Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

citral; 3,7-dimethylocta-2,6-dienal

EC Number: 226-394-6
CAS Number: 5392-40-5

CLH-O-0000001412-86-225/F

Adopted

14 September 2018

14 September 2018

CLH-O-0000001412-86-225/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **citral; 3,7-dimethylocta-2,6-dienal**

EC Number: **226-394-6**

CAS Number: **5392-40-5**

The proposal was submitted by **Denmark** and received by RAC on **14 September 2017**.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Denmark has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **17 October 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **1 December 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Andrew Smith**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **14 September 2018** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	605-019-00-3	citral; 3,7-dimethyloct a-2,6-dienal	226-394-6	5392-40-5	Skin Irrit 2 Skin Sens 1	H315 H317	GHS07 Wng	H315 H317			
Dossier submitters proposal	605-019-00-3	citral; 3,7-dimethyloct a-2,6-dienal	226-394-6	5392-40-5	Skin Irrit 2 **Modify** Skin Sens 1A	H315 H317	GHS07 Wng	H315 H317			
RAC opinion	605-019-00-3	citral; 3,7-dimethyloct a-2,6-dienal	226-394-6	5392-40-5	Skin Sens 1 **Retain** Skin Irrit 2	H315 H317	GHS07 Wng	H315 H317			
Resulting Annex VI entry if agreed by COM	605-019-00-3	citral; 3,7-dimethyloct a-2,6-dienal	226-394-6	5392-40-5	Skin Irrit 2 Skin Sens 1	H315 H317	GHS07 Wng	H315 H317			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Citral has an existing harmonised classification for the hazards skin irritation and skin sensitsation. In their proposal, the Dossier Submitter (DS) only addressed skin sensitization. No amendment to the classification for skin irritation was considered necessary.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Proposal before public consultation

The sensitising properties of citral have been intensively studied in both animals and humans. Citral already has a harmonised classification as Skin Sens. 1, and it is one of the established reference skin sensitisers listed in the guidance document of OECD TG 429 (local lymph node assay). Both guideline and non-guideline studies in animals are available; the positive results of numerous local lymph node assays, Guinea pig maximisation tests and a Buehler test are directly applicable for classification and sub-categorisation. A large number of human patch tests are also available. Citral is a component of one of the standardised fragrance mixtures used in the European baseline series used for diagnostic patch testing in dermatological clinics. Follow-up testing with the single fragrance substances is done routinely in many clinics; the sensitising properties of citral are well documented. Results of historical human volunteer studies are also available for citral and provide supporting evidence for sub-categorisation.

All of the available animal studies on citral are positive for sensitisation. Four studies (two local lymph node assays, one Guinea pig maximisation test and the Buehler test) indicate a strong potency. The remaining studies either indicate that citral is a skin sensitiser of moderate potency, or do not allow conclusions on potency due to the design of the studies (doses used, lack of quantification of response). Robust study information is not available for most of the animal studies, so conclusions on sub-categorisation cannot be made on the animal data alone.

The human data provide substantial evidence of the strong sensitising effects of citral, especially based on the results of patch tests with selected patients. Data are available from thousands of selected and unselected patients, with well over 400 published cases of positive reactions. Although robust study information is not available for some of the older volunteer studies in humans (human repeat insult patch tests and maximisation tests: HRIPTs and HMTs), the studies generally confirm the sensitising properties of citral and indicate a moderate potency.

There is wideapread use of citral as a fragrance in cosmetics and other consumer products, and a high tonnage is placed on the market (1000 – 10000 tonnes/year). Although frequent or daily exposure to citral is anticipated, the overall exposure to citral is estimated to be relatively low based on information on how citral is used in these products.

Overall, there is a high frequency of skin sensitisation in human patch tests (≥ 2.0% in 10 of 11 patch tests with selected dermatitis patients and ≥ 1.0% in 5 of 14 patch tests with unselected dermatitis patients) and a high number of published cases, set against an estimated low exposure. This justifies classification in sub-category 1A. The animal data are not uniform in their results with respect to a potency assessment, however four guideline studies are available which confirm a strong sensitising potency of citral. Collectively, the available data fulfil the criteria for classification of citral in sub-category 1A.

Comments received during public consultation

Comments were received from three Member State Competent Authorities (MSCAs), three non-governmental groups of dermatologists, an expert individual, a manufacturer and a trade association.

Differing views on sub-categorisation were expressed. Some contributors supported the proposal to classify in sub-category 1A, however the expert individual and manufacturer concluded that the data supported classification in sub-category 1B. The trade association criticised the approach taken and did not support classification in category 1A; however, it was not clear from their comments whether they felt category 1 or 1B was appropriate. One MSCA commented that both the human and animal data were borderline between the two sub-categories.

Two non-governmental groups provided a short statement supporting the proposal to classify in sub-category 1A. The remaining contributors provided comprehensive comments, covering the animal data, human data and exposure considerations.

Animal data

All three MSCA agreed with the DS that due to the lack of detail/information about most of the animal studies, conclusions on the potency could not be made based on the animal data alone; one noted that it was difficult to assess the reliability of the studies in the absence of reliability scores. One MSCA, the expert individual and the manufacturer commented that the animal data supported classification in sub-category 1B.

A MSCA, a non-governmental group and the manufacturer noted the effect of vehicle on the results of the LLNAs. Four studies used acetone:olive oil (AOO), which is the standard and most commonly used vehicle in the LLNA, whereas ten assays used mixtures of ethanol:diethyl phthalate (EtOH:DEP). An increase in the sensitising potency for citral was seen in the LLNAs using EtOH:DEP; two of the LLNAs with EtOH:DEP gave EC values < 2, which supports classification in sub-category 1A. The non-governmental group noted that the vehicle had an influence on the skin absorption of a substance and therefore its sensitising potency, but pointed to an experimental study which concluded that EtOH:DEP provided a suitable vehicle for use in the LLNA (Betts *et al.*, 2007). The group concluded that it was acceptable to use this solvent and noted that all experiments using EtOH:DEP were performed by the fragrance industry since this vehicle is considered more appropriate with regard to the exposure from fragranced consumer products.

Generally, the manufacturer noted that there was a significant range of EC3 values for citral (1.2 – 15%), and that EC3 values varied even when the studies were conducted by the same laboratory with the same solvent. Specifically, the manufacturer mentioned that the 3 LLNAs with EC3 values below or close to the cut-off of 2% had been repeated by the same laboratory with a comparable protocol, all giving different EC values (i.e., > 2%). Furthermore, 2 of these studies used tocopherol or BHT/tocopherol/eugenol mixes, which did not represent standard vehicles for

LLNAs. Therefore, the reliability of these studies for classification purposes could not be confirmed. The manufacturer commented that the variability, validity and reproducibility of the results had to be taken into account. Given that most studies gave EC values > 2% the manufacturer concluded that the animal data supported classification in sub-category 1B.

The manufacturer and one MSCA highlighted limitations regarding the Bühler test (i.e., dosing regime and animal numbers).

Human data

Two MSCAs provided an analysis of the data and agreed with the DS that the human patch test data provided the key evidence for the assessment of potency. One authority agreed that "high frequency" could be assigned to the selected patients, however disagreed that it could also be assigned to unselected patients. They also questioned the inclusion of data from North American and Korean studies, given that the available exposure data refered to the European situation only. The second MSCA noted that the HRIPT studies were performed over a range of concentrations, but resulted in few cases of sensitisation. In order to clarify the outcome of the HRIPTs, it was suggested that these studies were evaluated and discussed further in the CLH report, if possible. The remaining MSCA fully supported the statement that there was a high frequency of sensitisation for citral in humans, however questioned why different concentrations (0.1-5%) of citral were used in the patch tests. They noted that citral was a skin irritant, and as such some reported reactions could be due to irritation rather than sensitisation.

The expert individual, a clinician based in Germany, concluded that the animal data supported classification in sub-category 1B, and that the human data were insufficient to overrule the animal data. He would not have used the data from selected patients for hazard or risk assessment given the heterogeneous nature of the selection process. Of the fragrances in the standard series used for patch testing, citral was not a substance that had given an especially high frequency of responses in non-selected patients; several substances had given higher response rates. When sensitising frequencies (clinical data) and exposure frequencies (volumes in consumer products) were compared for the standard series, as an indicator of risk, citral appeared not to be of high concern.

The manufacturer and the industry association disagreed with the DS's assessment of the human patch test data. They argued that it is impossible to know the induction exposure levels and the conditions of the patients in the studies showing a high frequency of reactions to Citral. Due to the clearly defined induction exposure conditions used in the HRIPTs and the HMTs, they considered these studies to be a more useful source for the assessment of potency. The industry association disagreed that the HRIPT and HMT studies, which did not indicate a high sensitisation potency of citral, were supporting information only, and argued that the absence of robust study information could not be used to prove lower relevance of this information in the classification decision. The manufacturer had provided the DS with further details of these studies, and stated that all of the tests in human volunteers supported classification in sub-category 1B.

Although the manufacturer accepted that the cumulative data on selected dermatitis patients met the criteria of a "high frequency" of cases according to the CLP criteria, a meta-analysis of all other data for unselected dermatitis patients (including two new studies published in 2017 – see Additional Key Elements) met the criteria for low frequency. According to this analysis, the positive response rate was 0.89% (192/21692 patients tested).

Exposure

One MSCA accepted that some consumer products contained high levels of citral, but noted that these exceptions mainly refered to products that were not intended for long skin contact. They, and another MSCA, thus agreed that exposure to citral could generally be regarded as "low" due to an relative exposure index of 4 that was calculated when considering the frequency of exposure to citral (the score '0' was given for concentration/dose in the meaning of the CLP guidance, table 3.3). The MSCA who thought that the classification was a borderline argued that the overall score for the exposure data could be 5 (rather than 4, as proposed by the DS), which would have led to the category "relatively high exposure" (rather than "relatively low exposure").

The manufacturer and the industry association disagreed with the DS's assessment that exposure to citral was 'low', and suggested that the content of the substance in consumer products leading to the induction of sensitisation had been underestimated. In addition, they noted that exposure to citral occurs also from natural food sources, e.g. citrus fruits. It was not possible to know if those patients who had responded positively on patch testing with citral had mostly been induced by low concentrations.

Although the International Fragrance Association (IFRA) had in 2006 issued a limit of 1% on the content of citral in many consumer products, the manufacturer and industry association disagreed that this was additional evidence for a 'low exposure'. The limit would not have translated through to many of the products actually being used for some years later, and potentially as late as 2013. Furthermore, the manufacturer argued that the DS had not provided adequate justification for excluding from their analysis products that were exempt from the IFRA limit, and historical exposures to other products containing > 1% citral. The manufacturer noted that most publications reporting a high frequency of reactions in unselected patients and selected patients covered clinical patch test studies that were carried out in periods including up to 2013. The manufacturer and industry association both commented that actual and historic exposures to concentrations > 1% citral should have given a dose or concentration score of 2, which would have led to an additive exposure index of 2+2+2=6 and would have defined exposure as relatively high.

The manufacturer concluded that the low frequency of positive patch test results in unselected dermatitis patients combined with a strong potential for high estimated exposure both from a historical and current perspective provided a justification for a classification in sub-category 1B.

Analysis of further information received during the public consultation

During the public consultation, the manufacturer provided information about two additional studies.

The aim of the first of these was to report the prevalence of sensitisation to the 26 EU-labelled fragrance allergens (one of which is citral) from 2010 to 2015, using data from a single university clinic (University Hospotal Herlev-Genofte, Denmark) on consecutive, unselected patients (Bennike *et al*., 2017). The study reported a positive reaction rate to citral of 0.39% from 2010 to 2015. The publication also reported a clear decreasing prevalence trend from 2010 to 2015.

The aim of the second study (Mowitx *et al.*, 2017) was to investigate the frequency of allergic reactions to fragrance mix I (FM I),fragrance mix II (FM II) and their ingredients in consecutive patients. The data showed 1.1% positive reactions to citral (22/2248) during the period 2009 - 2012, and 1.3% (30/2248) positive reactions during 2013-2015.

In their response to the public consultation, one MSCA indicated that further evaluation and discussion of the HRIPT studies would have assisted in the assessment of citral. During the public consultation, the manufacturer provided further information about these tests, including full study reports for 3 of the 6 studies. This additional information is summarised in the following table.

Unless otherwise stated, the tests involved nine 24 h occluded induction applications (3 times a week over 3 weeks), followed approximately 2 weeks later by a 24 hour occluded challenge application to a virgin site. Reactions were read at patch removal and again at 24 and 72 hours after patch removal. Similarly, unless stated, no information was provided in the study report on the sex, age, ethnicity or health condition of the volunteers.

Additional information on the Human Repeat Insult Patch Tests			
Study details and Reference	**Participants**	**Results**	**RAC observations**
Reactions read at 24, 48 and 72 hours after patch removal. 1.2% citral in 3:1 DEP:ethanol (1400 µg/cm^2) RIFM (2004b)	101 volunteers (30 male and 71 female, age range 18-69). Subjects did not exhibit any dermatological or other medical condition which would preclude topical application of the test material.	No reactions (0/101)	No evidence of sensitising potential was observed.
Fifteen 24 hours occluded induction patches (3 times a week) followed 14 days later by a 24 hour occluded challenge patch. Reactions were read at patch removal and 24 and 48 hours later. Induction and challenge: 4% citral in petrolatum (444 µg/cm^2) RIFM (1971a)	50 volunteers.	No reactions (0/50)	No evidence of sensitising potential was observed. Relatively small group size limits statistical power of the study.
Induction and challenge: 1% citral in alcohol SDA 39C (775µg/cm^2) RIFM (1965)	40 volunteers (11 males and 29 females).	No reactions (0/40)	No evidence of sensitising potential was observed. Relatively small group size limits statistical power of the study.
Induction and challenge: 5% citral in alcohol SDA 39C (3875 µg/cm^2) RIFM (1964a)	8 volunteers (all female). No information on the age, ethnicity or	5/8 reactions	A high number of volunteers (62.5%) reacted to a high induction dose. This would support classification in category

	health condition of the volunteers is available.		1B (although category 1A cannot be excluded, as doses < 500µg/cm were not tested).
Induction and challenge: 0.5% citral in ethanol (388 µg/cm^2) RIFM (1964b)	41 volunteers (12 males and 29 females).	0/41 reactions	No evidence of sensitising potential was observed. Relatively small group size limits statistical power of the study.
Patches were semi-occluded after the 6th patch. Induction: 8% citral in petrolatum (applications 1-2), 4% citral in petrolatum (applications 3-9). Concentration was lowered to reduce the occurrence of irritation. Challenge: 4% Opdyke (1979)	40 volunteers (5 male and 35 females, aged between 16 and 60).	19/40 reactions	A high number of volunteers (48%) showed reactions during this study. The precise dose (per unit area of skin) is not clear from the study report, but according to information received during the public consultation it was > 3000 µg/cm^2. This study supports classification in Category 1B (although Category 1A cannot be excluded, as doses < 500µg/cm were not tested).

The manufacturer also provided study reports for the HMT. Sensitisation was observed in all but one of these studies, however as they were all conducted at high induction doses (≥ 1379µg/cm^2), they could not be used to support sub-categorisation. Therefore additional information about these studies is not presented here.

Assessment and comparison with the classification criteria

Animal data

The sensitising potential of citral has been tested comprehensively in both Guinea pigs and mice. As shown in the following tables, there was limited reporting of the results from some of the Guinea pig studies, but overall there is sufficient, reproducible evidence from both species to demonstrate that citral should be classified as a skin sensitiser.

A total of 14 LLNAs, 6 GPMTs and 1 Buehler test are documented in the CLH report.

All of the LLNAs were well conducted. Thirteen of the studies were conducted according to OECD TG 429. A range of EC3 values was reported (1.2 – 15%). In 2 of the 14 LLNA, a high potency of citral was demonstrated (EC3 values < 2%), i.e., which would support classification in sub-category 1A. In 1 LLNA, the result was borderline between category 1A and 1B (EC3 = 2.1%). In the remaining LLNAs, a moderate potency was demonstrated (EC3 > 2%). Comments received during the public consultation suggested that the variability could be due to the different vehicles used in the studies. However, RAC notes that even when the same vehicle was used, significantly different EC3 values were obtained in separate studies. For example, when 1:3 Ethanol:DEP was

used as the vehicle, EC3 values of 1.2% and 6.3% were obtained by the same laboratory (using the same strain and sex of mice).

Summary of the available Local Lymph Node Assays*		
Number of studies	**Result (EC3 values)**	**Assessment by RAC against CLP criteria**
2 studies (both reported in 2009)	1.2%, 1.5%	Skin Sens. Cat. 1A
12 studies (2002-2012)	2.1%, 3.7%, 4.6%, 4.6%, 5.3%, 5.8%, 6.3%, 6.3%, 6.8%, 12.6%, 13%, 14.1%	Skin Sens. Cat. 1B

**In addition, an early study was conducted in 1992. Limited information is available about this study, which reported a range of EC values (7-15%). At this time, the LLNA was still under development.*

In one of the GPMT, 60% of animals responded at an intradermal induction dose of 0.2%, which would support classification in sub-category 1A. Three of the studies suggest that citral is a moderate skin sensitiser (40% responding at a 0.4% intradermal dose in one study; 100% responding at a 25% intradermal dose in the other two studies) however it cannot be excluded that a high response would also have been seen if lower induction doses were used; these studies therefore cannot be used for sub-categorisation. In the remaining two GPMT, sensitisation was observed but not quantified; therefore these studies cannot be used for sub-categorisation either.

In the Buehler test, sensitisation was observed in 100% of animals with an induction concentration of 20% citral. Although fewer animals were used in this study than required by the guideline, the study supports classification in sub-category 1A.

Summary of the available Guinea pig studies		
Method (study date)	**Result**	**Assessment by RAC against CLP criteria**
Maximisation (1991) Induction: 0.2% (intradermal) Challenge: 0.5%	Positive reactions observed in 6/10 animals (60%)	Sub-category 1A
Maximisation (1986) Induction: 10% (intradermal) Challenge: 10%	Sensitisation observed	Not possible
Maximisation (1985) Induction: 0.4% (intradermal) Challenge: 0.25%	Positive reactions observed in 4/10 animals (40%)	Moderate potency (sub-category 1B), however lacking data to exclude sub-category 1A.
Maximisation (1978) Induction: 25% (intradermal) Challenge: 10, 5 and 5%	Positive reactions observed in 100% of animals	Moderate potency (sub-category 1B), however lacking data to exclude sub-category 1A.
Maximisation (1978) Induction: 25% (intradermal) Challenge: 10, 5 and 5%	Positive reactions observed in 100% of animals (except after 144 hours after a 5% challenge, where 60%	Moderate potency (sub-category 1B), however lacking data to exclude sub-category 1A.

Summary of the available Guinea pig studies		
Method (study date)	**Result**	**Assessment by RAC against CLP criteria**
	positive reactions were observed).	
Maximisation (1977) Induction: 5% (intradermal) Challenge: subirritant	Sensitisation observed	Not possible
Buehler, modified (1973) Induction: 20%	Positive reactions observed in 5/5 animals (100%)	Sub-category 1A

To summarise, all of the available animal studies indicate that citral is a skin sensitiser. However, the studies gave varying indications of potency. Four of the studies (two LLNAs, one GPMT and a Buehler test) indicate a strong potency for citral. Thirteen studies (all LLNAs) suggest that citral is a moderate sensitiser, and support classification in sub-category 1B. The remaining studies (all GPMT) do not provide clear support for sub-categorisation.

Overall, although it is clear that citral is a skin sensitiser, a reliable estimate of potency cannot be derived from the animal data. The reason for the variability in the animal data is not known. Given this profile, Skin Sens. 1 (H317) without sub-categorisation is considered by RAC the most appropriate classification based on the animal data alone.

Human data

The available human data consists of case studies, HRIPT, HMT and diagnostic patch tests.

Case studies

Three case studies are summarised in the CLH report. One study from the UK reported positive reactions to citral (2.0% in petrolatum (pet.)) in 5 out of 9 beauticians with bilateral hand dermatitis. Another study reported strong positive reactions to citral in a patient with recurrent allergic contact cheilitis (inflammation of the lips). In a third study, four bakers with hand eczema were patch tested with 0.5% citral (in pet.); one of the four tested positive. These case studies are consistent with the results of the human patch tests discussed below.

HRIPT data

A number of volunteer HRIPTs have assessed the skin sensitisation potential of citral. Although the conduct of such studies is not permitted for compliance with CLP for ethical reasons, it is possible to take account of such data as part of a weight of evidence analysis if it is available historically. According to the ECHA guidance, positive responses at induction doses ≤ 500 µg/cm^2 support classification in sub-category 1A, and positive responses at induction doses > 500 µg/cm^2 support classification in sub-category 1B.

The HRIPTs documented in the CLH report used induction doses ranging from 388 to > 3000 µg/cm^2. In four of the studies, no skin reactions were observed. The highest dose tested in these four studies was 1400 µg/cm^2; this study also used the highest number of volunteers and therefore has the greatest statistical power. This study used male and female volunteers covering a wide age range, although information on the skin type or ethnicity of the volunteers was not provided in the study report.

Skin reactions were observed in the remaining two HRIPT studies. One of these used a very high induction dose (3875 µg/cm^2) and a low number of volunteers (8). The induction dose used in the other study is not clear, but is understood to be > 3000 µg/cm^2. These two studies suggest that citral is a moderate sensitiser, and support classification in sub-category 1B. It is not known whether the volunteers in these two studies would have responded to a lower induction dose (i.e., category 1A cannot be excluded), although RAC notes that no reactions were seen in the other HRIPT studies conducted at lower doses. The absence of detailed information about the volunteers precludes further analysis. Overall, the HRIPT data confirm the sensitising properties of citral, but do not provide sufficient support for sub-categorisation.

HMT studies

The historic HMT studies were all conducted using high induction doses (> 500 µg/cm^2), and sensitisation was observed in 13 of the 14 studies. As it is not known whether the individuals in these studies would have responded to lower induction doses, the data from the HMT studies confirm the sensitising properties of citral, but cannot be used to support sub-categorisation.

Overall, the HRIPT and HMT studies support classification of citral in Skin Sens. Cat. 1. However, the data do not provide sufficient support for sub-categorisation.

Human Diagnostic Patch Tests

The diagnostic patch tests provide supporting information to the classification assessment. They were conducted according to standardised guidelines and with well defined challenge conditions. A total of 25 patch tests were documented in the CLH report, covering both selected (11 studies) and unselected (14 studies) patients (see tabulated information, below). Selected patients are those who have a known skin condition and who are suspected of having a contact allergy to fragrances/cosmetics, or other patients with a history of skin symptoms provoked by scented products (aimed testing). Unselected patients are groups of patients for whom allergic contact dermatitis is generally suspected.

Summary of the human diagnostic patch tests			
Test substance[a]	**Study details**	**% of patients testing positive**	**Frequency[b]**
Selected patients			
Citral, 2%	Multicentre project (Germany, Austria, Switzerland).	16.2% (n = 1058)	High
Citral, 2%	Multicentre study, Hungary	3.4% (19/565)	High
Citral, 2%	Belgium	11.2% (23/205	High
Citral, 2% (vehicle not reported)	The Netherlands	6.7% (2/30)	High
Citral, 2%	Spain	2.3% (2/86)	High
Citral, 2%	Denmark & Sweden	4.3% (28/658)	High
Citral, 2%	Multicentre project, 6 countries, not specified	16.7% (13/78)	High

Citral, 5% (vehicle not reported)	310 cosmetic dermatitis patients, 408 non-cosmetic patients and 122 control subjects. Country not stated.	2.6% cosmetic dermatitis patients (8/310) 2.2% non-cosmetic patients (9/408)	High High
Citral, 2% (vehicle not reported)	310 cosmetic dermatitis patients, 408 non-cosmetic patients and 122 control subjects. Country not stated.	0.4% cosmetic dermatitis patients (1/240) 0.3% non-cosmetic dermatitis patients	Low/moderate Low/moderate
Citral, 2%	The Netherlands	2.6% (n =182)	High
Citral, 5%	155 cosmetic dermatitis patients and 159 other eczema/dermatitis patients	2.6% cosmetic dermatitis patients (4/155) 3.1% dermatitis/eczema patients	High High
Unselected patients			
Citral, 2%	UK	1.0% (20/1951)	High
Citral, 3.5%	Sweden	0.92% (6/655)	Low/moderate
Citral, 1.5%	Sweden	0.66% (7/1055)	Low/moderate
Citral, 2%	Denmark	0.3% (4/1502)	Low/moderate
Citral, 2%	The Netherlands	0.6% (2/320)	Low/moderate
Citral, 2%	Multicentre study: Germany, Austria, Switzerland	0.6% (13/2021)	Low/moderate
Citral, 1%	Multicentre study: Germany, Denmark, Sweden, UK, Belgium	0.35% (6/1701)	Low/moderate
Citral, 2%	Multicentre study: Germany, Denmark, Sweden, UK, Belgium	0.7% (12/1701)	Low/moderate
Citral, 2%	Multicentre study: Germany, Denmark, Sweden, UK, Belgium	1.1% (21/1855)	High
Citral, 2%	Multicentre study; country not known	1.0% (19/1825)	High
Citral, 0.1%	Multicentre study, Denmark	0% (0/192)	Low/moderate
Citral, 1%	Multicentre study, Denmark	0% (0/192)	Low/moderate
Citral, 1%	North America	1.7% (4/228)	High

Citral, 2%	Multicentre study, Korea	1.2% (5/422)	High

[a]*in petrolatum, unless otherwise stated.*

[b]*Relatively high or low frequency of occurrence of skin sensitisation, according to Table 3.4.2-b in the Guidance on the Application of the CLP criteria:*

Human diagnostic patch test data	High frequency	Low/moderate frequency
General population studies	≥ 0.2%	< 0.2%
Dermatitis patients (unselected, consecutive)	≥ 1.0%	< 1.0%
Selected dermatitis patients (aimed testing)	≥ 2.0%	< 2.0%

In patch tests on selected dermatitis patients, positive reactions ranged between 0.3 and 16.7%, and "high frequencies" (≥ 2.0%) were seen in 10 out of 11 tests.

In unselected dermatitis patients, positive reactions ranged between 0 and 1.7%. Complete absence of positive reactions was observed in 2 of the 14 tests, which both employed 192 test subjects (these two tests were conducted using 0.1%, and 1.0% citral in pet.).

Relatively high frequencies of positive reactions (≥ 1.0%) were seen in 5 of the 14 studies, however two of these studies were conducted outside of the EU (i.e., in North America and Korea). Given that the classification criteria require the frequency of responses to be compared with the exposure data, and exposure data is only available for the EU, these non-EU studies are excluded from the analysis. This leaves 3 out of 12 studies on unselected patients showing sensitisation rates equal to or higher than 1% (1.0%, 1.0% and 1.1%), 7 of the studies showing a low/moderate sensitisation rate (i.e. < 1.0%) and 2 of the studies showing no sensitisation at all. The largest study tested 2021 patients, and found a low/moderate frequency of sensitisation.

In addition to the patch tests, an experimental study is reported in the CLH proposal which investigated the possible role of the skin irritation response in relation to polysensitisation to fragrances. 100 volunteer patients with confirmed fragrance contact allergy (i.e., selected patients) were patch tested with 27 fragrance chemicals; 9.0% of patients tested positive to citral (2.0% in pet.). The results of this study are consistent with the results of the human patch tests on selected patients discussed above.

For classification purposes, the major limitation of the diagnostic patch tests is that the induction doses are not known. To account for this, the CLP guidance describes principles for deriving an exposure index leading to an assessment of relatively high or low exposure that can be matched against the patch test data to inform on potency and sub-categorisation.

Citral is widely used as fragrance ingredient in cosmetic and household cleaning products. In 2006, IFRA recommended maximum levels of citral in leave-on cosmetic products between 0.04-1.4%, and 1.0-5.0% in rinse-off cosmetic products. However, it is not clear how quickly or completely products on the market came to adhere to these recommendations.

In 2012, the Scientific Committee on Consumer Safety (SCCS) considered a number of surveys on the presence and content of certain fragrances in consumer products, based mostly on labelling information. Citral was present in 8.2 – 44% of the products covered; the SCCS concluded that

exposure to citral is foreseeable in daily life. Further surveys (conducted by the Danish EPA on the Danish Market) have found citral to be present in day-to-day cosmetic products such as deodorants, soaps, shampoo/conditioner, lotions and creams, and household cleaning products such as cleaning agents, stain removers and air care products. The surveys suggest that citral is generally found in low concentrations (< 0.06%) in cosmetic products, however high concentrations were found in other products; massage oils (up to 3.25%), eterical oils/scented oils (up to 78%) and air fresheners (up to 26%). Data from the Danish Product Register (which contains information on hazardous substances in mixtures for professional use) confirm that citral is used in a wide range of products on the market, especially cleaning products. The concentrations are generally lower than 0.1%, however concentration above 1% are found in fragrance mixtures and scented oils.

The REACH Substance Evaluation (SEv) dossier on citral refers to the estimated exposure values in the REACH registration dossier. These are 47-100µg/cm^2 for workers (depending on the exposure scenario) and 47-50 µg/cm^2 for consumers. The exposure values are based on the highest concentrations of citral reported by the registrants in the exposure scenarios for the use in cleaning agents, which correspond to < 1.5% for workers and < 0.5% for consumers. However, it is noted in the SEv conclusion that products with higher concentrations of citral are found on the Swedish market.

In characterising the nature of the exposure of EU citizens to citral in order to make a comparison with the numbers of positive patch tested individuals, RAC is mindful that there is much uncertainty about the nature of the products that may have induced the sensitisation, the periods during which the induction occurred, and the concentrations encountered by those being induced. Although according to the DS the IFRA limits have helped to reduce exposure, it is possible that patients may have been exposed to consumer products containing unrestricted concentrations of citral as late as 2013 (according to comments received from industry during the public consultation).

Exposure data	Indicator of relatively low exposure	Indicator of relatively high exposure	Assessment by RAC
Concentration/dose at induction	< 1.0% < 500 µg/cm^2	≥ 1.0% ≥ 500 µg/cm^2	The content of citral in many consumer and professional products appears to have decreased significantly in recent years; surveys suggest that current levels may be very low. However, it also appears that higher content levels (≥ 1.0%) will have prevailed during the periods when most of the contact allergy patients were induced to citral. *Conclusion: relatively high exposure*
Repeated exposure	< once/daily	≥ once/daily	Given the wide range of consumer products shown to contain citral, repeated exposure every day seems very likely. *Conclusion: relatively high exposure*

Number of exposures (irrespective of the concentration of the sensitiser)	< 100 exposures	≥ 100 exposure	Given the types of consumer and professional products shown to contain citral, it is highly likely that individuals will have been exposed 100s of times. *Conclusion: relatively high exposure*

This assessment contrasts with the view of the DS, who concluded that concentration/dose levels at induction were relatively low.

In accordance with the CLP criteria, this assessment of relatively high skin exposure indicates that citral should not be regarded as a high potency skin sensitiser in spite of the high number of positive patch test results reported.

Conclusion

Citral already has the harmonised classification Skin Sens. 1; H317. Both the animal and human data presented by the DS confirm that citral is a skin sensitiser.

Under the CLP Regulation, classification into sub-categories is permitted when the data are sufficient. The DS noted especially that the high number of positive patch tests seen in patients attending dermatitis clinics over the last 20-30 years may justify sub-categorisation, accounting for high potency.

However, the results of the available animal studies are not consistent, and a reliable estimate of potency cannot be derived from them. The results from HRIPTs clearly support classification. However, these data cannot be used to support sub-categorisation because information about the sensitising potential of sufficiently low doses of citral to assess potency is lacking. Similarly, the HMT studies were all conducted at high induction doses. The results of these studies support classification as Skin Sens. 1, but cannot be used for sub-categorisation.

RAC agrees with the DS that high frequencies of sensitisation were observed in some of the diagnostic patch tests (in selected and unselected patients, and in the high number of published cases), however, the exposures responsible for inducing sensitisation in these individuals may have been relatively high, but it is not entirely clear. Given this uncertainty, the diagnostic patch tests cannot be used to support sub-categorisation.

Therefore, RAC concludes that the sensitising properties of citral have been confirmed, however the available data are not sufficient for sub-categorisation. Therefore, RAC concludes that classification as **Skin Sens. 1; H317 (May cause an allergic skin reaction)** is warranted for citral.

The available data are not sufficient to the establishment of a specific concentration limit. Furthermore, the data do not suggest that citral has an extreme potency.

Additional references

Bennike, Zachariae and Johansen (2017). Non-mix fragrances are top sensitizers in consecutive dermatitis patients – a cross-sectional study of the 26 EU-labelled fragrance allergens. *Contact Dermatitis*, 77: 270-279.

Betts, Beresford, Dearman, Lalko, Api and Kimber (2007) The use of ethanol:diethylphthalate as a vehicle for the local lymph node assay. *Contact Dermatitis*, 56:70-75

Mowitz, Svedman, Zimerson, Isaksson, Pontén and Bruze (2017). Simultaneous patch testing with fragrance mix I, fragrance mix II and their ingredients in southern Sweden between 2009 and 2015. *Contact Dermatitis*, 77: 280-287.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).