

OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD
PRODUCTS INTENDED FOR CONSUMERS

CONCERNING

HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE
(Lyral®)

adopted by the SCCNFP during the 26th plenary meeting
of 9 December 2003

1. Terms of Reference

1.1. Context of the question

4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde is used as a fragrance ingredient in cosmetic products. It is not regulated in an Annex to the Cosmetics Directive but is one of the 26 fragrance ingredients identified by the SCCNFP (*Fragrance allergy in consumers: a review of the problem, analysis of the need for appropriate consumer information and identification of consumer allergens (adopted by the SCCNFP during the plenary session of 8 December 1999)*) as being a recognized allergen in fragrance compounds.

The European Commission has received a letter from the University Louis Pasteur, Strasbourg, France with data demonstrating that current consumer exposure to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in cosmetic products exceeds the threshold for elicitation in sensitized individuals and that exposure is likely to induce a significant level of sensitization in the population. The data was generated through a 5th Framework programme: *Fragrance chemical allergy: a major environmental and consumer health problem in Europe (QLK4-CT-1999-01558)*.

The letter was also sent to COLIPA who replied that results of additional studies were to be expected by mid-November 2003 and appended two documents (1. Fine fragrance: understanding usage patterns and exposure ; 2. Perfume allergens: why contact allergy risk management should not be based on eliciting concentrations of the allergens).

1.2. Request to the SCCNFP

- * Is 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde safe for use in cosmetic products taking into account the data provided?
If not, does the SCCNFP consider 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde is safe if used up to a maximum concentration in cosmetic products and do the data provided indicate such a concentration?
- * And/or does the SCCNFP recommend any further restrictions with regard to the use of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde as a fragrance in cosmetic products?

1.3 Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.

The extent to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

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SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

2. Toxicological Evaluation and Characterisation

2.1. General

INCI name	:	hydroxyisohexyl 3-cyclohexene carboxaldehyde
Synonyms	:	4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde
Trade name	:	Lyral®
CAS n°	:	31906-04-4
EINECS n°	:	250-863-4

2.2. Epidemiology

4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde is a fragrance ingredient widely used in cosmetic products. Initial testing of its allergenic potential in animal and human experimental studies was negative.

Ref 1

However, in a screening study for fragrance contact allergy, 106 patients were tested with 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde 5% and 1% in petrolatum. 3 (2.8%) had a positive patch test reaction to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde 5% and 1 (0.9%) to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde 1%. Clinical relevance was not firmly established.

Ref 2

In a systematic study of patients with eczema showed that 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde was a common contact allergen in this group. 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde (5% in petrolatum) gave a positive reaction in 2.7% of 1855 patients (range 1.2-17%) in a multicentre European study. All patients were carefully questioned regarding a history of reactions to scented products in the past and were grouped into four categories: certain, probable, questionable and none. 24 patients reacted to both 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde and the standard 'fragrance mix', but 21(1.1%) reacted positively only to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde. Of 124 patients with a 'certain' history of fragrance intolerance, 53.2% reacted to the fragrance mix and a further 7.2% to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde only. If any kind of history of fragrance intolerance was given, 80% (40 of 50) of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde allergic individuals had a 'positive' history whilst only 58.6% (123 of 210) patients reacting to the standard fragrance mix

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had such a history. This difference was significant ($P<0.01$). 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde was identified by gas chromatography – mass spectroscopy in some products which had caused an allergic contact dermatitis in four typical patients who showed a patch test positive reaction to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde with a negative or doubtful reaction to the fragrance mix. The authors recommended routine testing with 5% 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in patients undergoing patch testing.

Ref 3

When 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde was tested by the German Contact Dermatitis Research Group, 62 (1.9%) of 3245 consecutive patch tested patients with eczema in 20 departments showed a positive reaction to 5% 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in petrolatum. In half of these individuals there was clinical relevance. One third of the reactions to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde were graded ++ and +++. 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde was tested in parallel with the standard fragrance mix in 3185 patients. Of these, 300 (9.4%) reacted to the fragrance mix, and 59 (1.9%) to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde. In 40 patients, positive reactions to both occurred, which is 13.3% of those reacting to the fragrance mix, and 67.8% of those reacting to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde. The concordance of positive test reactions to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde and the fragrance mix was considered to be low. This data lead to the inclusion of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in the standard patch test series recommended in Germany for routine evaluation of individuals with eczema.

Ref 4

Of 1281 patients patch tested to the standard fragrance mix and 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in Zurich , 169 (13.2%) patients showed a positive patch test to the fragrance mix, 34 (2.7%) to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde and 146 (11.4%) to the fragrance mix alone. In 11 out of the 34 patients (32%) patch test were positive to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde but not to the fragrance mix, and 23 out of 34 patients (67.6%) were exclusively positive to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde. Sensitisation to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde was considered to be clinically relevant in 17 out of 34 cases (50%) and likely out of 34 cases (20.6%). The authors concluded that in a significant proportion of patients who are allergic to ingredients of fragrances, 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde is able to identify fragrance-allergic individuals who would not have been found by testing with the fragrance mix.

Ref 5

4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde has been shown to be an important allergen for individuals with hand eczema.

Ref 6

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4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde has been shown to be a relevant allergen in a number of case reports:

Ref 7, 8, 9 ,10

4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde has now been identified as a contact allergen in the local lymph node assay (EC3 value 17.1) .

Ref 11

2.3. Data submitted

The data on 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde generated through a 5th Framework programme: *Fragrance chemical allergy: a major environmental and consumer health problem in Europe (QLK4-CT-1999-01558)* has now been published.

Ref 12

18 eczema patients, whom on previous patch testing had shown at least a '+' reaction (palpable erythema) to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde 5% in petrolatum were included in the two studies. Control subjects were eczema patients who were negative to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde 5% on patch testing.

Study A) Patch Tests

4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde (purity by GC-MS >99%) was 10-fold serially diluted from 6% w/v to 6 ppm in ethanol. 15µl of solution was absorbed onto filter discs in Finn Chambers® and applied to the upper back for 2 days. Readings were made at D2, D3 and D7. The threshold response was defined as the weakest concentration giving a visible skin response in a continuous line of patch test reactions starting with 6% w/v 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in ethanol.

One or more reactions to the dilution patch series were found in all but one subject (17/18). The non-reactor at this repeat testing had previously given a ++ reaction to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde 5% and had abstained from using perfumed products.

From a dose-response curve derived from the data, it can be calculated that the dose of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde eliciting a reaction in 10% of the group was 29 ppm (95% confidence limits 7-69 ppm) and 50% reacted to 662 ppm (95% confidence limits 350-1250 ppm). These figures correspond to 0.9 µg/cm² and 20 µg/cm² respectively given the application of 15 µl solution to 0.5 cm² of patch test area under Finn Chambers™.

Study B) Use Tests

A repeated open application (ROAT) was made to a 3 x 3 cm area of skin on the volar aspect of the forearm. Two drops (30 mg of solution) of a 0.5% solution of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in ethanol were applied twice daily for two

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weeks. If there was no reaction, the applications were continued with 3% w/v 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in ethanol for a further two weeks. A positive reaction was defined as erythema covering at least 25% of the test area and papules, regardless of number.

In 16/18 cases (89%) a positive ROAT was found. In 11 cases the ROAT was positive to the low concentration (0.5% 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in ethanol) and 5 to the high concentration (3% 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in ethanol). The two most sensitive subjects began reacting after only two applications. All controls were negative.

In the group reacting to the low dose, the median amount applied to elicit a reaction was 15.3 µg 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde/cm² (range 3.4 – 22.2). In the group reacting to the higher dose, the mean dose applied was 126.3 µg 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde/cm² (range 40.5 – 226.2).

In combining the data from the two studies (same individuals), it was found that in those having a positive ROAT to the low concentration of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde had a median threshold for reacting to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde on patch testing at 0.06% (range 2% - < 0.0006%). For those with a positive ROAT at the high concentration, had a median threshold for reacting to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde on patch testing at 2% (range 6% - < 0.002%).

The above data are relevant to individuals who are already allergic to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde and evaluate the doses required to elicit an allergic contact reaction on their previously sensitized skin.

Although the individuals evaluated may have acquired contact allergy to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde from its use in cosmetics, 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde is also recommended for use in household products .

Ref 13

2.4. Discussion

A survey of marketed products showed that 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde was present in 46% of fine fragrances >1% and with an average concentration of 3.2%.

Ref 14

Using a risk assessment model for induction of contact allergy, a sensitization reference dose for 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde at 10 µg/cm² in a fine fragrance was determined. The sensitization reference dose signifies that exposure exceeding this limit are likely to induce sensitization, which is clearly the case with 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde at current usage levels in fine fragrances.

Ref 15

A European survey has shown that deodorants may contain up to 0.18% 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde. A content of 0.1% 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in a deodorant corresponds to an exposure of 5 µg 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde/cm²/application. It is likely that the amount will differ according to the type of deodorant. There is a similarity to exposure to an allergen from its presence in a deodorant and exposure during patch testing. On patch testing, 10% of individuals react to 0.9 µg 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde/cm² (equivalent to about 0.02% 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde in a deodorant) which is much lower than potential exposure during ordinary deodorant use. There is no published information on the principles for calculating a sensitization reference dose for deodorants.

Ref 16, 17

3. Opinion of the SCCNFP

- * **Is 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde safe for use in cosmetic products taking into account the data provided?**

The available data clearly demonstrate that 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde is an important contact allergen. In recent large European surveys, it has been shown that in patients with eczema 1.9 – 2.7% react to 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde 5% in petrolatum on routine testing. The allergy is often relevant. The frequency of contact allergy in the general population is unknown. The proportion of individuals with eczema who are evaluated by diagnostic patch testing will depend on the accessibility of appropriate facilities within their geographical location in Europe.

Therefore, the current use levels of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde are unsafe as current use levels have both caused the induction and elicitation of contact allergy to it.

Additionally, although the presence of it in a finished cosmetic product will be identified on ingredient labels if present at 10ppm (0.001%) in leave on products or 100ppm (0.01%) in rinse off cosmetic products, only that unknown proportion of individuals who have been clinically tested will be able to avoid cosmetics that are potentially harmful to them.

Industry has recommended that 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde should not be used at a level greater than 1.5% in a finished cosmetic product. This recommended level far exceeds levels known to be a risk to the consumer.

Ref 18

- * **If not, does the SCCNFP consider 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde is safe if used up to a maximum concentration in cosmetic products and do the data provided indicate such a concentration?**

Results from the experimental data above, and a risk assessment model, suggest that a safe level of exposure for the consumer would be in the range of 0.9 µg /cm² to 10 µg /cm².

*** And/or does the SCCNFP recommend any further restrictions with regard to the use of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde as a fragrance in cosmetic products?**

Based on the information presently available, a concentration of up to 0.02% in a finished cosmetic product will have a low potential to *induce* sensitisation, or *elicit* allergic contact reactions in those consumers already sensitised to this fragrance chemical.

Although strictly a risk management matter, because of the importance of 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1 carboxaldehyde as an allergen for the consumer, a more easily recognised INCI name than hydroxyisohexyl 3-cyclohexene carboxaldehyde may be of assistance to the consumer.

4. References

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