this additionally provided information clarifies some questions raised by the SCCS, there are still some open issues which will be highlighted below.

Kantar population and parameters of the Crème RIFM model

The SCCS has raised issues around the use of the Kantar database before. Regarding the differences between the percentage of individuals exposed to body lotion and face cream in the Kantar database, compared to published European data (Ficheux *et al.* 2017, Garcia-Hidalgo *et al.* 2017), the Kantar population may not reflect the European population. Compared to European data by Ficheux *et al.* and Garcia-Hidalgo *et al.,* the percentage of users of body lotion in the Kantar database is much lower. From the provided description of the methodology, it seems likely that the probabilistic assessment was based on the entire adult population, with no adjustments made regarding body lotion use. Since body lotion is the largest contributor to consumer exposure, this may lead to severe underestimation of the exposure of the European population. Hence, the derived adjustment factors may not be appropriate.

Further, since the Crème RIFM model is used to provide the aggregate exposure for each body part, which is then used to derive UCL's, more information is necessary on the parameter choices in the model, e.g. the selected population.

Response from the Applicant

The Creme RIFM Aggregate Exposure Model contains habits and practices data from Kantar Worldpanel database. These data are updated on an on-going basis; the next scheduled update is planned for 2024. The publications concerning European consumer habits & practices cited by the SCCS will be carefully reviewed in the 2024 update. Given that this process is not yet completed, we have included in the dossier a presentation that step by step describes how the currently used adjustment factors are derived. Preliminary assessment of the data from the most up to date Kantar Worldpanel database appears to be closer to the data in the papers shared by the SCCS on European consumer habits & practices. Once the data has been integrated, there will be a recalculation of the assessment factors. As mentioned above, such updates will have to happen on a regular basis to ensure the data reflects the most up to date habits and practices data.

The SCCS appreciates the response and recommends that more emphasis should be put on *European consumer habits & practices* when recalculating SAF. In addition, the SCCS appreciates the description of key parameters considered in the Creme RIFM aggregate exposure model (see Table 4).

3.4.3.2 Application of QRA2 to Citral

To demonstrate use of the QRA2 approach for establishing upper concentration limits for fragrance ingredients in finished products, two product types were selected by the Applicant: solid deodorant, a 'leave-on' product; and bar soap, a 'rinse-off' hand washing, bathing, showering product. These products were chosen because they are the products within their IFRA Product Categories with the highest exposures which set the limits for all products within their respective categories (Table 6). Citral was selected as the example fragrance ingredient.

Step 1. Determination of the NESIL for Citral

The NESIL may be derived from combinations of human and *in vivo* animal data, and is expressed as a dose per unit area (e.g., µg/cm²) value. WoE NESIL can most readily be established using data from animal studies, specifically the murine local lymph node assay (LLNA), and then taking existing (historical) human studies into account. Adjuvant tests in animals (e.g., GPMT) and non-adjuvant tests in guinea pigs (e.g., Buehler) are not used as primary data sources for defining NESILs. The approach of identifying NESILs based on all available data was recently described in a manuscript (Lee *et al.*, 2022).

According to the Applicant, the data available for Citral that were considered in deriving the NESIL consisted of 15 LLNAs, five HRIPTs, and 14 HMTs (section 3.3.1.2). Data from six GPMTs and one Buehler test were considered as supporting evidence.

The LLNA EC3 values ranged from 1.2% (300 µg/cm^2) in EtOH:DEP (1:3) to 13.9% (3475 µg/cm^2) in AOO. Lalko and Api (2008) reported a weighted mean EC3 value based on the vehicle used was 5.7% which is equivalent to a dose of 1414 µg/cm^2 (Kimber *et al.*, 2003; ECHA, 2022). It has long been recognised that LLNA EC3 values for an individual skin sensitiser involve the type of variability often seen with biological determinations (Basketter *et al.*, 2007). Where multiple determinations are made, typically they are distributed around the "true" value. For example, the 2007 publication reported over 30 determinations of the EC3 value for isoeugenol, ranging from 0.7% to 2.9%, but with clear clustering towards the mean value of 1.5%. Indeed, the general experience is that a level of spread of 2-3x above and below the mean is what is typically found. It has been demonstrated also that EC3 values show a good degree of correlation with HRIPT NOELs (Gerberick *et al.*, 2001b; Griem *et al.*, 2003; Schneider and Akkan, 2004; Basketter *et al.*, 2005; Api *et al.*, 2015).
In one HRIPT, Citral induced sensitisation at an exposure of 3876 µg/cm^2 in 5/8 subjects. No sensitisation was induced in the other four HRIPTs, with the NOELs ranging from 388 µg/cm^2 to 1417 µg/cm^2. There was no identifiable NOEL among the HMTs conducted with petrolatum vehicle as all tested concentrations resulted in the induction of skin sensitisation. The single HMT using Citral at 5% (3448 µg/cm^2) in butylene glycol failed to induce sensitisation. The HRIPT NOEL of 1417 µg/cm^2 would be given precedence over the HMT data as the study was conducted in 101 volunteers according to standardized protocol following a published method and was well documented.

The Buehler Test results and five of the six GPMTs support the classification of Citral as a weak skin sensitiser. One GPMT classified Citral as a moderate sensitiser. None of these studies were judged to require a revision to LLNA/HRIPT based NESIL.

Given all the above, the weight of evidence leads to a NESIL of 1400 µg/cm^2. The guinea pig studies demonstrate that Citral is a weak to moderate skin sensitiser. The LLNA data delivers a weighted mean value for the EC3 equivalent to 1414 µg/cm^2, also consistent with the conclusion of moderate skin sensitising potential. Finally, crucially, predictive human testing whilst clearly positive at the highest dose evaluated, was negative at 1417 µg/cm^2. Rounding down to two significant figures indicates that an appropriate and pragmatic NESIL for Citral is 1400 µg/cm^2.

SCCS comment on NESIL derivation for Citral
The SCCS agrees with the Applicant that a NESIL of 1400 µg/cm^2 can be derived from all available data for Citral. This fragrance is a very data-rich compound and the results from *in vitro*, animal and human studies are in line with each other. This provides confidence in the NESIL.
For future evaluations, the SCCS will assess the WoE NESIL derivation for other data-poor fragrances/other cosmetic ingredients on a case-by-case basis.

Step 2. Determination of the Acceptable Exposure Level (AEL) for Citral

In the Applicant's dossier, the AEL for Citral in two different product types has been calculated: solid deodorant and bar soap.

For solid deodorants the total SAF is 300, based on a SAF 10 for interindividual variability, 1 for product, 3 for frequency/duration, and 10 for skin condition. The SAF for skin condition is 10 as these products are applied to the axillae where the skin is easily irritated due to a combination of factors including the unique environment of the axillae (humid, oil rich sebum production and site for perspiration). There may also be acute transient irritation due to

product application or mechanical irritation. Shaving may produce an acute transient irritation response.

Thus, the AEL for a solid deodorant is 1400 µg/cm^2 ÷ 300 = **4.7 µg/cm^2**

For bar soap the total SAF is 300, based on a SAF 10 for interindividual variability, 1 for product, 3 for frequency/duration, and 10 for skin condition. The SAF for skin condition is 10 because, in addition to hand washing, the product may be used all over the body including the axillae and intimate regions. Bar soaps are not expected to be irritant and no additional contribution to skin condition is expected from product irritation.

Thus, the AEL for a bar soap is 1400 µg/cm^2 ÷ 300 = **4.7 µg/cm^2**

SCCS comments on product choice
It is not clear why bar soap and deodorant were chosen to illustrate the approach for Citral and whether the same procedure was followed for other product categories where Citral is used. The SCCS understands that bar soap and deodorant have only been used for illustration and that the same calculations have been performed for all other product categories. Please inform the SCCS if this assumption is wrong and clarify how the aggregation was done.

Response from the Applicant
Bar soap and deodorant products were selected as being representative for rinse-off and leave-on product types, respectively. In addition, they are the product types which drive the QRA2 upper concentration levels for their respective product categories: solid deodorant/antiperspirant drives Category 2 and bar soap drives Category 9. The same procedure used for the example products, solid deodorant and bar soap, is followed for all product categories where Citral is used. The Citral upper concentration levels, calculated in the knowledge of aggregate exposure for all product categories, are provided in the adjusted dossier (Table 7 of the current Opinion).

Step 3A. Determination of the Consumer Exposure Level (CEL) for Citral

For solid deodorants, the Cowan-Ellsberry *et al.* (2008) deodorant/antiperspirant data were used by the Applicant instead of those of Loretz *et al.* (2006) and Hall *et al.* (2007) because Cowan-Ellsberry *et al.* (2008) used measured 90th percentile exposure (amount) and surface area data and integrated them into a *per diem* exposure. The 90th percentile for product amount was 1.77 g/day and the 90th percentile surface area was 193.6 cm^2.

Thus, the CEL for solid deodorants is **9.1 mg/cm^2/day** (1770/193.6= 9.14 mg/cm^2/day).

The CEL for bar soap was derived using a hand wash scenario with a daily use amount of 20.0 grams (10 uses of 2 grams each), applied to a skin surface area of 840 cm^2, and a retention factor of 0.01 (EPA, 1997; SCCS, 2012).

Thus, the CEL for bar soap is **0.2 mg/cm^2/day** (20000/840 x 0.01 =0.24 mg/cm^2/day).

SCCS comments on CEL for Citral
Initially, the reasoning for the choice of parameters from Cowan-Ellsberry *et al.* 2008 was not made sufficiently clear in the Applicant's dossier, because the "hierarchy for selecting data based on quality and scope" was not reported. Cowan-Ellsberry *et al.* (2008) determined the axilla surface in 60 men and women representative of the distribution of weights and heights in the US. The SCCS considers that this parameter is sufficiently similar in the EU and the US, so that the study can be used for the European population. It should be noted that the value of 193.6 cm^2 as P90 for surface area – and thus also the value of 9.1 mg/cm^2 - refers to axillas of women (P90 for one axilla in females is reported to be 96.8, and for males 154.8

cm^2), which reported a higher use per surface than men. This choice is therefore conservative. However, compared to Loretz *et al.* (2006), the use amounts varied less: probably because in Cowan-Ellsberry *et al.* (2008) only one product type was used by either sex: females used a solid formulation, and males a deo roll-on. This may result in a lower P90 than for the distribution of products that are on the market, but no data are available on this.

According to the SCCS Notes of Guidance (12th revision, 2023), the target protection goal is the 95th percentile of the European population. By deterministically combining the P90 for substance amount and P90 for surface area, as done by Cowan-Ellsberry *et al.* (2008), it is not guaranteed that the P95 is achieved. From Loretz *et al.* (2006) data on P95 are also available: The P95 for amount of solid antiperspirant used per day is 2.32 g/day, which together with the P90 for surface area of 193.6 cm^2 yields a **CEL of 12.0 mg/cm^2/day.** This value is proposed by the SCCS as being sufficiently conservative.

For bar soap, the default value for skin surface area proposed by the SCCS is 860 cm^2. The proposed value of 840 cm^2 has not been explained, but it is more conservative for deriving an amount per surface and is therefore accepted by the SCCS.

Response from the Applicant
In cases where there is more than one habits and practices data source for the same product, the highest value, (i.e., the most conservative value) is used. Cowan-Ellsberry et al. (2008) deodorant/antiperspirant data were used in preference to CTFA and COLIPA data because Cowan-Ellsberry et al. (2008) used measured 90th percentile exposure (amount) and surface area data and integrated it into a per diem exposure.

Bar soap and deodorant products were selected as being representative for rinse-off and leave-on product types, respectively. In addition, they are the product types which drive the QRA2 upper concentration levels for their respective product categories: solid deodorant/antiperspirant drives Category 2 and bar soap drives Category 9. The same procedure used for the example products, solid deodorant and bar soap, is followed for all product categories where Citral is used. The Citral upper concentration levels, calculated in the knowledge of aggregate exposure for all product categories, are provided the adjusted dossier of the Applicant (Table 7 in the current Opinion).

Additional SCCS comment on CEL for Citral
Since the data from Loretz *et al.* (2006) are more conservative than Cowan-Ellsberry *et al.* (2008), the SCCS retains the CEL above.

Step 3B. Calculation of initial maximum use levels by individual product type (Unadjusted Upper Concentration Level (UCL))

According to the Applicant

For a solid deodorant, the **UCL** for Citral is calculated as
((4.7 µg/cm^2 x 0.001 mg/µg) ÷ 9.1 mg/cm^2/day) x 100 **= 0.05 %**

Thus, the **unadjusted** UCL for Citral in a deodorant is 0.05%.

For a bar soap, the **UCL** for Citral is calculated as
((4.7 µg/cm^2 x 0.001 mg/µg) ÷ 0.2 mg/cm^2/day) x 100 **= 2.33 %**

Thus, the **unadjusted** UCL for Citral in a bar soap is 2.33%.

In Table 6, an overview is given of the UCL of Citral for the driving product in the 12 different product categories (1-12).

SCCS comment on UCL for Citral

Recalculation of the UCL with a CEL of 12.0 mg/cm2/day yields a starting value for the UCL of 0.04%. This then results in changes of the aggregate exposure that can only be followed up by using the aggregate model.

The SCCS understands "exposure" as the CEL of the respective products. It is advisable to use unequivocal denominations for parameters and result variables.

The SCCS is of the opinion that the addition of the term '**unadjusted**' to the UCL per product (in the text above as well as in Table 6 below) better clarifies the difference between the initial UCL and the UCL after aggregate exposure.

Table 6: Product Categories and their key parameters. Parameters are total SAF, Exposure, max Citral use level (unadjusted UCL) and QRA2 aggregate adjustment factor

Category	Category Description	Product Type that Drives Exposure	SAF	Exposure mg/cm²/day	Max. Citral Use Level for Driving Product[1] - Unadjusted UCL	QRA2 Aggregate Adjustment Factor
1	Leave on products generally applied to the lips	Lipstick	100	11.8	0.12%	0.91
2	Leave on products generally applied to the axillae	Solid Deodorants & Antiperspirants	300	9.1	0.05%	0.63
3	Products generally applied to the face using fingertips	Eye Products	100	2.17	0.65%	1.00
4	Fragrancing products generally applied to the neck, face and wrists	Fine Fragrance Products	100	2.21	0.63%	0.95
5	Leave on products applied to the face and body using the hands (palms)	Insect repellent (intended to be applied to the skin)	100	3.02	0.46%	0.33
6	Products with lip and oral exposure	Toothpaste	100	1.27	1.1%	0.32

Category	Category Description	Product Type that Drives Exposure	SAF	Exposure mg/cm²/day	Max. Citral Use Level for Driving Product[1] - Unadjusted UCL	QRA2 Aggregate Adjustment Factor
7	Products applied to hair with hand contact	Hair sprays	30	2.2	2.1%	0.58
8	Products with significant anogenital exposure	Baby wipes; NA[2]	300	7.4	0.063%	NA[3]
9	Rinse off products with body and hand exposure	Bar soap	300	0.2	2.33%	0.50
10	Household care products with mostly hand contact	Hand dishwashing detergent	100	0.2	7.0%	0.60
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	Feminine hygiene liners; NA[2]	300	0.2	2.33%	NA[2]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Example – Candles; NA[2]	Not Restricted			NA[2]

[1] Calculated maximum use level for Citral considering only exposure to the product type that drives the category, not yet adjusted for aggregate exposure.
[2] Not Applicable (NA). The products in these categories are not included in the Creme RIFM model because exposure is negligible. Therefore, aggregate exposure is not considered when calculating the acceptable levels of fragrance ingredients.

Step 4-9. Determination of maximum use levels considering aggregate exposure (Upper concentration level based on QRA2)

According to the Applicant, to derive the maximum use level considering aggregate exposure, the $UCL_{product}$ for the individual product of interest is multiplied by the appropriate Category QRA2 Aggregate Adjustment Factor to derive the final UCL (Table 7).

For a solid deodorant, the UCL considering aggregate exposure for Citral is calculated as 0.05 % x 0.63 = **0.032%.**

For a bar soap, the UCL considering aggregate exposure for Citral is calculated as 2.33 % x 0.5 = **1.2%.**

Table 7 summarizes the Upper Concentration Levels (UCL) for Citral for all fragranced consumer product categories which are considered safe with regard to the induction of skin sensitization based on the QRA2 methodology.

Table 7. Upper Concentration Levels for Citral based on QRA2 for all product categories.

Category	Category Description	Category Product Examples[1]	SCCS Product Category[2]	Unadjusted UCL[3]		UCL Based on QRA2[4]
1	Leave on products generally applied to the lips	Lipstick	Make-up products – lipstick; lip salves	0.12%		0.11%
2	Leave on products generally applied to the axillae	Solid Deodorants & Antiperspirants	Leave-on skin & hair cleansing products – deodorant non-spray	0.05%		0.032%
3	Products generally applied to the face using fingertips	Eye Products of all types, facial make-up and foundation	Make-up products – liquid foundation, eye make-up, mascara, eyeliner, make-up remover	0.65%		0.65%
4	Fragrancing products generally applied to the neck, face and wrists	Fine Fragrance Products	Fragrances – Eau de toilette spray, perfume spray; Men's cosmetics – aftershave	0.63%		0.60%
5	Leave on products applied to the face and body using the hands (palms)	Body Creams, oils, lotions of all types; Facial moisturizers and creams; Hand creams; baby creams, oils, talc	Leave-on skin & hair cleansing products – body lotion; face cream, hand cream; Baby care products; Sun care cosmetics – Sunscreen lotion/cream	0.46%		0.15%
6	Products with lip and oral exposure	Toothpaste, mouthwash	Oral care products – toothpaste, mouthwash	1.1%		0.35%
7	Products applied to hair with hand contact	Hair permanent or other hair chemical treatments(rinse-off), rinse-off hair dyes	Leave-on skin & hair cleansing products – hair styling, Oxidative/permanent hair dyes, Semi-permanent hair dyes (and lotions)	2.1%		1.2%

Category	Category Description	Category Product Examples[1]	SCCS Product Category[2]	Unadjusted UCL[3]		UCL Based on QRA2[4]
8	Products with significant anogenital exposure	Baby wipes, tampons, intimate wipes	Baby wipes and intimate wipes	0.063%		0.063%
9	Rinse off products with body and hand exposure	Bar soap, shampoo, conditioner (rinse-off), body washes and shower gels, Shaving creams of all types	Rinse-off skin & hair cleansing products – shower gel, hand wash soap, bath oil, salts, etc., shampoo, hair conditioner; Men's cosmetics – shaving cream	2.33%		1.2%
10	Household care products with mostly hand contact; Household aerosol/spray products	Hand dishwashing detergent, hand wash laundry detergent; Air freshener sprays, manual, including aerosol and pump	NA[4]	7.0%		4.2%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	Feminine hygiene liners, diapers, toilet paper (dry), Facial tissues (dry), paper towels, napkins	NA[5]	2.33%		2.3%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Candles, laundry detergents for machine wash (e.g., pods)	NA[5]			Not Restricted

1 Only a few product examples are provided for each category.
2 SCCS Product Categories taken from the 12th Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation.
3 Calculated maximum use level for Citral considering only exposure to the product type that drives the category, not yet adjusted for aggregate exposure.
4 The UCL for each product category is derived by multiplying the maximum use level of Citral for the product type that drives the category by the aggregate adjustment factor for that category as provided in Table 5.
5 Not applicable as these products are not included in the Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation.

SCCS comments on determination of maximum use levels for Citral

As already mentioned in the previous QRA Opinion (SCCS/1589/17), the SCCS understands that in the approach presented, the overall SAF is applied for each product category separately, and only the upper concentration levels are aggregated to derive the final upper concentration limits for each product.

To avoid confusion, the SCCS is of the opinion that the 'Upper concentration level (UCL) based on QRA2' (right column of Table 7) should be called the 'Maximum concentration level (per product) considering aggregate exposure'. This should then also be used in the title of Step 4-9 and in the text of that paragraph.

Furthermore, the described process leads to a maximal use of the exposure limits defined by the NESIL. Since cosmetics are not the only product category that may contain Citral, this approach will always lead to an aggregate CEL that exceeds safe limits.

The SCCS understands that the Applicant sometimes uses the terminology "weighting factor" for reducing the UCL rather the "adjustment factor" for the UCL. The wording should be consistent.

Aggregate exposure of any fragrance is calculated for various cosmetic products, but what about exposure to the fragrance from other products? The methodology to derive safe use concentrations per (cosmetic) product is designed to maximise aggregate exposure until all available 'safety space' is used. Therefore, in the safety evaluation there seemed to be hardly any room left for exposure to other product types beyond cosmetics. This means that any exposure to another product category will lead to exceeding the safe limit. Has building in some room for other exposures been considered? The SCCS acknowledges that implementing such additional, non-cosmetic exposures quantitatively in the QRA methodology would be difficult. Nevertheless, on a case-by-case basis, such additional skin exposure, which may be more pronounced and thus relevant in some cases, should be addressed as far as possible. Furthermore, any change in product use or in exposure might lead to having to update product concentrations.

Response from the Applicant

Aggregate exposure determined using the Creme RIFM model considers exposure to fragrance from a total of 71 consumer products of different types. In addition to cosmetics, exposure from household care products (e.g., laundry, cleaning, dish care) and air care products (e.g., aerosol sprays, plug-ins, scented candles) are included in the calculation of aggregate exposure. Dermal exposure may occur during use of aerosol air-care products too, so they are factored in for the calculation of aggregate exposure for QRA2. All products in the model have habits and practices data from Kantar and/or other sources. These habits and practices data are updated every 6–8 years. A list of the individual products has been added to the Citral dossier as Appendix 3, Section 13.3.

This is described in Annex VIa of the current Opinion.

RIFM conducts concentration of use surveys on individual fragrance ingredients every 5 years. For the survey, fragrance compounders report the use levels of a given fragrance ingredient in fragrance compounds (intended for a specific product type). These data are combined with the use concentrations of fragrance compounds in product types as reported by the consumer product manufacturers directly to Creme Global. Not only are the exposure data surveyed every 5 years, but the habits and practices data are also regularly updated, and the model is being expanded to include other regions of the world and additional product types when data become available (e.g. baby products). This is expected to facilitate an expansion to encompass the 87 products surveyed for fragrance concentrations which are in the model Data Portal. A list of these products is provided in the revised dossier as Appendix 4, Section 13.4.

This is described in Annex VIb of the current Opinion.

3.4 SAFETY EVALUATION

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3.5 DISCUSSION

Special investigation:
Application of QRA2 to Citral: Specific points of concern

Determination of the NESIL
In the previous Opinion on QRA2, SCCS raised several questions on the WoE guidelines for the NESIL derivation. Following this, an extensive clarification was provided by the Applicant and several articles were published. After careful reading all the available information, the SCCS concludes that the information is still fragmented and that a practical guide for the WoE NESIL derivation is needed.

The SCCS agrees with the Applicant that a NESIL of 1400 µg/cm2 can be derived from all available data for Citral. This fragrance is a very data-rich compound and the results from *in vitro*, animal and human studies are in line with each other. This provides confidence in the NESIL.
For future evaluations the SCCS will assess the WoE NESIL derivation for other data-poor fragrances/other cosmetic ingredients on a case-by-case basis.

Application of SAFs
In the previous QRA opinion (SCCS/1589/17), the SCCS commented on the use of different SAFs in the QRA2 method and proposed some changes. While SAFs for interindividual variability and frequency of product use are plausible to use, the SAFs for skin site condition and product are still not clear to the SCCS. It should be made clearer in the methodology description that the SAF's are associated with product categories and which assumptions are made. Some of the SAFs (e.g. skin condition SAF) make the impression that they are related to body parts and not to products, but rather they rely on assumptions on which body parts a product category is applied. These assumptions need to be made more transparent, e.g. by a table listing all assumptions in relation to the product categories.
Overall, although not all questions raised earlier by the SCCS have been answered, the overall rationale for the different SAFs is more clear and acceptable. The exception is the product SAF of 0.3, which the SCCS still finds questionable.

Body sites
The rationale provided for the body sites including differentiation according to skin properties, occlusion levels, product types etc. has not been adequately explained.
According to the Applicant, one of the steps includes a safety assessment per body site and the most vulnerable site determines the safety. This is logical, but as such is not transparent where the SAF is considered in the above equations. From the example of Citral, it is clear that the SAF is included in the AEL. But it is not clear how the aggregate exposure for a specific body site can be related to the product-specific AEL. As different products may be used on a body site, they will then need to be related to one common AEL to determine a risk. It is not clear which AEL can be chosen for this comparison. This needs to be made clear in the methodology description.
Since the SAFs are crucial to guarantee the conservatism of the method, for acceptance of the approach, it needs to be transparent in regard to how they are incorporated within the different steps of the method, and how they are considered when aggregating exposure from different product types for one body site. Unfortunately, the example with bar soap and deodorant for Citral further in this Opinion does not clarify this issue, because these categories are not used on the same body sites.

Product categories
The rationale behind the construction of the product categories is still not sufficiently clear.

The major concern of the SCCS regarding product categories and body sites is that all relevant exposures that occur at the same time are considered in the exposure calculation. It needs to be clarified if the broader product categories created in QRA2 are just a means to bundle according to recommended concentration levels or whether it is also assumed in the calculation that only one product per broad product category is used at the same time. The latter approach would not be acceptable to the SCCS.

Kantar population and parameters of the Crème RIFM model

The SCCS has raised issues around the use of the Kantar database before. Regarding the differences between the percentage of individuals exposed to body lotion and face cream in the Kantar database compared to published European data, the Kantar population may not reflect the European population. Compared to European data of users of body lotion in the Kantar database is much lower. From the provided description of the methodology, it is most probably that the probabilistic assessment is based on the entire adult population and no adjustments have been made regarding body lotion use. Since body lotion mostly is the largest contributor to consumer exposure, this may lead to severe underestimation of the exposure of the European population. Hence, the derived adjustment factors may not be appropriate. The SCCS appreciates the response that the publications concerning European consumer habits & practices cited by the SCCS will be carefully reviewed in the 2024 update of the Kantar database. The SCCS recommends that more emphasis should be put on European consumer habits & practices when recalculating SAF. In addition, the SCCS appreciates the description of key parameters considered in the Creme RIFM aggregate exposure model.

Aggregate exposure of cosmetic products and beyond cosmetics

Aggregate exposure of any fragrance is calculated for various cosmetic products, but there will also be exposure to the fragrance from other products. The methodology to derive safe use concentrations per (cosmetic) product is designed to maximize aggregate exposure until all available 'safety space' is used. Therefore, in the safety evaluation there seemed to be hardly any room left for exposure to other product types beyond those considered in the Kantar database, being mainly cosmetics. The SCCS acknowledges the difficulty to implement such additional, non-cosmetic exposures quantitatively in the QRA methodology. Nevertheless, on a case-by-case basis, such additional skin exposure, which may be more pronounced and thus relevant in some cases, should be addressed as far as possible. Furthermore, any change in product use or in exposure might lead to having to update product concentrations.

The SCCS appreciates the response from the Applicant in which an overview has been given of all the 71 products considered in the Kantar database, with a significant amount of non-cosmetic products.

Application of the methodology now and in the future

QRA2 is an improvement to QRA1 and is still in development. As outlined above, some aspects of the current proposed methodology based on the Crème RIFM model are not fully clear. The methodology is applicable for data-rich substances like Citral. However, for the assessment of future substances with less data more clarification as well as some case-by-case adjustments to the methodology may be needed.

In future, QRA2 should be further updated based on new exposure information as well as new technologies and developments for instance in NAMs.

4. CONCLUSION

The SCCS concludes the following:

1. *In light of the data provided and taking under consideration the derived upper safe levels using QRA2 methodology for the sensitisation endpoint, does the SCCS consider Citral safe when used as a fragrance ingredient in cosmetic products up to the maximum concentrations provided in the dossier submission?*

The SCCS has noted some aspects of the QRA2 methodology that still need clarification and possible refinement. While some questions remain, the SCCS is of the opinion that the assessment based on QRA2 methodology has indicated that Citral can be considered safe in relation to the induction of sensitisation at the concentrations proposed for use in cosmetic products.

2. *Does the SCCS have any further scientific concerns with regard to the use of QRA2 to derive safe upper levels for Citral or for fragrance allergens in general?*

Whilst the proposed QRA2 methodology is an improvement to QRA1 methodology, the SCCS recommendation is specific for the sensitisation potential of Citral at the proposed use concentrations. More case studies are needed to further confirm the applicability of this approach to other fragrances and other cosmetic ingredients. Until then, the SCCS will consider the suitability (for a population not already sensitised) of this methodology for other fragrances and other cosmetic ingredients on a case-by-case basis.

5. MINORITY OPINION

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7. GLOSSARY OF TERMS

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 158

8. LIST OF ABBREVIATIONS

ACD	allergic contact dermatitis
AEL	acceptable exposure level
AOP	adverse outcome pathway
CAS	chemical abstracts service
CEL	consumer exposure level to a fragrance ingredient of interest from use of a single product
CEL_{agg}	consumer exposure level to a fragrance ingredient resulting from concomitant use of a number products
CNIH	confirmation of no induction in humans (formerly referred to as HRIPT)
GLP	good laboratory practice
GPMT	guinea pig maximisation test
h-CLAT	human cell line activation test
HPLC	high performance liquid chromatography
HRIPT	human repeated insult patch test
IDEA	International Dialogue for Evaluation of Allergens
KE	key event
LLNA	local lymph node assay
MIT	minimal induction threshold
NESIL	no expected sensitization induction level
QRA	quantitative risk assessment
RFI	relative fluorescence intensity
SAF	sensitization assessment factor
UCL	upper concentration level
$UCL_{product}$	upper concentration level in an individual product
WoE	weight of evidence

Further abbreviations see SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 158

ANNEX I

Details on in vitro and guinea pig studies (supportive data for NESIL derivation)

Table A.1: Details on in vitro sensitization tests with Citral

In vitro test	Reference	Guideline/ method	Concentrations	Readings	Results	Conclusions
1 Direct peptide reactivity assay	Natsch et al., 2013	Equivalent to OECD 442C	100mM stock solution, 5mM in cysteine peptide reaction mixture, 25mM in lysine peptide reaction mixture	Relative concentrations of the peptide following a 24-hour reaction time are determined by high performance liquid chromatography	Citral induced a mean cysteine peptide depletion of 85.7% and a mean lysine peptide depletion of 16.9%. The overall peptide mean depletion was 51.3%.	Based on the overall mean peptide depletion, Citral would be classified as highly reactive, and thus identified as a skin sensitiser.
2 Direct peptide reactivity assay	Bauch et al., 2012	Equivalent to OECD 442C	100mM stock solution, 5mM in cysteine peptide reaction mixture, 25mM in lysine peptide reaction mixture	Relative concentrations of the peptide following a 24-hour reaction time are determined by high performance liquid chromatography	Citral induced a mean cysteine peptide depletion of 78.59% and a mean lysine peptide depletion of 8.63%. The overall peptide mean depletion was 43.6%	Based on the overall mean peptide depletion, Citral would be classified as highly reactive, and thus identified as a skin sensitiser.
3 KeratinoSens™ assay	Natsch et al., 2013	Equivalent to OECD 442D	12 final in-well concentrations of 2000, 1000, 500, 250, 125, 62.5, 31.25, 15.63, 7.81, 3.91, 1.95, and 0.98 µM	Luciferase activity and cytotoxicity following a 48-hour incubation time are determined by luminescence detection and MTT assay	Citral induced a EC1.5 of 23.16 µM, a EC3 of 67.36 µM, and an IC50 of 182.8 µM	Based on the results, Citral would be classified as sensitising
4 Human cell line activation test	Nukada et al., 2012	Equivalent to OECD 442E	8 concentrations based on the concentration resulting in 75% cell viability (CV75) determined in a preliminary test ranging from 1.2× CV75 to 0.335 × CV75	Cell surface expression of CD86 and CD54 measured by flow cytometry following a 24 h chemical exposure	Citral induced a EC150 of 8.41 µg/mL, a EC200 of 15 µg/mL, and an MIT of 8.41 µg/mL. The CV 75 was 24 µg/mL	Based on the results, Citral would be classified as sensitising

Table A.2: Details on Guinea pig studies with Citral

	Method/ guideline	Reference	Species/ strain Sex, Group size	Vehicle	Concentrations	Dermal induction	Challenge	Readings	R
1	GPMT according to Magnusson and Kligman, 1969	Klecak et al., 1977	Guinea pig/ outbred Himalayan white spotted Males and females , group size not reported	Vehicle not reported for intradermal induction, petrolatum for topical induction and challenge	Intradermal induction: 5% test substance dissolved in vehicle, with/without Freund's complete adjuvant (FCA)	7 days after intradermal induction 25% test substance in petrolatum fixed by occlusive dressing for 48 h	14 days following dermal induction at the maximum non irritating concentration in petrolatum fixed by an occlusive dressing for 48 h	24, 48 h after patch removal according to Draize	S o
2	GPMT according to Magnusson and Kligman, 1969	Goodwin and Johnson 1985	Guinea pig/ not specified Males and females , 10 animals/group	Vehicle not reported	Intradermal induction: 0.4% test substance dissolved in vehicle,with/without Freund's complete adjuvant (FCA)	7 days after intradermal induction at 1%	14 days following dermal induction at 0.25%	24, 48 h after patch removal	P w (
3	GPMT according to Magnusson and Kligman, 1969, equivalent/similar to OECD 406	Ishihara et al., 1986 cited in Lalko and Api, 2008	Guinea pig/ not specified Sex and group size Not specified	Vehicle not reported	Intradermal induction: 10% test substance dissolved in vehicle, with/without Freund's complete adjuvant (FCA)	7 days after intradermal induction at 10%	14 days following dermal induction at 10%	24, 48 h after patch removal	P w t p r p
4	GPMT according to Magnusson and Kligman, 1969, equivalent/similar to OECD 406	Basketter et al., 1991	Guinea pig/ Dunkin Hartley Males and females , 10 animals/group	Vehicle not reported	Intradermal induction: 0.2% test substance dissolved in vehicle, with/without Freund's complete adjuvant (FCA)	7 days after intradermal induction at 5%	14 days following dermal induction at 5% and a second challenge at 0.5%	24, 48 h after patch removal	P w o a c b s
5	GPMT according to Magnusson and Kligman, 1969, equivalent/similar to OECD 406	ECHA dossier for Citral, study 001	Guinea pig/ Parbright white Female, 10 for 1st challenge, 5 for rechallenges, 5 per control group	Citral substance no. 77/ 711 Vehicle: Paraffin oil DAB07	Intradermal induction: 25% test substance dissolved in paraffin oil DAB7, with/without Freund's complete adjuvant (FCA)	7 days after intradermal induction at 25% in paraffin oil DAB7	Challenge: 14 days following dermal induction at 10% in paraffin oil DAB7 Re-challenge: First and second rechallenges at 5% in paraffin oil DAB7	24 and 72 h after patch removal; first rechallenge test at 24 h and control at 24 and 72h after patch removal; second rechallenge test and control at 24, 48, and 72 h after patch removal	F p w 1 t (a r r o (a
6	GPMT according to Magnusson and Kligman, 1969, equivalent/similar to OECD 407	ECHA dossier for Citral, study 002	Guinea pig/ Parbright white Female, 10 for 1st challenge, 5 for rechallenges, 5 per control group	Citral substance no. 77/ 711 Vehicle: Paraffin oil DAB08	Intradermal induction: 25% test substance dissolved in paraffin oil DAB7, with/without Freund's complete adjuvant (FCA)	7 days after intradermal induction at 25% in paraffin oil DAB7	Challenge: 14 days following dermal induction at 10% in paraffin oil DAB7 Re-challenge: First and second rechallenges at 5% in paraffin oil DAB8	24 and 72 h after patch removal; first rechallenge test at 24 h and control at 24 h and 6 days (144 h) after patch removal; second rechallenge test and control at 24, 48, and 72 h after patch removal	F p w 1 t (a r r o (
7	Buehler test, according to Buehler 1965	Lalko and Api, 2008; RIFM 1973	Guinea pig, 5 per group	Vehicle petrolatum	Induction: 20% in petrolatum		20% in petrolatum	24 and 48 after patch removal	F p w 1 a

ANNEX II

Details on human sensitization studies with Citral

HRIPT

1. Study Design:

Reference:	Lalko and Api, 2008; RIFM 2004b
Date of report:	2004
Guideline/method:	Human Repeat Insult Patch Test (HRIPT)
Species: Human	18+ years
Group size:	30 males and 71 females
Test substance:	Citral
Vehicle:	Diethyl phthalate:Ethanol (DEP:EtOH), 3:1
Concentrations:	Induction: 1.2% Citral 3:1 DEP:EtOH.
Challenge:	1.2% Citral 3:1 DEP:EtOH
Readings:	Challenge test at 24 and 48 h after patch removal.
GLP:	No
Published:	Yes

Material and methods:
Citral was tested at 1.2% Citral 3:1 DEP:EtOH in 30 male and 71 female volunteers. 0.3 mL of the test material was applied to a 25 mm Hill Top Chamber® (patch area of 2.54 cm2), resulting in a dose of 1417 µg/cm2. Patches were applied every Monday, Wednesday, and Friday for three consecutive weeks for a total of nine induction exposures. The challenge was performed 2 weeks after the last induction exposure by application of 1.2% Citral 3:1 DEP:EtOH. The challenge application site was scored 24 and 48 hours after removal of the patch.

Results:
Following challenge, no reactions were observed in any of the 101 volunteers.

Conclusion:
It is noted that this HRIPT originally was reported as conducted at 1400 µg/cm^2, (Reference: RIFM, 2004b), perhaps having been rounded down to 2 significant figures. Nevertheless, the actual concentration was as detailed here, with the study being compliant with the fully detailed RIFM HRIPT protocol (Reference: Politano and Api, 2008; Na *et al.*, 2021). Consequently, it was demonstrated that Citral does not have the potential to induce dermal sensitisation in humans at a dose of 1417 µg/cm^2 under occlusive patch conditions.

2. Study Design

Reference:	Lalko and Api, 2008; RIFM 1964a
Date of report:	1964
Guideline/method:	Human Repeat Insult Patch Test (HRIPT)
Species:	Human 18+ years
Group size:	8 females
Test substance:	Citral
Vehicle:	alcohol SDA 39C
Concentrations:	Induction: 5% Citral in alcohol SDA 39C. Challenge: 5% in alcohol SDA 39C
Readings:	Challenge test at 24 and 48 h after patch removal.
GLP:	No
Published:	Yes

Material and methods:
Citral was tested at 5% in alcohol SDA39C eight female volunteers. 0.5 mL of the test material was applied to a patch with a 1-inch square Webril pad (6.45 cm2), resulting in a dose of 3876 µg/cm2. Patches were applied every Monday, Wednesday, and Friday for three consecutive weeks for a total of nine induction exposures. The challenge was performed 2 weeks after the last induction exposure by application of 5% Citral in alcohol SDA39C. The challenge application site was scored 24 and 48 hours after removal of the patch.
Results:
Following challenge, positive reactions were observed in 63% (5/8) of the volunteers. Approximately 7 months later, four of the subjects who had reactions at the initial challenge were rechallenged with both a patch and an open application. Two of the four subjects reacted to the patch challenge and none (0/4) reacted to the open challenge.

Conclusion:
It was demonstrated that Citral has the potential to induce dermal sensitisation in humans at a dose of 3876 µg/cm^2 under patch conditions.

3.Study Design

Reference:	Lalko and Api, 2008; RIFM 1964b
Date of report:	1964
Guideline/method:	Human Repeat Insult Patch Test (HRIPT)
Species:	Human 18+ years
Group size:	12 males and 29 females
Test substance:	Citral
Vehicle:	alcohol SDA 39C
Concentrations:	Induction: 0.5% Citral in alcohol SDA 39C. Challenge: 0.5% in alcohol SDA 39C
Readings:	Challenge test at 24 and 48 h after patch removal.
GLP:	No
Published:	Yes

Material and methods:
Citral was tested at 0.5% in alcohol SDA39C in 12 male and 29 female volunteers. 0.5 mL of the test material was applied to a patch with a 1-inch square Webril pad (6.45 cm2), resulting in a dose of 388 µg/cm2. Patches were applied every Monday, Wednesday, and Friday for three consecutive weeks for a total of nine induction exposures. The challenge was performed 2 weeks after the last induction exposure by application of 0.5% Citral in alcohol SDA39C. The challenge application site was scored 24 and 48 hours after removal of the patch.

Results:
Following challenge, no reactions were observed in any of the 41 volunteers.

Conclusion:
It was demonstrated that Citral does not have the potential to induce dermal sensitisation in humans at a dose of 388 µg/cm2 under patch conditions.

4.Study Design

Reference:	Lalko and Api, 2008; RIFM 1965
Date of report:	1965
Guideline/method:	Human Repeat Insult Patch Test (HRIPT)
Species:	Human 18+ years
Group size:	11 males and 29 females
Test substance:	Citral
Vehicle:	alcohol SDA 39C
Concentrations:	Induction: 1.0% Citral in alcohol SDA 39C.

	Challenge: 1.0% in alcohol SDA 39C
Readings:	Challenge test at 24 and 48 h after patch removal.
GLP:	No
Published:	Yes

Material and methods:
Citral was tested at 1% in alcohol SDA39C in 11 male and 29 female volunteers. 0.5 mL of the test material was applied to a patch with a 1-inch square Webril pad (6.45 cm2), resulting in a dose of 775 µg/cm2. Patches were applied every Monday, Wednesday, and Friday for three consecutive weeks for a total of nine induction exposures. The challenge was performed 2 weeks after the last induction exposure by application of 1% Citral in alcohol SDA39C. The challenge application site was scored 24 and 48 hours after removal of the patch.

Results:
Following challenge, no reactions were observed in any of the 40 volunteers.

Conclusion:
It was demonstrated that Citral does not have the potential to induce dermal sensitisation in humans at a dose of 775 µg/cm2 under patch conditions.

5.Study Design

Reference:	Lalko and Api, 2008; RIFM 1971a
Date of report:	1971
Guideline/method:	Human Repeat Insult Patch Test (HRIPT)
Species:	Human 18+ years
Group size:	50
Test substance:	Citral
Vehicle:	petrolatum
Concentrations:	Induction: 4% Citral in petrolatum.
	Challenge: 4% in petrolatum.
Readings:	Challenge test at 24 and 48 h after patch removal.
GLP:	No
Published:	Yes

Material and methods:
Citral was tested at 4% in petrolatum in 11 male and 29 female volunteers. 0.2 mL of the test material was applied to a patch with a 6.45 cm2 Webril pad, resulting in a dose of 1240 µg/cm2. Patches were applied every Monday, Wednesday, and Friday for three consecutive weeks for a total of nine induction exposures. The challenge was performed 2 weeks after the last induction exposure by application of 4% Citral in petrolatum. The challenge application site was scored 24 and 48 hours after removal of the patch.

Results:
Following challenge, no reactions were observed in any of the 50 volunteers.

Conclusion:
It was demonstrated that Citral does not have the potential to induce dermal sensitisation in humans at a dose of 1240 µg/cm^2 under patch conditions.

Table A.3 : Overview of Human Maximization tests with Citral

Test Substance Concentration Vehicle	Dose Volume/Patch Area	Induction Dose ($\mu g/cm^2$)	Incidence of Positive Responses	References
8% in petrolatum	1 mL / 14.5 cm^2	5517	33% (8/24)	Lalko and Api, 2008; RIFM 1971b
5% in petrolatum	1 mL / 14.5 cm^2	3448	64% (16/25)	Lalko and Api, 2008; RIFM 1974a
5% in petrolatum	1 mL / 14.5 cm^2	3448	56% (14/25)	Lalko and Api, 2008; RIFM 1974c
5% in petrolatum	1 mL / 14.5 cm^2	3448	48% (12/25)	Lalko and Api, 2008; RIFM 1974c
5% in petrolatum	1 mL / 14.5 cm^2	3448	32% (8/25)	Lalko and Api, 2008; RIFM 1974c
5% in petrolatum	1 mL / 14.5 cm^2	3448	46% (11/24)	Lalko and Api, 2008; RIFM 1974d
5% in butylene glycol	1 mL / 14.5 cm^2	3448	0% (0/25)	Lalko and Api, 2008; RIFM 1974e
4% in petrolatum	1 mL / 14.5 cm^2	2759	12% (3/25)	Lalko and Api, 2008; RIFM 1972b
4% in petrolatum	1 mL / 14.5 cm^2	2759	12% (3/25)	Lalko and Api, 2008; RIFM 1972c
4% in petrolatum	1 mL / 14.5 cm^2	2759	20% (5/25)	Lalko and Api, 2008; RIFM 1972c
4% in petrolatum	1 mL / 14.5 cm^2	2759	36% (9/25)	Lalko and Api, 2008; RIFM 1971c
4% in petrolatum	1 mL / 14.5 cm^2	2759	16% (4/25)	Lalko and Api, 2008; RIFM 1971c
4% in petrolatum	1 mL / 14.5 cm^2	2759	20% (5/25)	Lalko and Api, 2008; RIFM 1971c
2% in petrolatum	1 mL / 14.5 cm^2	1379	8% (2/24)	Lalko and Api, 2008; RIFM 1971d

Annex III

Detailed description of Hazard identification and WoE NESIL derivation (as provided in the revised Applicant's dossier)

Hazard Identification

The first step in deriving a WoE NESIL is hazard identification to determine if the substance in question is a skin sensitizer. All available data should be collected and evaluated not only for the outcome of the study but also the reliability of the data, e.g., was the study conducted according to an OECD Testing guideline using good laboratory practices, and whether sufficient study details provided including the identity and purity of the material tested. The types of data to be considered includes historical *in vivo* data from guinea pig studies (e.g., guinea pig maximization test, Buehler test, Open Epicutaneous Test, etc.) and the murine local lymph node assay (LLNA). NAM data from assays which assess protein binding (e.g., the direct peptide reactivity assay (DPRA), the kinetic DPRA), keratinocyte activation (e.g., KeratinoSens™, LuSens), and dendritic cell activation (e.g., human Cell Line Activation Test (h-CLAT), U-SENS, GARD®skin) can be used for hazard identification when combined using a defined approach such as the '2 out of 3' or 'Integrated Testing Strategy (ITSv1, ITSv2)' as described in the OECD Guideline No. 497 (OECD 2021). Information from various *in silico* tools such as the OECD Toolbox (OECD), Tissue Metabolism Simulator for predicting skin sensitization (TIME-SS; Laboratory of Mathematical Chemistry, Bourgas, Bulgaria), and DEREK (Lhasa Ltd., Leeds, UK) can also be considered. While no human tests are ever conducted for hazard identification, existing human data can be evaluated, including historical information from the Human Maximization Test (HMT), the Human Repeat Insult Patch Test (HRIPT) (Na *et al.*, 2022a; Politano and Api, 2008). In addition, information from diagnostic patch tests conducted for clinical purposes can provide evidence relating to the presence or absence of hazard. If an unequivocal positive response in humans is found, then the chemical in question is a skin sensitizer. The use of human data in the derivation of the NESIL will be discussed further below.

If no data are found or if the available data are not sufficient, testing with at least two NAMs covering different key events of the skin sensitization Adverse Outcome Pathway (i.e., covalent binding to protein, activation of keratinocytes, activation of dendritic cells) should be conducted. Read across to data for structurally similar analogues may also be used to establish sensitization hazard. There are a number of approaches by which suitable analogues are identified (Wu *et al.*, 2010; Date *et al.*, 2020; Moustakas *et al.*, 2022; Lester *et al.*, 2023). Some approaches involve the use of *in silico* tools and computational methods to help with the expert review of potential candidate molecules. Others follow a set of rules to guide selection of analogues. Endpoint specific rules for selecting suitable analogues for read across for skin sensitization have been developed (Moustakas *et al.*, 2022), the most important is that the candidate molecule(s) must have the same structural features that drive protein reactivity as those in the chemical of interest. If the chemical of interest has more than one structural alert, then the read-across analogue must also have all those alerts.

When clear negative results are obtained in human, animal, or NAM studies, the material in question would be non-sensitizing. A lack of protein binding alerts from the *in silico* tools adds additional support for classification as a non-sensitizer. If this is the outcome of the data evaluation, no NESIL is needed because a QRA is not required.

If the outcome of the evaluation of all pieces of evidence is that that the fragrance ingredient should be considered as a skin sensitizer, the next step is to examine the data to determine its sensitizing potency.

Dose Response, Determination of Sensitization Potency

When determining sensitization potency, a weight of evidence approach with all available data should be used with the key sources being historical human data (e.g., HRIPT, CNIH), animal (LLNA), *in silico* (e.g., OECD Toolbox, TIMES-SS) and *in vitro* data (e.g., DPRA, kDPRA, KeratinoSens, h-CLAT, and other NAMs). Other data sources that may be used as supporting evidence are guinea pig tests (e.g., GPMT, Buehler) and diagnostic patch test data.

Historically, data from *in vivo* tests have been used to assess sensitization potency. The LLNA is the most informative as dose response data are obtained and the estimated concentration to induce a threshold positive response, the EC3 value, can be calculated using linear interpolation (Basketter *et al.*, 1999). EC3 values are calculated as a % concentration which is then converted to a dose per unit area (i.e., µg/cm^2) using a conversion factor of 250 (e.g., an EC3 of 1% is equivalent to 250 µg/cm^2) (Basketter *et al.*, 2005). LLNA EC3 values have been shown to correlate with human sensitization no-observed-effect levels (Gerberick *et al.*, 2001b; Griem *et al.*, 2003; Schneider and Akkan, 2004; Basketter *et al.*, 2005; Basketter and McFadden, 2012; Api *et al.*, 2015; Basketter *et al.*, 2018). Two different potency categorization schemes based on EC3 values have been published and are shown below in Table 4 (ECETOC 2003; Kimber *et al.*, 2003; SCCS, 2023).

Table A.1: Potency categorization of skin sensitizers according to LLNA EC3 values.

	SCCS (2023)		ECETOC (2003); Kimber *et al.*, (2003)	
Potency Category	EC3 (%)	EC3 µg/cm^2	EC3 (%)	EC3 µg/cm^2
Extreme	≤ 0.2	≤ 50	< 0.1	< 25
Strong	> 0.2 - ≤ 2.0	> 50 - ≤ 500	≥ 0.1 - < 1.0	≥ 25 - < 250
Moderate	> 2	> 500	≥ 1.0 - < 10	≥ 250 - < 2500
Weak	-	-	≥ 10 - ≤ 100	≥ 2500 - ≤ 25,000

Na *et al.*, (2022a) published dose ranges that can be assigned to potency categories based on human data (HRIPT/HMT) and LLNA EC3 values (Table 5). The ranges assigned to LLNA EC3 values align with those of ECETOC (2003) and Kimber *et al.*, (2003).

Table A.2: **Potency category dose ranges**

Potency Category	Human NOEL (HRIPT/HMT) (µg/cm^2)	LLNA EC3 (µg/cm^2)
Extreme	< 25	< 25
Strong	25 – 500	25 - < 250

Potency Category	Human NOEL (HRIPT/HMT) (µg/cm^2)	LLNA EC3 (µg/cm^2)
Moderate	500 – 2500	250 - < 2500
Weak	>2500 - 10,000	2500 - 25,000
Extremely weak	> 10,000	
Non-sensitizer	Negative	

Guinea pig tests, specifically the Guinea Pig Maximization Test (GPMT) and the Buehler test, were designed for the purpose of hazard identification. While they are not well suited for potency categorization, several schemes have been published that utilize the induction concentration and the incidence of positive responses to provide an estimate of the relative sensitization potency (ECETOC 2003; Kimber *et al.*, 2003; Basketter *et al.*, 2005; ECHA 2012). It is important to note that for the GPMT, the scheme reported by ECHA (2012) and Basketter *et al.*, (2005) use the intradermal induction concentration and the scheme reported in the ECETOC Technical Report No. 87 (ECETOC 2003) and by Kimber *et al.*, (2003) use the topical induction concentration (Table 6), while the Buehler test employs only topical induction treatments (Table 7).

Table A.3: Potency categorization of skin sensitizers according to the GPMT

Basketter *et al.*, (2005); ECHA (2012)			ECETOC (2003); Kimber *et al.*, (2003)		
Intradermal induction concentration	Incidence of Sensitization (30-60%)	Incidence of Sensitization (≥60%)	Topical induction concentration	Incidence of Sensitization (30-60%)	Incidence of Sensitization (≥60%)
≤ 0.1	Strong*	Extreme	< 0.1	Strong	Extreme
> 0.1 - ≤ 1	Moderate*	Strong*	≥ 0.1 - < 1	Moderate	Strong
> 1	Moderate	Moderate*	≥ 1 - < 10	Weak	Moderate
* Acknowledged by the EU expert group that this categorization is associated with a high degree of uncertainty			≥ 10 - ≤ 100	Weak	Weak

Table A.4: Potency categorization of skin sensitizers according to the Buehler Test

ECHA (2012)			ECETOC (2003); Kimber *et al.*, (2003)		
Induction concentration	Incidence of Sensitization (15-60%)	Incidence of Sensitization (≥60%)	Induction concentration	Incidence of Sensitization (15-60%)	Incidence of Sensitization (≥60%)
≤ 0.2	Strong*	Extreme	< 0.1	Strong	Extreme
> 0.2 - ≤ 20	Moderate*	Strong*	≥ 0.1 - < 1	Moderate	Strong

ECHA (2012)			ECETOC (2003); Kimber *et al.*, (2003)		
> 20	Moderate	Moderate*	≥ 1 - < 10	Weak	Moderate
* Acknowledged by the EU expert group that this categorization is associated with a high degree of uncertainty			≥ 10 - ≤ 100	Weak	Weak

NAMs currently validated by OECD are primarily for hazard identification. The kDPRA can be used alone for United Nations Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS) categorization as 1A or non-1A. Using the Defined Approaches ITSv1 and ITSv2, the DPRA, h-CLAT and *in silico* predictions from either DEREK or the OECD Toolbox, respectively, may be combined to derive UN GHS subcategorizations of 1A, 1B, or not categorized. GARD®skin Dose-Response is being evaluated as a method to provide UN GHS subcategorizations of 1A, 1B, or not categorized (Gradin *et al.*, 2020). To be of use for risk assessment, NAM based approaches need to provide continuous potency data and not just UN GHS subcategories. Several approaches are in the early stages of evaluation; the SENS-IS assay (Cottrez *et al.*, 2016; Na *et al.*, 2022b), a modification of GARD®skin which includes a dose-response and provides an EC3-equivalent value (Gradin *et al.*, 2021), regression models which use kDPRA, KeratinoSens and h-CLAT data (Natsch and Gerberick 2022; Natsch 2023) and a Bayesian Network approach (Jaworska *et al.*, 2015). Assessing their performance for use in risk assessment is a high priority.

If no dose response data are found or if the available data are not sufficient, read across to data for structurally similar analogues, as described above, may also be used to establish a potency category.

Determination of the WoE NESIL

In deriving a NESIL, an overall WoE approach is utilized. This decision-making approach considers all available data which includes a strategic combination of data derived from NAMs along with historical animal and human data, when available, as well as data obtained through read-across on structurally and/or mechanistically related chemicals.

A WoE NESIL, expressed as a dose per unit area of skin (i.e., μg/cm^2), is an exposure to a skin sensitizer which should not result in the induction of sensitization in humans. When deriving a WoE NESIL, all available data, including data from structural analogues, are considered. Diagnostic patch test data, which can be considered at the hazard identification step, are not considered in deriving a NESIL because the test is for elicitation of an allergic reaction in an already sensitized individual and, therefore, does not provide quantitative exposure information with regards to the induction of sensitization.

Annex IV

Supplementary table with various SAFs per product type (Api *et al.*, 2020)

Appendix Table 1: SAFs for Fragrance materials in Different Product Types. Contribution of different SAFs and Rationale for Product SAF and Skin Condition SAF

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Category 1 - products applied to the lips						
Lip products[a]	10	1	3*	3*	A SAF of 3* is applied because the site is applied to the lips (highly vascular and there is exposure to mucous membranes and possible exposure to dry or chapped lips). Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Toys	10	1	3*	3*	These products are placed have been placed in Category 1. There are no exposure data available; should exposure data become available, then the products will be re-categorized. Due to the possibility of ingestion of small amounts of fragrance materials from the use of the aforementioned allowable product categories (such as oral care, lip products or certain types of toys), materials present in the fragrance must not only comply with IFRA Standards but must also have an approved flavor materials status as defined by the IOFI Code of Practice.	100
Category 2 - Products applied to the axillae						
Deodorants & antiperspirants of all types including fragranced body sprays[a]	10	1	3*	10	The SAF is 10 as these products are applied to the axillae where the skin is easily irritated due to a combination of factors including the unique environment of the axillae (humid, oil-rich sebum production and site for perspiration). There may also be acute transient irritation due to product application or mechanical irritation. Shaving may produce an acute transient response.	300
Category 3 - Products applied to the face using fingertips						
Eye products (Includes: eye shadow, mascara, eyeliner, eye make-up)	10	1	3*	3*	The SAF is 3* because product is applied to the peri-ocular site and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Makeup (foundation)[a]	10	1	3*	3*	SAF is 3* because the product is applied to the face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Make-up remover[a]	10	1	3*	3*	SAF is 3* because the product may be applied to eyelids (peri-ocular region) and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Nose pore strips	10	1	3*	3*	SAF is 3* because the product is applied to the nose with minimal skin contact. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Wipes or refreshing tissues for faces, neck, hands, body	10	1	3*	3*	SAF is 3* because the product may be applied to eyelids (peri-ocular region) and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Body paint	10	1	3*	3*	SAF is 3* because the product may be applied to eyelids (peri-ocular region), face and body. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Make-up remover for face, eyes, and lips[b]	10	1	3*	3*	The SAF is 3* because product is applied to the peri-ocular site, lips and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Masks: face and lips and around the eyes mask	10	1	3*	3*	SAF is 3* because the product may be applied to the face, lips and peri-ocular region. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Facial masks (facial treatment)	10	1	3*	3*	SAF is 3* because the product may be applied to eyelids (peri-ocular region) and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Category 4 - Fine Fragrance						
Fine fragrance all types (eau de toilette, perfume, cologne etc.) [a]	10	1	3*	3*	The area is the neck, wrists, antecubital fossa. Irritation from shaving may produce an acute transient response. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

1

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Fragranced bracelets	10	1	3*	3*	The area is the wrists. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Ingredients of perfume kits	10	1	3*	3*	The area is the neck, wrists, antecubital fossa. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Scent pads, foil packs	10	1	3*	3*	The area is the neck, wrists, antecubital fossa. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Scent strips for hydroalcoholic products	10	1	3*	3*	The area is the neck, wrists, antecubital fossa. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hair perfume	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there may also be exposure to the scalp. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Category 5 - Products applied to the face and body using the hands (palms), primarily leave-on						
Facial cream (moisturizing)/facial balm[a]	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

2

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Moisturizer face, eyes, and lips	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face, peri-ocular site and lips. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hand cream[a]	10	1	3*	3*	The SAF is 3* because the product is applied to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Body creams, lotions[a]	10	1	3*	10	The SAF is 10 because the area is the entire body which may include areas of inflamed skin, i.e.: intimate regions and axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Nail care products including cuticle creams etc.	10	1	3*	3*	The SAF is 3* because some nail care products are applied to the fingers and the back of the hands.	100
Foot care products (creams & powders)	10	1	3*	3*	The SAF is 3* because the product is applied to the feet and may be applied with the palms of the hands.	100
Baby cream	10	1	3*	10	The SAF is 10 because the area is the entire body which may include areas of inflamed skin, i.e.: intimate regions and axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Baby oil	10	1	3*	10	The SAF is 10 because the area is the entire body which may include areas of inflamed skin, i.e.: intimate regions and axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300

1

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Baby powder/talc	10	1	3*	10	The SAF is 10 because the area of exposure will possibly include the whole body[33] including the peri-anal region. The skin integrity of some exposed areas may be compromised (diaper rash) [62].	300
Insect repellent (intended to be applied to the skin)	10	1	3*	3*	The SAF is a 3*. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hand sanitizers	10	1	3*	3*	The SAF is 3* because the product is applied to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Face toner/astringent/anti-bacterial cleansers[b]	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face and peri-ocular site. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
All powders and talcs (except baby powders and talcs)	10	1	3*	10	The SAF is 10 because the area of exposure will possibly include the whole body[33] including the peri-anal region. The skin integrity of some exposed areas may be compromised (diaper rash) [62].	300
Category 6 - Products with oral and lip exposure						
Toothpaste[a]	10	1	3*	3*	The SAF is a 3*. The sites are the lips and mouth. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Mouthwash[a]	10	1	3*	3*	The SAF is a 3*. The sites are the lips and mouth. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Category 7 - Products applied to the hair with some hand contact						

2

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Hair sprays[a]	10	1	3*	1	The SAF is 1 because it is applied to the hair with minimal exposure of the scalp and hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	30
Hair styling aids (mousse, gels, leave-in conditioners) [a]	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there will also be exposure to the scalp and the palms of the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hair permanent or other hair chemical treatments (e.g. relaxers) but not hair dyes	10	1	3*	3*	It is recognized that these product types involve repeated low-frequency exposure. In order to define a per diem exposure, a conservative surrogate product has been chosen, which is hair styling aids.	100
Dry shampoo or waterless shampoo	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there will also be exposure to the scalp and the palms of the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hair deodorizer	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there may also be exposure to the scalp and the palms of the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hair dyes	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there will also be exposure to the scalp and the palms of the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

1

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Category 8 - Products with significant ano-genital exposure						
Intimate wipes	10	1	3*	10	The skin site SAF is 10 because peri-anal region is involved.	300
Tampons	10	1	3*	20	SAF is 20 because close, occluded contact occurs with non-keratinized mucosa (vaginal mucous membrane)[37,40-48] and exposure may occur for extended periods of time. This area may be prone to irritation. Farage, 2003	600
Baby wipes	10	1	3*	10	The SAF is 10 because the peri-anal region may be exposed. The area is primarily the baby's buttocks, groin, lower stomach and upper thighs where the skin integrity may be compromised (diaper rash) [62] and could involve mucous membrane exposure[37,40-48].	300
Wet toilet paper	10	1	3*	10	The SAF is 10 because the peri-anal region may be exposed.	300
Category 9 - Products with body and hand exposure, primarily rinse off						
Bar soap[a]	10	1	3*	10	The SAF is 10 because product may be used all over the body including the axillae and intimate regions. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Shampoo[a]	10	1	3*	10	The SAF is 10 because the product is applied to the head (hair) and scalp with the hands and may also be used over the entire body as a shower gel. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300

2

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Face washes, gels, scrubs[b]	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Conditioner (rinse-off) [a]	10	1	3*	3*	SAF is 3* because the product is applied to the head (hair) and scalp with the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Liquid soap[a]	10	1	3*	3*	The SAF is 3* because product may be used on the hands and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Body wash/shower gels[a]	10	1	3*	10	The SAF is 10 because product may be used all over the body including intimate regions and axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Bath gels, foams, mousses	10	1	3*	10	The SAF is 10 because product may be used all over the body including intimate body regions and the axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Baby wash, bath, shampoo	10	1	3*	10	The SAF is 10 because product may be used all over the body including intimate body regions and the axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300

1

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Foot care products (feet are placed in a bath for soaking)	10	1	3*	3*	The SAF is 3* because product is used on the feet. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Shaving creams, foams, gels[b]	10	1	3*	3*	The SAF is a 3* because the area is a part of the face.	100
Depilatory, hair removal creams, foams, gels (including facial) [b]	10	1	3*	10	The SAF is 10. It has been judged that the use of depilatories may lead to an irritation that requires 10-fold assessment factor compared to the conditions of the confirmatory tests (e.g. HRIPT).	300
Waxes for mechanical hair removal[b]	10	1	3*	3*	The SAF is 3* because many skin sites could be exposed. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation as the wax is inert and contact time with skin is brief.	100
Face and lips scrubs	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face and lips. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Facial cleansing wipes and cleanser wipe-off products[b]	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face, peri-ocular site and lips. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Cleanser for face, eyes, and lips	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face, peri-ocular site and lips. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

2

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Shampoos for pets	10	1	3*	3*	The SAF is 3* because the product is exposed to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Category 10 - Household care products with mostly hand contact						
Aerosol air fresheners[a]	10	1	3*	1	SAF is a 1 because the exposure may include the upper extremities of the body.	30
Hand wash laundry detergent[b]	10	1	3*	3*	The SAF is 3* because the product is exposed to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Laundry pre-treatment (all types)[b]	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is limited contact with the hands.	100
Hand dishwashing detergent[b]	10	1	3*	3*	The SAF is 3* because the product is exposed to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hard surface cleaner (all types)[b]	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is limited contact with the hands.	100
Laundry detergents with skin contact (e.g. liquids, powders)[b]	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100

1

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Dry cleaning kits	10	1	3*	3*	The SAF is 3* because although the stain removing components of this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100
Toilet seat wipes	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100
Fabric softeners - liquids[b]	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100
Fabric Softeners - dryer sheets[b]	10	0.3	3*	3*	The SAF is 3* because limited contact with the hands is anticipated.	30
Bath cleaners, bleach, disinfectants, floor cleaner, kitchen cleaner, multi-purpose cleaner, soft surface cleaners, cleaner, window cleaner, furniture polishes (sprays and wipes), limescale removers[b]	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100
Washing up liquids[b]	10	1	3*	3*	The SAF is 3* because limited contact with the hands is anticipated.	100
Other household cleaning products (fabric cleaners, carpet cleaners, leather cleaning wipes, starch sprays, stain removers, fabric enhancing sprays)	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100
Animal sprays (all types)	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100
Floor wax	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, minimal contact with the hands is anticipated.	100
Fragranced oil for lamp rings, reed diffusers, etc.	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100
Odored distilled water (that can be added to steam irons)	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100

2

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
In-wash scent booster pastilles	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100
Category 11 - Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate						
Feminine hygiene conventional pads, liners, interlabial pads	10	1	3*	10	The SAF is 10 because the contact is predominantly with stratified, squamous keratinized epithelium (Farage et al. 2003).	300
Diapers (baby and adult)	10	1	3*	10	The SAF is 10 because the peri-anal region may be exposed. The area of exposure will possibly include the whole body[33]. The skin integrity may be compromised (diaper rash) [62]. There may also be mucous membrane exposure [37,40-48].	300
Tights with moisturizers	10	1	3*	10	The SAF is 10 because contact with skin is anticipated and will be longer than brief. The ano-genital area may be exposed.	300
Scented socks, gloves	10	1	3*	3*	The SAF is 3* because contact with skin is anticipated and will be longer than brief.	100
Facial tissues (dry tissues)	10	0.3	3*	3*	The SAF is 3* because contact with the hands, lips, and face is anticipated.	30
Napkins	10	0.3	3*	3*	The SAF is 3* because contact with the hands, lips, and face is anticipated.	30
Paper towels	10	0.3	3*	3*	The SAF is 3* because contact with the hands is anticipated.	30
Toilet paper (dry)	10	0.3	3*	10	The SAF is 10 because the peri-anal region may be exposed. The area of exposure will possibly include the whole body[33]. The skin integrity may be compromised[62]. There may also be mucous membrane exposure [37,40-48].	100

1

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Wheat bags	10	1	3*	3*	The SAF is 3* because contact with skin is anticipated and will be longer than brief.	100
Solid fertilizers (pellet or powder)	10	1	3*	3*	The SAF of 3* has been attributed because the product may come into contact with the hand and uncovered extremities. No additional contribution to skin condition is expected from product irritation	100
Face Masks (paper/protective, e.g. surgical mask)	10	1	3*	3*	The SAF is 3* because contact with skin is anticipated and will be longer than brief.	100
Category 12 - Products not intended for direct skin contact, minimal or insignificant transfer to skin						
Candles[a]	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Closed air fresheners[a]	10	0.3	3*	1	The SAF is 1 because there is only rare accidental contact with the skin.	10
Laundry detergents with minimal skin contact (e.g. pods)[b]	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Air fresheners and fragrancing of all types (*concentrated aerosol with metered doses (range 0.05-0.5mL/spray)*, plug-ins, solid substrate, membrane delivery, electrical, potpourri, powders, fragrancing sachets, incense, liquid refills, air freshening crystals) [a]	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Air delivery systems	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Cat litter	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10

2

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Deodorizers/maskers not intended for skin contact (e.g. fabric drying machine deodorizers, carpet powders)	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Fuels	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Insecticides (e.g. mosquito coil, paper, electrical, for clothing)	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Joss sticks or incense sticks	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Machine dishwash detergent, deodorizers and rinse aids[b]	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Paints	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Plastic articles (excluding toys)	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Scratch and sniff	10	1	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Scent pack	10	1	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Scent delivery system (using dry air technology)	10	1	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Shoe polishes	10	1	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Toilet blocks	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10

*In keeping with convention, values of 0.1, 0.3, 1, 3, 10, 30, 100 and 300 are used such that when multiplying SAF values, 3 is treated as an integer when multiplied with 1, 10, 100 to give 3, 30 300 but when multiplied by itself it is considered as the number 3 approximates √10 (c. 3.16) such that 3 x 3 = 10.

Note: Products that contain sunscreens are not addressed separately but are included in the major product types (e.g. lip creams with sunscreen are included in lip product category).

[a]Consumer products in the Creme RIFM Aggregate Exposure Model, Version 2.0 (2018)

[b]Consumer products in the next version of the Creme RIFM Aggregate Exposure Model Version 3.0 (expected to launch Q3, 2019).

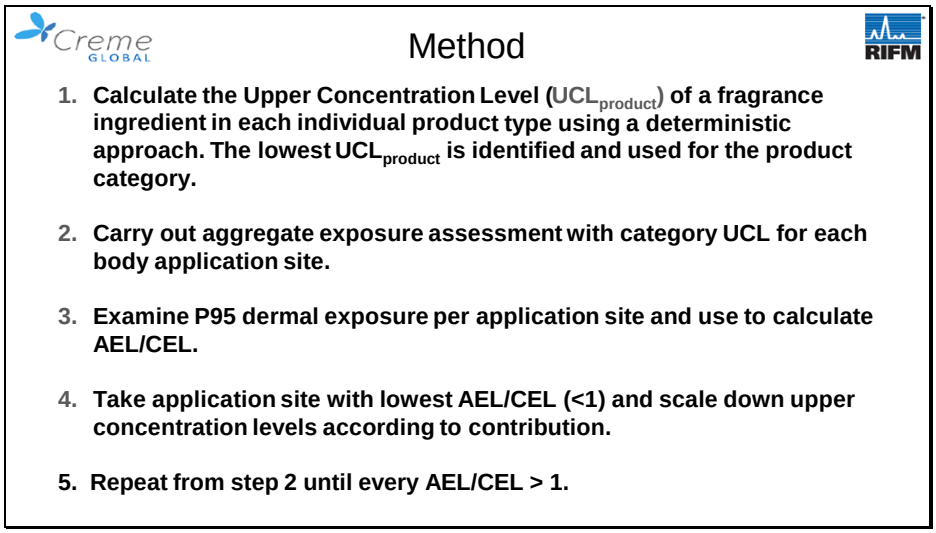
Annex V

Derivation of the aggregate adjustment factor (from the revised Applicant's dossier)

The following slides contain a detailed walk through of the derivation of the aggregate adjustment factors using the current Kantar data.

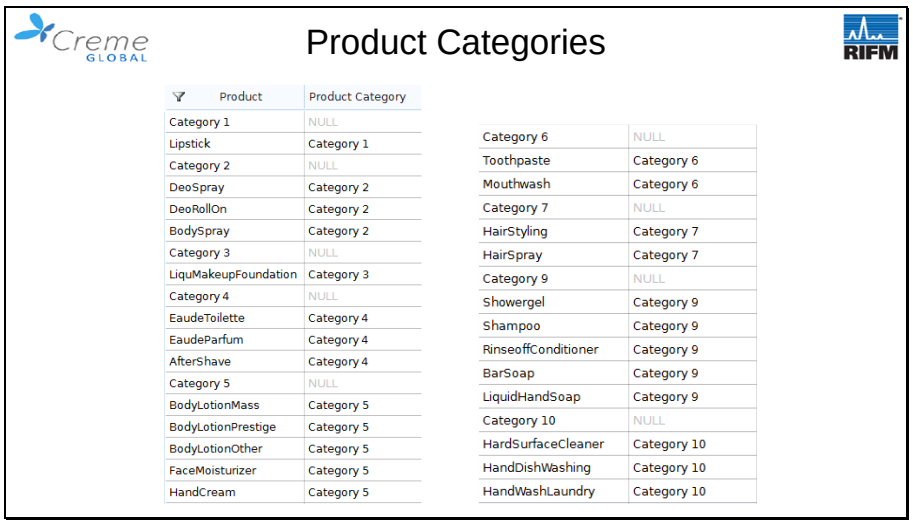
Derivation of Aggregate Exposure Adjustment Factors

Slide 1



Derivation of the Aggregate Exposure Adjustment Factors is a multi-step, iterative process. The basic steps are shown above and will be demonstrated in more detail in subsequent slides.

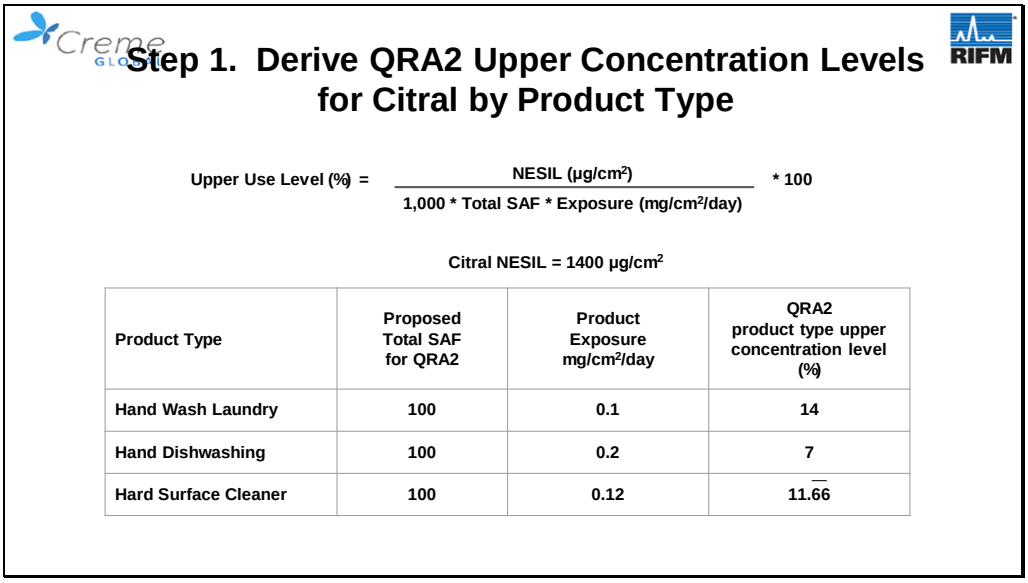
Slide 2



Product	Product Category
Category 1	NULL
Lipstick	Category 1
Category 2	NULL
DeoSpray	Category 2
DeoRollOn	Category 2
BodySpray	Category 2
Category 3	NULL
LiquMakeupFoundation	Category 3
Category 4	NULL
EaudeToilette	Category 4
EaudeParfum	Category 4
AfterShave	Category 4
Category 5	NULL
BodyLotionMass	Category 5
BodyLotionPrestige	Category 5
BodyLotionOther	Category 5
FaceMoisturizer	Category 5
HandCream	Category 5
Category 6	NULL
Toothpaste	Category 6
Mouthwash	Category 6
Category 7	NULL
HairStyling	Category 7
HairSpray	Category 7
Category 9	NULL
Showergel	Category 9
Shampoo	Category 9
RinseoffConditioner	Category 9
BarSoap	Category 9
LiquidHandSoap	Category 9
Category 10	NULL
HardSurfaceCleaner	Category 10
HandDishWashing	Category 10
HandWashLaundry	Category 10

To facilitate implementation of QRA2 based IFRA Standards, products were grouped into categories based on the body sites exposed and application type (e.g., rinse off or leave on).
For each product category, the lowest $UCL_{product}$ across all the products within the category will be used for that category. Examples of the products considered in the derivation of the aggregate exposure adjusted UCLs are shown above.

Slide 3



Step 1. Derive QRA2 Upper Concentration Levels for Citral by Product Type

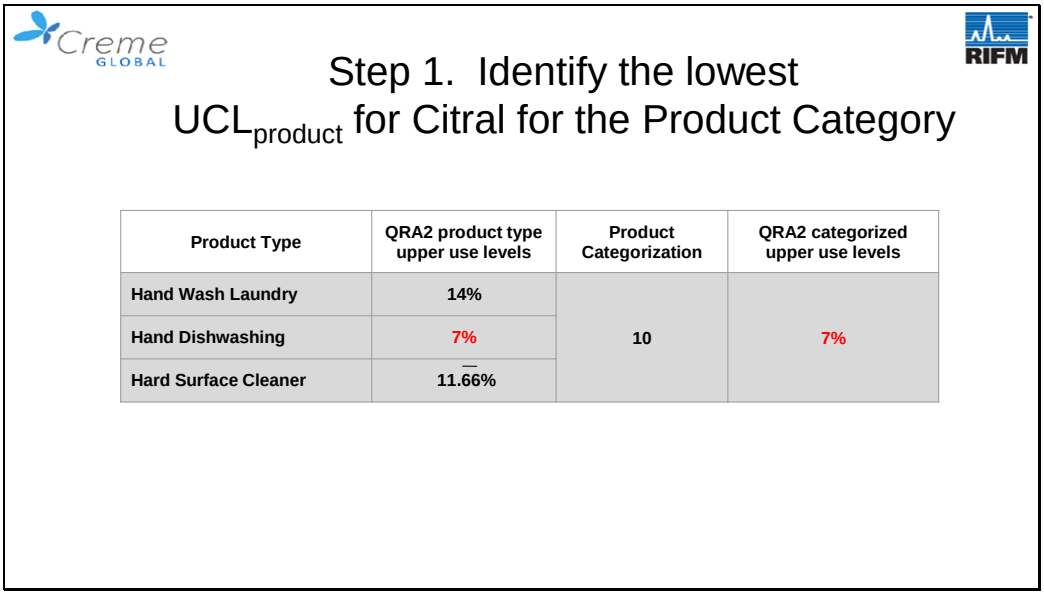
$$\text{Upper Use Level (\%)} = \frac{\text{NESIL } (\mu g/cm^2)}{1{,}000 * \text{Total SAF} * \text{Exposure } (mg/cm^2/day)} * 100$$

Citral NESIL = 1400 µg/cm²

Product Type	Proposed Total SAF for QRA2	Product Exposure mg/cm²/day	QRA2 product type upper concentration level (%)
Hand Wash Laundry	100	0.1	14
Hand Dishwashing	100	0.2	7
Hard Surface Cleaner	100	0.12	11.66

For the first step, the $UCL_{product}$ is calculated for each product type. Shown above are the resulting $UCL_{product}$ for three household care products.

Slide 4

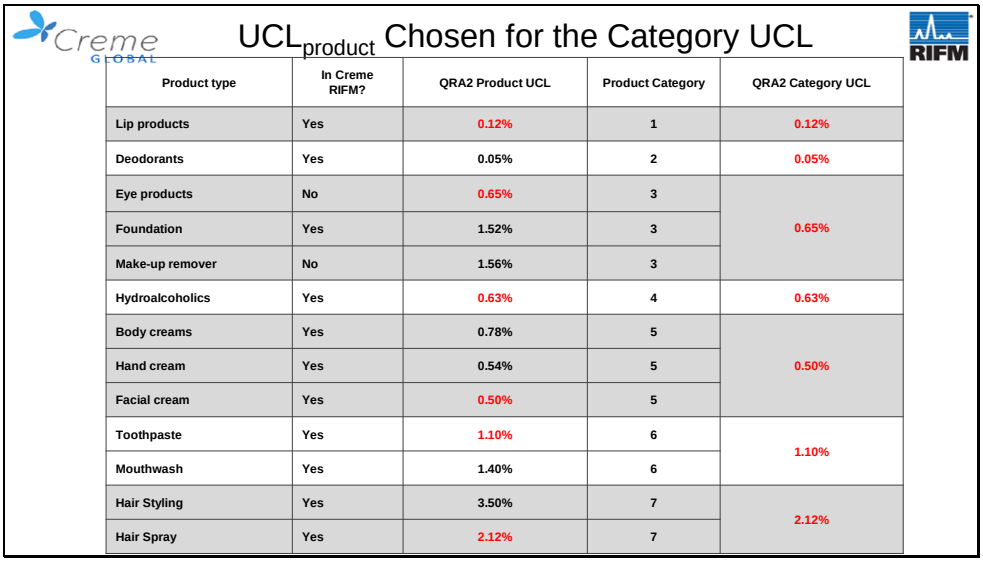


Step 1. Identify the lowest $UCL_{product}$ for Citral for the Product Category

Product Type	QRA2 product type upper use levels	Product Categorization	QRA2 categorized upper use levels
Hand Wash Laundry	14%	10	7%
Hand Dishwashing	7%		
Hard Surface Cleaner	11.66%		

For the household care products, the lowest $UCL_{product}$ was 7% for hand dishwashing products. This value is used for all products within the household care Category 10. Using the lowest $UCL_{product}$ for the category represents a conservative approach.

Slide 5

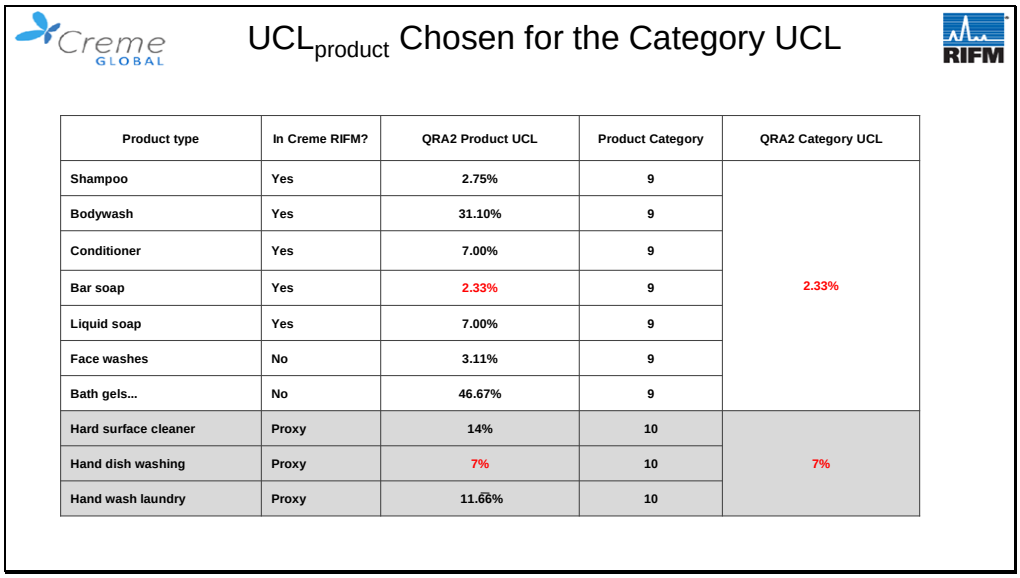


$UCL_{product}$ Chosen for the Category UCL

Product type	In Creme RIFM?	QRA2 Product UCL	Product Category	QRA2 Category UCL
Lip products	Yes	0.12%	1	0.12%
Deodorants	Yes	0.05%	2	0.05%
Eye products	No	0.65%	3	0.65%
Foundation	Yes	1.52%	3	
Make-up remover	No	1.56%	3	
Hydroalcoholics	Yes	0.63%	4	0.63%
Body creams	Yes	0.78%	5	0.50%
Hand cream	Yes	0.54%	5	
Facial cream	Yes	0.50%	5	
Toothpaste	Yes	1.10%	6	1.10%
Mouthwash	Yes	1.40%	6	
Hair Styling	Yes	3.50%	7	2.12%
Hair Spray	Yes	2.12%	7	

The lowest $UCL_{product}$ within each category is identified and is used as the UCL for that product category. Shown above are the results for product categories 1 to 7.

Slide 6

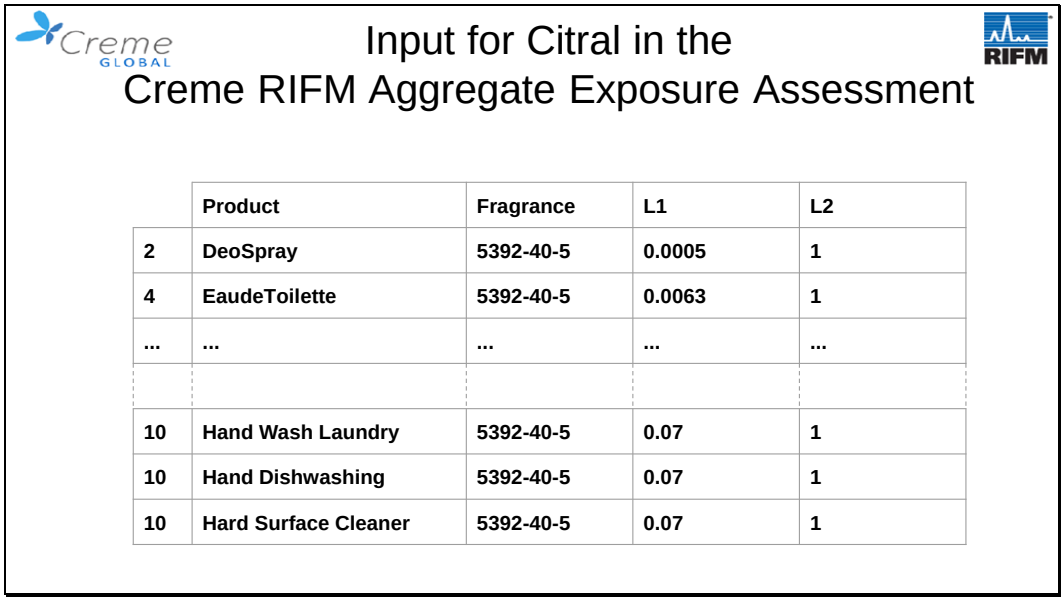


$UCL_{product}$ Chosen for the Category UCL

Product type	In Creme RIFM?	QRA2 Product UCL	Product Category	QRA2 Category UCL
Shampoo	Yes	2.75%	9	2.33%
Bodywash	Yes	31.10%	9	
Conditioner	Yes	7.00%	9	
Bar soap	Yes	2.33%	9	
Liquid soap	Yes	7.00%	9	
Face washes	No	3.11%	9	
Bath gels...	No	46.67%	9	
Hard surface cleaner	Proxy	14%	10	7%
Hand dish washing	Proxy	7%	10	
Hand wash laundry	Proxy	11.66%	10	

The lowest $UCL_{product}$ within each category is identified and used as the UCL for the product category. Shown above are the results for product categories 9 and 10. Note that category 8, products with significant anogenital exposure (e.g., tampons) is not shown since those products are not currently in the Creme RIFM aggregate exposure model.

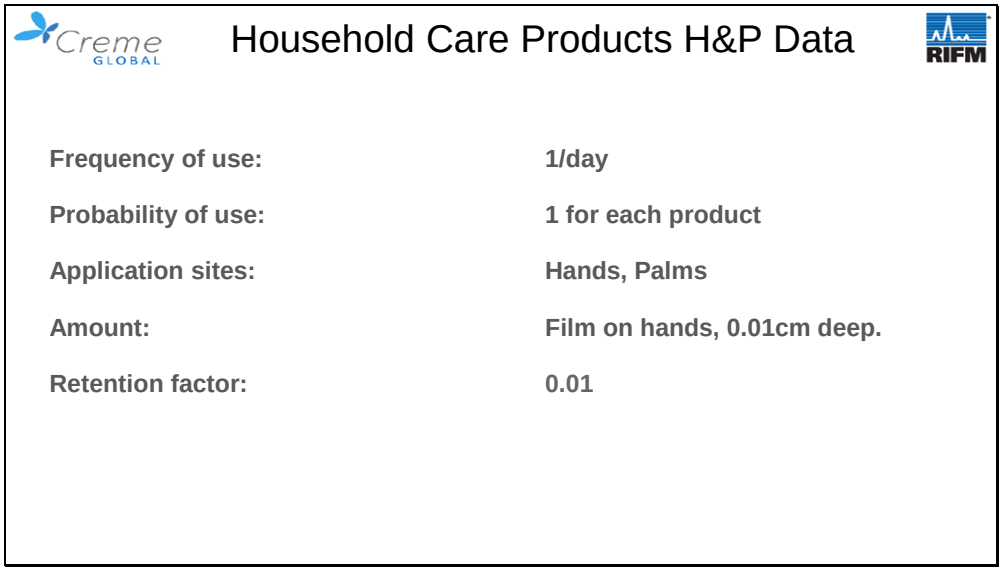
Slide 7



	Product	Fragrance	L1	L2
2	DeoSpray	5392-40-5	0.0005	1
4	EaudeToilette	5392-40-5	0.0063	1
...	...	...	...	...
10	Hand Wash Laundry	5392-40-5	0.07	1
10	Hand Dishwashing	5392-40-5	0.07	1
10	Hard Surface Cleaner	5392-40-5	0.07	1

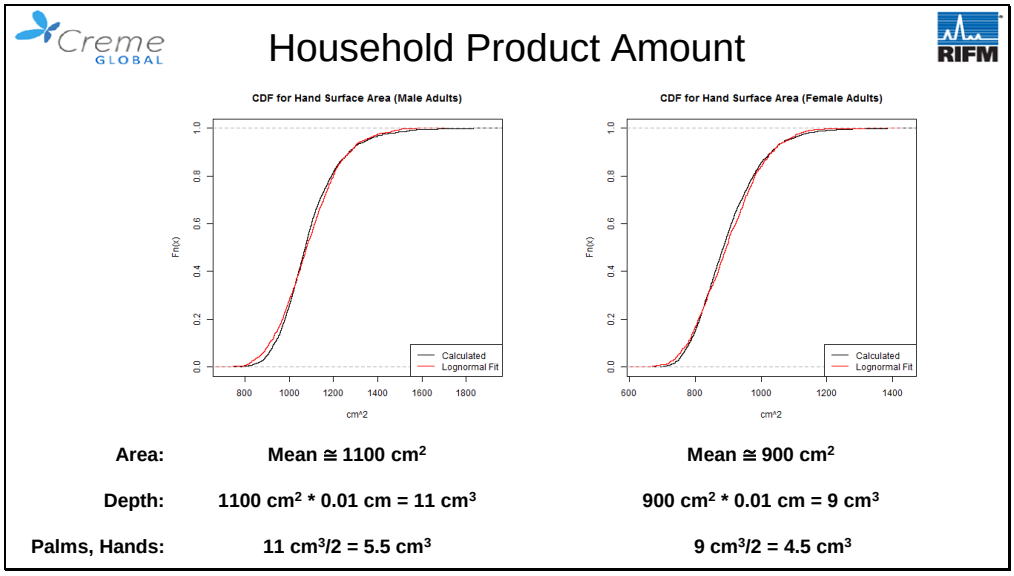
The key data used in the Creme RIFM model are concentration data on fragrance ingredients used in fragrance mixtures (L1 in the table above) together with the concentrations of fragrance mixtures used in the final products (L2 in the table above). These data are collected in a systematic method by RIFM from all their member companies every five years. Shown above are the input data for several of the product categories.

Slide 8



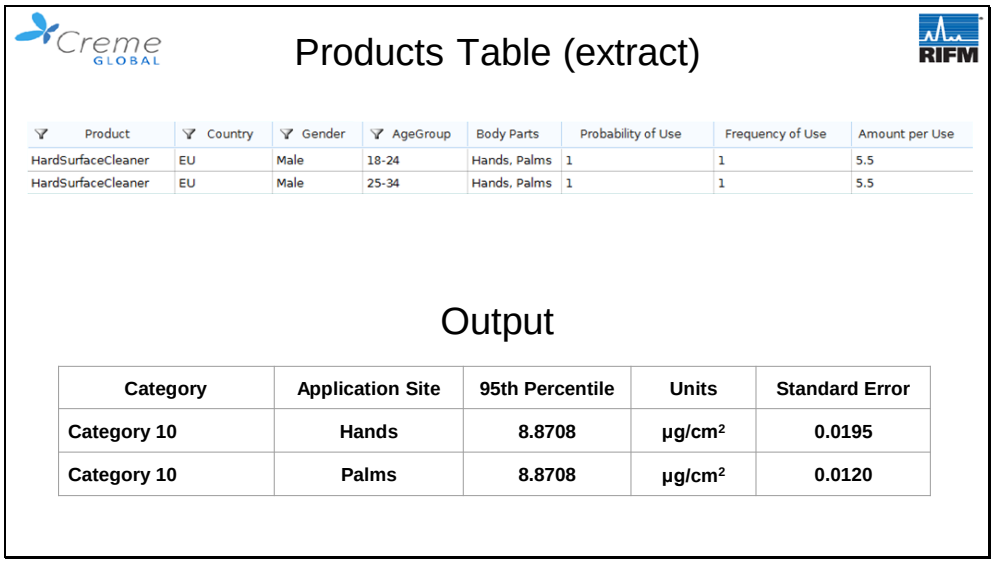
For determination of the current aggregate adjustment factors, the habits & practices (H&P) data used for the household care products are shown above.

Slide 9



The exposure for the palms and hands is calculated using the habits and practices data and the RIFM survey concentrations (i.e., L1 and L2).

Slide 10



Above is the model output for category 10 hands and palms exposure. Probabilistic modelling allows use of all data which enables assessment of the full variability in product uses. Calculations that make use of the variability in the input data provides variation in the output data. The output of the model is the estimated 95th percentile. The Creme RIFM model calculates the exposure for each product used by a subject, derived from the highest product use day during a seven-day period as recorded in the Kantar diary, and it does this for all subjects. Taking the data from the highest product use day brings additional conservatism to the QRA2 process.
The table at the top is an excerpt. "Hands" in both tables means "back of hands".

Slide 11

AEL/CEL_{Agg} by Application Site

Application Site	Inter-individual SAF	Product SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL_{Agg}	AEL/CEL_{Agg}
Palms	10	1	3	3	100	1400	14	34.0276	0.4114
Lips	10	1	3	3	100	1400	14	30.9190	0.4528
Intra-oral	10	1	3	3	100	1400	14	28.3802	0.4933
Axillae	10	1	3	10	300	1400	4.7	7.4170	0.6337
Back of Hand	10	1	3	3	100	1400	14	15.4863	0.9040

After the model calculated the 95th percentile aggregate Consumer Exposure Level (CEL_{agg}) in µg/cm^2 for all products at each of the 18 application sites, it is compared to the AEL. The important consideration is that the CEL_{agg} must be less than the AEL, i.e., the $AEL/CEL_{agg} \geq 1$ for all 18 application sites. Body sites with an AEL/CEL_{agg} less than 1 indicate which $UCL_{product}$ must be lowered. In the table above there are five body sites with AEL/CEL_{agg} less than 1. Since the palms have the lowest AEL/CEL_{agg} amongst these five, product categories which result in exposure to this body site will be examined first.

Adjust for Palms

Product Category	95th Percentile Dermal Exposure (µg/cm²)	Relative Contribution	Percentage Relative Contribution	UCL Weighting Factor	Adjusted UCL
5	14.4288	14.4288/44.4678 = 0.3245	32.45%	1 - 0.3245 = 0.6755	0.5% * 0.6755 = 0.3378%
9	10.6489	10.6489/44.4678 = 0.2395	23.95%	1 - 0.2395 = 0.7605	2.33% * 0.7605 = 1.7720%
7	9.3915	9.3915/44.4678 = 0.2112	21.12%	1 - 0.2112 = 0.7888	2.12% * 0.7888 = 1.6723%
10	8.8708	8.8708/44.4678 = 0.1995	19.95%	1 - 0.1995 = 0.8005	7% * 0.8005 = 5.6035%
4	1.1278	1.1278/44.4678 = 0.02536	2.536%	1 - 0.02536 = 0.9746	0.63% * 0.9746 = 0.6140%
Total	44.4678	1	100%	-	

Slide 12

The relative contribution from those individual products categories to palm exposure is determined. Since not all product categories will have an equal contribution to aggregate dermal exposure it is necessary to approximate their relative contributions to the total body site exposure.

The reduction for the CEL_{agg} is determined as follows: for each product category the exposure at the application site to the fragrance ingredient is estimated over all products within the category. The sum of all category level exposures is calculated as:

Category Sum = Exposure Category 1 + Exposure Category 2 + … + Exposure Category 12

Then for each product category, the exposure for the category is divided by the category sum above to obtain a Relative Contribution to the total skin application site exposure for the category. The relative contribution will have a value ranging from 0 to 1.

$$\textit{Relative Contribution Category} = \frac{\textit{Exposure Category}}{\textit{Category Sum}}$$

A Weighting Factor is calculated for each product category by subtracting its relative contribution from 1.

Weighting Factor Category = 1 – Relative Contribution Category$_1$

The Weighting Factor is applied to the initial (or current as the process is iterative) category UCL to reduce it.

*Adjusted UCL Category = Initial UCL Category * Weighting Factor Category$_i$*

Slide 13

Recalculate AEL/CEL$_{Agg}$ (Palms)

Application Site	Inter-individual SAF	Product SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL$_{Agg}$	AEL/CEL$_{Agg}$
Lips	10	1	3	3	100	1400	14.0	31.0658	0.4507
Intra-oral	10	1	3	3	100	1400	14.0	28.5133	0.4910
Palms	10	1	3	3	100	1400	14.0	24.9656	0.5608
Axillae	10	1	3	10	300	1400	4.7	7.0605	0.6657
Back of Hand	10	1	3	3	100	1400	14.0	11.3860	1.2296

The CEL$_{agg}$ is recalculated using the new UCL values and is compared to the AEL. Body sites with an AEL/CELa$_{gg}$ less than 1 indicate which UCL must lowered further.

Adjust for Palms Multiplication Factor (MF)

Product Category	95th Percentile Dermal Exposure (µg/cm^2)	Relative Contribution	Percentage Relative Contribution	UCL Weighting Factor with MF	Adjusted UCL
5	14.4288	14.4288/44.4678 = 0.3245	32.45%	1 - (0.3245 * 2) = 0.3510	0.5% * 0.3510 = 0.1755%
9	10.6489	10.6489/44.4678 = 0.2395	23.95%	1 - (0.2395 * 2) = 0.5210	2.33% * 0.5210 = 1.2139%
7	9.3915	9.3915/44.4678 = 0.2112	21.12%	1 - (0.2112 * 2) = 0.5776	2.12% * 0.5776 = 1.2245%
10	8.8708	8.8708/44.4678 = 0.1995	19.95%	1 - (0.1995 * 2) = 0.6010	7% * 0.6010 = 4.2070%
4	1.1278	1.1278/44.4678 = 0.02536	2.536%	1 - (0.02536 * 2) = 0.9493	0.63% * 0.9493 = 0.5980%
Total	44.4678	1	100%	-	

Slide 14

The aggregate dermal exposure is recalculated with the Weighting Factor adjusted UCL. In cases where the adjustment of the UCL with the Weighting Factor is too low (i.e., results in an AEL/CEL$_{agg}$ < 1), a Multiplication Factor (MF) is assigned a value to greater than 1 to amplify the effect of each category's Relative Contribution. When the adjustment of the Weighting Factor is too high, the MF is assigned a positive value less than 1 to reduce the effect. The MF assigned is established empirically using iterative calculations. No one product category is treated differently compared to other categories, maintaining the principle of applying the greatest reduction to the UCL of product categories that lead to the highest exposures. Here, since the Weighting Factor adjusted UCL still resulted in AEL/CEL$_{agg}$ < 1 for the palms, a MF of 2 was applied to the Weighting Factor and a new adjusted UCL was calculated.

Slide 15

Recalculate AEL/CEL_{Agg} (Palms MF)

Application Site	Inter-individual SAF	Product SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL_{Agg}	AEL/CEL_{Agg}
Lips	10	1	3	3	100	1400	14.0	30.1620	0.4642
Intra-oral	10	1	3	3	100	1400	14.0	28.1722	0.4969
Axillae	10	1	3	10	300	1400	4.7	7.0488	0.6668
Palms	10	1	3	3	100	1400	14.0	16.6172	0.8425
Back of Hand	10	1	3	3	100	1400	14.0	7.8471	1.7841

The CEL_{agg} is recalculated again using the new UCL values and is compared to the AEL. Body sites with an AEL/CEL_{agg} less than 1 indicate which UCL must lowered more. Here the AEL/CEL_{agg} for the palms is close to 1 and lips is the body site with the lowest AEL/CEL_{agg} which will be adjusted next.

Slide 16

Adjust for Lips

Product Category	95th Percentile Dermal Exposure ($\mu g/cm^2$)	Relative Contribution	Percentage Relative Contribution	UCL Weighting Factor	Adjusted UCL (no MF)
6	28.1722	28.1722/32.1834 = 0.8754	87.54%	1 - 0.8754 = 0.1246	1.1% * 0.1246 = 0.1371%
1	3.8275	3.8275/32.1834 = 0.1189	11.89%	1 - 0.1189 = 0.8811	0.12% * 0.8811 = 0.1057%
9	0.1198	0.1198/32.1834 = 0.003722	0.3722%	1 - 0.003722 = 0.9963	1.2139% * 0.9963 = 1.2094%
5	0.0639	0.06390/32.1834 = 0.001985	0.1985%	1 - 0.001985 = 0.9980	0.1755% * 0.9980 = 0.1752%
Total	32.1834	1	100%	-	

The relative contribution from those individual products categories to lip exposure is determined. A Weighting Factor is calculated as previously described for the palms on Slide 12, and is applied to the UCL.

Slide 17

Recalculate AEL/CEL_{Agg} (Lips)

Application Site	Inter-individual SAF	Product SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL_{Agg}	AEL/CEL_{Agg}
Palms	10	1	3	3	100	1400	14.0	16.5790	0.8444
Axillae	10	1	3	10	300	1400	4.7	6.7334	0.6980
Back of Hand	10	1	3	3	100	1400	14.0	7.8632	1.7804
Lips	10	1	3	3	100	1400	14.0	6.0858	2.3004
Intra-oral	10	1	3	3	100	1400	14.0	3.5418	3.9528

The CEL_{agg} is recalculated again using the new UCL values and is compared to the AEL. When the adjustment of the UCL with the Weighting Factor is too high, resulting in an AEL/CEL_{agg} which exceeds 1, the MF is assigned a positive value less than 1 to reduce the effect. Here the AEL/CEL_{agg} for the lips is now greater than 1 so the Weighting Factor will be reduced with a MF of less than 1.

Slide 18

Multiplication Factor (Lips)

*Upper Use Level Weighting Factor = 1 - (Contribution * Multiplication Factor)*

Multiplication Factor = 0.776

Product Category	Relative Contribution	Multiplication Factor	UCL Weighting Factor with MF	Adjusted UCL
6	0.8754	0.776	1 - (0.8754 * 0.776) = 0.3207	1.1% * 0.3207 = 0.3528%
1	0.1189	0.776	1 - (0.1189 * 0.776) = 0.9077	0.12% * 0.9077 = 0.1089%
9	0.003722	0.776	1 - (0.003722 * 0.776) = 0.9971	1.2139% * 0.9971 = 1.2104%
5	0.001985	0.776	1 - (0.001985 * 0.776) = 0.9985	0.1755% * 0.9985 = 0.1752%

The multiplication factor for lips, 0.776, was arrived at following several iterations. It was used to calculate a new Weighting Factor which was then used to derive a new adjusted UCL.

Slide 19

Recalculate AEL/CEL_{Agg} (Lips MF)

Application Site	Inter-individual SAF	Product SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL_{Agg}	AEL/CEL_{Agg}
Axillae	10	1	3	10	300	1400	4.7	6.7850	0.6927
Palms	10	1	3	3	100	1400	14.0	16.9376	0.8266
Lips	10	1	3	3	100	1400	14.0	11.6056	1.2063
Back of Hand	10	1	3	3	100	1400	14.0	7.8521	1.7830
Intra-oral	10	1	3	3	100	1400	14.0	9.2129	1.5196

The CEL_{agg} is recalculated again using the new UCL values and is compared to the AEL. Here the AEL/CEL_{agg} for the lips is now closer to 1 and axillae is the body site with the lowest AEL/CEL_{agg} which will be adjusted next.

Slide 20

Adjust for Axillae

Product Category	95th Percentile Dermal Exposure (µg/cm²)	Relative Contribution	Percentage Relative Contribution	UCL Weighting Factor	Adjusted UCL
2	6.5890	6.5890/7.2851 = 0.9044	90.44%	1 - 0.9044 = 0.0956	0.05% * 0.0956 = 0.00478%
5	0.4535	0.4535/7.2851 = 0.06225	6.225%	1 - 0.06225 = 0.9378	0.1752% * 0.9378 = 0.1643%
9	0.2426	0.2426/7.2851 = 0.03330	3.330%	1 - 0.03330 = 0.9667	1.2104% * 0.9667 = 1.1701%
Total	7.2851	1	100%	-	

The relative contribution from those individual products categories to axillae exposure is determined. A Weighting Factor is calculated as previously described for the palms on Slide 12, and is applied to the UCL.

Slide 21

Recalculate AEL/CEL_{Agg} (Axillae)

Application Site	Inter-individual SAF	Product SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL_{Agg}	AEL/CEL_{Agg}
Palms	10	1	3	3	100	1400	14.0	13.9895	1.0008
Axillae	10	1	3	10	300	1400	4.7	4.2334	1.1102
Lips	10	1	3	3	100	1400	14.0	11.8312	1.1833
Intra-oral	10	1	3	3	100	1400	14.0	9.2774	1.5090
Back of Hand	10	1	3	3	100	1400	14.0	5.9288	2.3614

The CEL_{agg} is recalculated again using the new UCL values and is compared to the AEL. Here the AEL/CEL_{agg} for the axillae is now greater than 1 so the Weighting Factor will be reduced with a MF of less than 1.

Slide 22

Multiplication Factor (Axillae)

*Upper Use Level Weighting Factor = 1 - (Contribution * Multiplication Factor)*

Multiplication Factor = 0.414

Product Category	95th Percentile Dermal Exposure (µg/cm²)	Relative Contribution	Percentage Relative Contribution	UCL Weighting Factor with MF	Adjusted UCL
2	6.5890	6.5890/7.2851 = 0.9044	90.44%	1 - (0.9044 * 0.414) = 0.6256	0.05% * 0.6256 = 0.03128%
5	0.4535	0.4535/7.2851 = 0.06225	6.225%	1 - (0.06225 * 0.414) = 0.9742	0.1752% * 0.9742 = 0.1707%
9	0.2426	0.2426/7.2851 = 0.03330	3.330%	1 - (0.03330 * 0.414) = 0.9862	1.2104% * 0.9862 = 1.1937%
Total	7.2851	1	100%	-	

The multiplication factor for axillae, 0.414, was arrived at after several iterations. It was used to calculate a new Weighting Factor which was then employed to derive a new adjusted UCL.

Slide 23

Recalculate AEL/CEL_{Agg} (Axillae MF)

Application Site	Inter-individual SAF	Product SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL_{Agg}	AEL/CEL_{Agg}
Palms	10	1	3	3	100	1400	14.0	16.9065	0.8280
Axillae	10	1	3	10	300	1400	4.7	4.3833	1.0723
Lips	10	1	3	3	100	1400	14.0	11.2722	1.2420
Intra-oral	10	1	3	3	100	1400	14.0	9.1450	1.5309
Back of Hand	10	1	3	3	100	1400	14.0	7.8981	1.7726

The CEL_{agg} is recalculated again using the new UCL values and is compared to the AEL.

Slide 24

Adjustment Factors

Citral NESIL = 1400 µg/cm²			
Product Categorization	QRA2 category limit	QRA2 aggregate adjustment factor	QRA2 agg. exp. adj. UCL
1	0.12%	0.9077	0.1089%
2	0.05%	0.6256	0.03128%
3	0.65%	1.0000	0.6500%
4	0.63%	0.9492	0.5980%
5	0.50%	0.3286	0.1643%
6	1.10%	0.3207	0.3528%
7	2.12%	0.5776	1.2245%
9	2.33%	0.5022	1.1701%
10	7.00%	0.6010	4.2070%

The ratio of the final category UCL divided by the initial determinist UCL determines the QRA2 aggregate adjustment factor for that product category. Since the aggregate adjustment factors are a function of the relative contribution of exposure from each product, they are independent of the fragrance ingredient being assessed and are always the same for fragrance ingredients used in products within a category.

Annex VI

A. Products included in the Creme RIFM Model.

Product	Product	Product
After Shave	Eau de Parfum	Kitchen Cleaner Spray
Air Freshener Aerosol	Eau de Toilette	Laundry Pre-treatment Spray
Air Freshener Plugin	Eye Cream	Lipstick
Antibacterial Cleaner Cream/Gel	Eye Makeup Remover Cream Rinse Off	Liquid Hand Soap
Antibacterial Cleaner Dilutable	Eye Makeup Remover Cream Wipe Off	Liquid Makeup Foundation
Antibacterial Cleaner Spray	Face Moisturizer	Makeup Remover Cream Rinse Off
Bar Soap	Face Wash	Makeup Remover Cream Wipe Off
Bath Cleaner Cream/Gel	Facial Cleansing Wipes	Medicated Face Wash/ Cleanser Rinse Off
Bath Cleaner Dilutable	Facial Scrub	Mouthwash
Bath Cleaner Spray	Floor Cleaner Cream/Gel	Multipurpose Cleaner Cream/Gel
Bleach Cream/Gel	Floor Cleaner Dilutable	Multipurpose Cleaner Dilutable
Bleach Dilutable	Floor Cleaner Spray	Multipurpose Cleaner Spray
Bleach Spray	Furniture Polish Cream/Gel	Rinseoff Conditioner
Body Lotion Mass	Furniture Polish Liquid	Scented Candles
Body Lotion Other	Furniture Polish Spray	Shampoo
Body Lotion Prestige	Hair Removal Cream	Shaving Cream
Body Spray	Hair Removal Foam	Shaving Foam
Cleaning Wipes	Hair Removal Gel	Shaving Gel
Cleanser Wipe Off	Hair Spray	Shower gel
Deo Roll-On	Hair Styling	Toner/Astringent
Deo Spray	Hand Cream	Toothpaste
Disinfectant Cream/Gel	Hand Wash Detergent	Washing up Liquid
Disinfectant Dilutable	Kitchen Cleaner Cream/Gel	Window Cleaner Spray
Disinfectant Spray	Kitchen Cleaner Dilutable	

B. Products in the RIFM concentration of use surveys

Product	Product	Product
After Shave	Deo Roll-On	Limescale Remover
Air Freshener Aerosol	Deo Spray	Lip balm
Air Freshener Plugin	Dishwasher Salt	Lipstick
Antibacterial Cleaner	Drain Unblocker	Liquid Hand Soap
Baby bath product	Eau de Parfum	Liquid Makeup Foundation
Baby eau de toilette	Eau de Toilette	Machine Dishwasher Detergent
Baby face cream	Eye shadow	Makeup Remover Cream Rinse Off
Baby facial cleansing wipes	Eye Cream	Makeup Remover Cream Wipe Off
Baby hair conditioner	Eyeliner	Mascara
Baby hand cream	Eye Makeup Remover Cream Rinse Off	Medicated Face Wash/Cleanser Rinse Off
Baby hand sanitizer	Eye Makeup Remover Cream Wipe Off	Mouthwash
Baby lip balm	Fabric Conditioner	Multipurpose Cleaner
Baby liquid soap	Face Moisturizer	Other Laundry Aids
Baby moisturizing cream	Face Wash	Oven Cleaner
Baby oil	Facial Cleansing Wipes	Rim Toilet Block
Baby ointment	Facial Scrub	RinseAid
Baby shampoo	Floor Cleaner	Rinse-off Conditioner
Baby shower gel	Furniture Polish	Scented Candles
Baby sunscreen	Hair Removal Cream	Shampoo
Baby toothpaste	Hair Removal Foam	Shaving Cream
Baby wind and weather cream	Hair Removal Gel	Shaving Foam
Baby wipes	Hair Spray	Shaving Gel
Bar Soap	Hair Styling	Shower gel
Bath Cleaner	Hand Cream	Sun care body
Bleach/Disinfectant	Hand Wash Detergent	Sun care face
Body Lotion Mass	In Cistern Block	Toner/Astringent
Body Lotion Prestige	Kitchen Cleaner	Toothpaste
Body Spray	Laundry Detergents	Washing up Liquid
Cleanser Wipe Off	Laundry Pre-treatment	Window Cleaner

Annex VII

Detailed description of product categorisation and consideration of regional draining lymph nodes (according to the revised Applicant's dossier)

The paper by Api *et al.* (2020) states that, as indicated in Table 3 below, the set of 18 non-overlapping skin sites ''was adapted from the list of application sites recorded by participants in a survey of consumer habits and practices (Kantar Database).'' It was clearly appropriate to define relevant body sites on the basis of consumer use patterns.

Table 3
Body sites used for aggregate exposure calculation.

Body site	Additional definition
Scalp	
Face	Does not include: eyes, lips, mouth, behind ears
Peri-ocular	The eyelid and surrounding skin around the eyes.
Lips	
Inside mouth	Buccal/inside cheek: does not include: lips
Neck	Does not include: behind ears
Behind ears	
Chest	Does not include: axillae, abdomen
Abdomen	Stomach region
Back	Does not include: axillae
Axillae	Under arm region
Arms	Does include: shoulder, forearm, upper arm; Does not include: wrists, hands, palms, axillae
Wrists	
Back of hand	Does not include: palms, wrists
Palms	
Anogenital	
Legs	Does include: buttocks, thighs, calves; Does not include: feet
Feet	

Api *et al.* (2020) goes on to explain that ''the criteria for selecting the application sites were that the whole body be covered, that no sites overlap, and that the sites be broad enough usefully to describe the behaviour of consumers, but specific enough that exposure in terms of quantity per unit area is not underestimated due to assigning too large a surface area.'' This again is a logical approach to make sure that the entire body is considered, but with no overlap between sites.

The important point then made by Api *et al.* (2020) is that: ''body skin is divided into separate regions since regional (draining) lymph nodes critical for the acquisition of skin sensitization function largely independently.'' It is well established that the central events in the acquisition of skin sensitization take place in lymph nodes draining the site of skin exposure to the chemical allergen. A critical mass of inducing signals is required in the draining lymph node for the effective induction of a T lymphocyte response that is necessary for skin sensitization. Those inducing signals include the arrival in draining lymph nodes, via afferent lymphatics, of epidermal Langerhans cells (LC), and other migratory dermal dendritic cells (DC), that bear the chemical allergen displayed in a form that will be recognized by responsive T lymphocytes (Kimber *et al.*, 2008; 2009; 2011; Yao and Kaplan, 2018).

In view of the fact that as the draining lymph nodes that drive the acquisition of skin sensitization function largely independently, then: ''where possible, aggregation of exposures sites served by completely different draining lymph nodes has been avoided. For these reasons, the calculation of aggregated exposure is made separately for each of the 18 non-overlapping skin sites listed in Table 3.''

The reason for not aggregating, for example, the body sites scalp, lips and head is that not all areas of the head, face and neck drain to the same lymph nodes. In fact, the lymphatic system of the head and neck is complicated and a number of different lymph nodes can be identified anatomically. Thus, for example: the parotid lymph node drains the sides of the face and scalp, the preauricular lymph node drains the face, the mastoid lymph node drains the neck, the occipital lymph node drains the back of the head, the submandibular lymph node drains the mouth region, the submental lymph node drains the chin area, the superficial cervical lymph node drains the area at the junction between the head and neck, and the buccal lymph node drains the region of the mouth. These lymphatics eventually drain into the deep cervical lymph nodes in the neck (Koroulakis *et al.*, 2022). It was therefore deemed appropriate to consider separately the different head, face and neck sites listed in Table 3 of Api *et al.* (2020).