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Review

A toxicologic and dermatologic assessment of cyclopentanones and cyclopentenones when used as fragrance ingredients ☆

The RIFM Expert Panel
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ABSTRACT

The cyclopentanone and cyclopentenone group of fragrance ingredients was critically evaluated for safety following a complete literature search. For high end users, calculated maximum dermal exposures vary from 0.002% to 15.16% in hydroalcoholic products; systemic exposures vary from 0.0003 to 0.7122 mg/kg/day. The cyclopentanones and cyclopentenones had a low order of acute toxicity and no significant toxicity in repeat dose studies. No mutagenic or genotoxic activity in bacteria and mammalian cell line assays was observed. Developmental toxicity was not observed. Minimal evidence of skin irritation in humans is associated with current levels of use. Eleven materials were tested undiluted for eye irritation; three were considered irritants. No phototoxic and photosensitization reactions were seen with nine materials tested. At concentrations higher than current reported use, 14 materials were non-sensitizing in HRIPT or maximization tests. 2-Hexylidene cyclopentanone, 2-heptylidenecyclopentan-1-one and 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one are weak sensitizers and have IFRA Standards. Risk of sensitization to the cyclopentanones and cyclopentenones is generally small under current levels of use. The Panel is of the opinion that there are no safety concerns for the cyclopentanones and cyclopentenones at reported levels of use and exposure as fragrance ingredients.

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1. Introduction

In 2010 complete literature searches were conducted on the cyclopentanones and cyclopentenones group of fragrance ingredients. The Expert Panel of the Research Institute for Fragrance Materials (RIFM) reviewed all the literature on this group of materials and this report summarizes safety data relevant to the risk assessment of the use of 25 of these materials (16 cyclopentanones and 9 cyclopentenones) as fragrance ingredients.

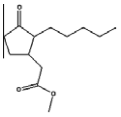
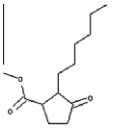
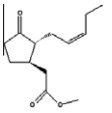
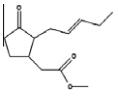
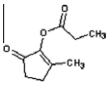
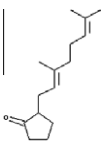
Cyclopentanones and cyclopentenones are used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. The report summarizes animal and human data, including studies with various exposure routes, and evaluates the risk from their use as fragrance ingredients. The scientific evaluation focuses on dermal exposure, which is considered to be the primary exposure route for these fragrance materials. Toxicity, metabolism and kinetic data obtained from studies using other routes of exposure have also been considered to assess the systemic fate and toxicity of the substances.

The current format includes a group summary evaluation paper and individual Fragrance Material Reviews (FMRs) on discrete chemicals. The group summary is an evaluation of relevant data selected from the large bibliography of studies and reports on the individual chemicals. These studies and reports are both primary data from RIFM and RIFM member companies, and peer-reviewed publications. The selected data were deemed to be relevant based on the currency of protocols, quality of the data, statistical significance and appropriate exposure. These are identified in tabular form in the group summary (Tables 2–10). Details that are provided in the tables are not always discussed in the text of the group summary. Separate publications on individual fragrance materials, which are called Fragrance Material Reviews (FMRs), are published concurrently with the group summary (Scognamiglio et al., in press-a–y). The FMRs contain a comprehensive summary of all unpublished and published reports, including complete bibliographies.

2. Chemical identity, regulatory status and exposure

In the United States, the regulatory status of three of these materials (2-hexylidene cyclopentanone; isojasmone; *cis*-jasmone) includes approval (21 CFR 172.515) by the Food and Drug Administration (FDA) and Generally Recognized as Safe (GRAS) as flavor ingredients (11 materials: methyl dihyrdrojasmonate; methyl jasmonate; cyclopentanone; 2-cyclopentylcyclopentanone; cyclotene propionate; 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone; 3-ethyl-2-hydroxy-2-cyclopenten-1-one; 2-hexylidene cyclopentanone; isojasmone; 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one; 3-methyl-2-(2-pentenyl)-2-cyclopenten-1-one) by the Flavor and Extract Manufacturers Association (FEMA, 1965, 1970, 1973, 1978, 1990, 1998, 2000, 2009). One of these materials (3-ethyl-2-hydroxy-2-cyclopenten-1-one) was also included in the Council of Europe's list of substances which may be used in foodstuffs (Council of Europe, 2000). Finally, the international joint FAO/WHO Expert Committee on Food Additives (JECFA, 1999, 2003, 2006) has evaluated seven of these materials (cyclopentanone; 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone; 3-ethyl-2-hydroxy-2-cyclopenten-1-one; 2-hexylidene cyclopentanone; isojasmone; 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one; 3-methyl-2-(2-pentenyl)-2-cyclopenten-1-one) and found them to have no safety concerns based on current levels of intake as food flavors. The cited approvals are for oral exposure, whereas the primary route of exposure for fragrance ingredients is dermal. How-

Table 1
Ketones cyclopentanones and cyclopentenones material identification, summary of volume of use, and dermal exposure.

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure (mg/kg/day)[b]	Maximum skin level (%)[c,d]
Keto esters					
Methyl dihydrojasmonate $C_{13}H_{22}O_3$ CAS#: 24851-98-7 Log K_{ow} (calculated): 2.98 Molecular Weight: 226.32 Vapor Pressure: <0.001 mm Hg at 20 °C Water Solubility: 91.72 mg/l at 25 °C	2-Amylcyclopentanoneacetic acid, methyl ester; Cyclopentaneacetic acid, 3-oxo-2-pentyl-, methyl ester; Dihyrojasmonic acid methyl ester; Hedione; Methydihydro-Jasmonate; Methyl (2-amyl-3-oxocyclopentyl) acetate; Methyldihydrojasmonate; Methyl 3-oxo-2-pentylcyclopentaneacetate; Methyl (3-oxo-2-pentylcyclopentyl) acetate; Methyl (2-pentyl-3-oxocyclopentyl) acetate; 3-Oxo-2-pentylcyclopentaneacetic acid, methyl ester		>1000	0.7122	15.16
Methyl hexyl oxo cyclopentanone carboxylate $C_{13}H_{22}O_3$ CAS#: 37172-53-5 Log K_{ow} (calculated): 2.98 Molecular Weight: 226.32 Vapor Pressure: 0.207 mm Hg at 25 °C Water Solubility: 91.72 mg/l at 25 °C	Cyclopentanecarboxylic acid, 2-hexyl-3-oxo-, methyl ester; Dihydro isojasmonate; Dihydrojasmonate; Jasmopol; Methyl 2-hexyl-3-oxocyclopentanecarboxylate		10–100	0.0596	0.65
Methyl jasmonate $C_{13}H_{20}O_3$ CAS#: 1211-29-6 Log K_{ow} (calculated): 2.76 Molecular Weight: 224.3 Vapor Pressure: <0.001 mm Hg at 25 °C Water Solubility: 143.5 mg/l at 25 °C	Cyclopentaneacetic acid, 3-oxo-2-(2-pentenyl)-, methyl ester (1R,2bZ); Methyl (1R-(1a,2b (Z)))-3-oxo-2-(pent-2-enyl) cyclopentaneacetate; Methyl 3-oxo-2-(2-pentenyl) cyclopentyl acetate; Methyl (3-oxo-2-pent-2-en-1-ylcyclopentyl) acetate; Methyl (2-pent-2-enyl-3-oxo-1-cyclopentyl) acetate		0.01–0.1	0.0015	0.08
Methyl 3-oxo-2-(pent-2-enyl) cyclopentaneacetate $C_{13}H_{20}O_3$ CAS#: 39924-52-2 Log K_{ow} (calculated): 2.76 Molecular Weight: 224.0 Vapor Pressure: 0.0653 mm Hg at 25 °C Water Solubility: 143.5 mg/l at 25 °C	Cyclopentaneacetic acid, 3-oxo-2-(2-pentenyl)-, methyl ester (isomer unspecified); Methyl (3-oxo-2-pent-2-en-1-ylcyclopentyl) acetate; Methyl 2-pentenyl-3-oxocyclopentaneacetate		0.1–1	0.0063	0.12
Monocycles					
Cyclopentanone C_5H_8O CAS#: 120-92-3 Log K_{ow} (calculated): 0.63 Molecular Weight: 84.12 Vapor Pressure: 12 mm Hg at 25 °C Water Solubility: 36850 mg/l at 25 °C	Adipic ketone; Dumasin; Ketocyclopentane; Ketopentamethylene		0.1–1	0.0005[e]	0.02[e]
2-Cyclopentylcyclopentanone $C_{10}H_{16}O$ CAS#: 4884-24-6 Log K_{ow} (calculated): 2.83 Molecular Weight: 152.37 Vapor Pressure: 0.00858 mm Hg at 25 °C Water Solubility: 283.6 mg/l at 25 °C	[1,1′-Bicyclopentyl]-2-one; 1,1′-Bi(cyclopentyl)-2-one		<0.01	0.0005[e]	0.02[e]
Cyclotene propionate $C_9H_{12}O_3$ CAS#: 87-55-8 Log K_{ow} (calculated): 1.84 Molecular Weight: 168.19 Vapor Pressure: 0.0114 mm Hg at 25 °C Water Solubility: 1671 mg/l at 25 °C	3-Methyl-2-(1-oxopropoxy)-2-cyclopenten-1-one; 2-Methyl-5-oxocyclopent-1-en-1-yl propanoate		0.1–1	0.0005[e]	0.02[e]
2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone $C_{15}H_{24}O$ CAS#: 68133-79-9 Log K_{ow} (calculated): 5.15 Molecular Weight: 220.36 Vapor Pressure: 0.00162 mm Hg at 25 °C Water Solubility: 1.358 mg/l at 25 °C	Apritone; Cyclopentanone, 2-(3,7-dimethyl-2,6-octadienyl)-; Decenyl cyclopentanone; (E)-2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone; 2-(3,7-Dimethylocta-2,6-dien-1-yl) cyclopentanone		0.01–0.1	0.0005[e]	0.02[e]

(*continued on next page*)

Table 1 (*continued*)

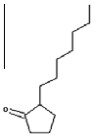
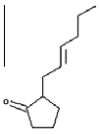
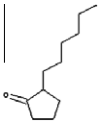
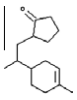
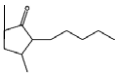
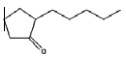
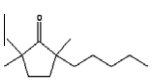
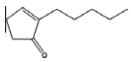
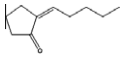
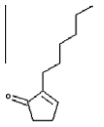
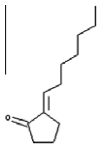
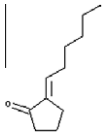
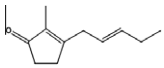
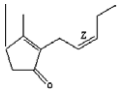
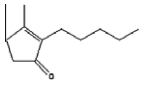
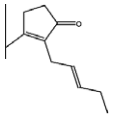
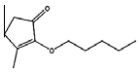
Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure (mg/kg/day)[b]	Maximum skin level (%)[c,d]
3-Ethyl-2-hydroxy-2-cyclopenten-1-one $C_7H_{10}O_2$ CAS#: 21835-01-8 Log K_{ow} (calculated): 1.78 Molecular Weight: 126.16 Vapor Pressure: 0.00103 mm Hg at 25 °C Water Solubility: 2878 mg/l at 25 °C	2-Cyclopenten-1-one, 3-ethyl-2-hydroxy-; 3-Ethyl-2-hydroxycyclopent-2-en-1-one; Ethyl Cyclotene		0.01–0.1	0.0005[e]	0.02[e]
2-Heptylcyclopentanone $C_{12}H_{22}O$ CAS#: 137-03-1 Log K_{ow} (calculated): 4 Molecular Weight: 182.31 Vapor Pressure: 0.0178 mm Hg at 25 °C Water Solubility: 20.63 mg/l at 25 °C	Alismone; Cyclopentanone, 2-heptyl-; Fleuramone; Projasmon		10–100	0.0209	0.67
Hexenylcyclopentanone $C_{11}H_{18}O$ CAS#: 34687-46-2 Log K_{ow} (calculated): 3.29 Molecular Weight: 166.26 Vapor Pressure: 0.0405 mm Hg at 25 °C Water Solubility: 98.69 mg/l at 25 °C	Cyclopentanone, 2-(2-hexenyl)-; 2-(2-Hexenyl) cyclopentanone		<0.01	0.0005[e]	0.02[e]
2-Hexylcyclopentanone $C_{11}H_{20}O$ CAS#: 13074-65-2 Log K_{ow} (calculated): 3.51 Molecular Weight: 168.28 Vapor Pressure: 0.00057 mm Hg at 25 °C Water Solubility: 63.27 mg/l at 25 °C	Cyclopentanone, 2-hexyl-; Hexyl cyclopentanone		1–10	0.0008	0.015
2-Hydroxy-3,4-dimethyl-2-cyclopenten-1-one $C_7H_{10}O_2$ CAS#: 21835-00-7 Log K_{ow} (calculated): 1.71 Molecular Weight: 126.15 Vapor Pressure: 0.00152 mm Hg at 25 °C Water Solubility: 3326 mg/l at 25 °C	None		<0.01	0.0005[e]	0.02[e]
2-(*p*-Menth-1-ene-10-yl) cyclopentanone $C_{15}H_{24}O$ CAS#: 95962-14-4 Log K_{ow} (calculated): 5.05 Molecular Weight: 220.56 Vapor Pressure: 0.000923 mm Hg at 25 °C Water Solubility: 1.655 mg/l at 25 °C	Cyclopentanone, 2-[2-(4-methyl-3-cyclohexen-1-yl)propyl]-; 2-[2-(4-Methylcyclohex-3-en-1-yl)propyl]cyclopentanone; Nectaryl		100–1000	0.0199	0.16
3-Methyl-2-pentylcyclopentan-1-one $C_{11}H_{20}O$ CAS#: 13074-63-0 Log K_{ow} (calculated): 3.43 Molecular Weight: 168.28 Vapor Pressure: 0.0691 mm Hg at 25 °C Water Solubility: 73.11 mg/l at 25 °C	Tetrahydro jasmone; Tetrahydro jasmone [3-methyl-2-pentylcyclopentanone); Tetrahydrojasmone		0.001–0.01	0.0005[e]	0.02[e]
2-Pentylcyclopentan-1-one $C_{10}H_{18}O$ CAS#: 4819-67-4 Log K_{ow} (calculated): 3.02 Molecular Weight: 154.53 Vapor Pressure: 0.836 mm Hg at 25 °C Water Solubility: 192.7 mg/l at 25 °C	2-*n*-Amylcyclopentanone; Cyclopentanone, 2-pentyl-; Delphone; 2-Pentylcyclopentanone		10–100	0.0008	0.012
2,2,5-Trimethyl-5-pentylcyclopentanone $C_{13}H_{24}O$ CAS#: 65443-14-3 Log K_{ow} (calculated): 4.34 Molecular Weight: 196.33 Vapor Pressure: 0.4 mm Hg at 20 °C Water Solubility: 8.956 mg/l at 25 °C	Cyclopentanone, 2,2,5-trimethyl-5-pentyl-; 2-Pentyl-2,5,5-trimethylcyclopentanone; 2,2,5-Trimethyl-5-pentylcyclopentan-1-one; Veloutone		10–100	0.0059	0.15

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure (mg/kg/day)[b]	Maximum skin level (%)[c,d]
α,β-Unsaturated monocycles					
Amylcyclopentenone[f] $C_{10}H_{16}O$ CAS#: 25564-22-1 Log K_{ow} (calculated): 3.22 Molecular Weight: 152.24 Vapor Pressure: 0.0497 mm Hg at 25 °C Water Solubility: 131.9 mg/l at 25 °C	2-Cyclopenten-1-one, 2-pentyl-; 2-Pentyl-2-cyclopentenone; 2-Pentylcyclopent-2-en-1-one		0	0	0
Cyclopentanone, 2-pentylidene[f] $C_{10}H_{16}O$ CAS#: 16424-35-4 Log K_{ow} (calculated): 3.22 Molecular Weight: 152.24 Vapor Pressure: 0.0896 mm Hg at 25 °C Water Solubility: 131.9 mg/l at 25 °C	2-Pentylidenecyclopentanone; 2-Pentylidenecyclopentan-1-one		0	0	0
Dihydroisojasmone $C_{11}H_{18}O$ CAS#: 95-41-0 Log K_{ow} (calculated): 3.71 Molecular Weight: 166.26 Vapor Pressure: 0.008 mm Hg at 20 °C Water Solubility: 43.35 mg/l at 25 °C	2-Cyclopenten-1-one, 2-hexyl-; 2-Hexylcyclopent-2-en-1-one; Isojasmone B11		1–10	0.0041	0.10
2-Heptylidenecyclopentan-1-one$C_{12}H_{20}O$ CAS#: 39189-74-7 Log K_{ow} (calculated): 4.2 Molecular Weight: 180.91 Vapor Pressure: 0.0103 mm Hg at 25 °C Water Solubility: 14.15 mg/l at 25 °C	Cyclopentanone, 2-heptylidene-; 2-Heptylidenecyclopentanone		< 0.01	0.0005[e]	0.02[e]
2-Hexylidene cyclopentanone $C_{11}H_{18}O$ CAS#: 17373-89-6 Log K_{ow} (calculated): 3.71 Molecular Weight: 166.26 Vapor Pressure: 0.008 mm Hg at 20 °C Water Solubility: 43.35 mg/l at 25 °C	Cyclopentanone, 2-hexylidene-; alpha-Hexylidenecyclopentanone; 2-Hexylidenecyclopentanone; Jasmalone		<0.01	0.0003	0.002
Isojasmone $C_{11}H_{16}O$ CAS#: 11050-62-7 Log K_{ow} (calculated): 3.55 Molecular Weight: 166.27 Vapor Pressure: 0.0972 mm Hg at 25 °C Water Solubility: 60.54 mg/l at 25 °C	2-Cyclopenten-1-one, 2-methyl-3-(2-pentenyl)-; 2-Hexyl-2-cyclopenten-1-one and 2-hexylidenecylopentanone (mixture); 2-Hexylidene cyclopentanone and 2-hexyl-2-cyclopenten-1-one (mixture); 2-Methyl-3-pent-2-enylcyclopent-2-enone; 2-Methyl-3-pent-2-en-1-ylcyclopent-2-en-1-one		0.1–1	0.0003	0.01
cis-Jasmone $C_{11}H_{16}O$ CAS#: 900488-10-8 Log K_{ow} (calculated): 3.55 Molecular Weight: 164.25 Vapor Pressure: 4.1 mm Hg at 25 °C Water Solubility: 60.54 mg/l at 25 °C	2-Cyclopenten-1-one, 3-methyl-2-(2Z)-2-pentenyl-; (*Z*)-3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one; 3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one; 3-Methyl-2-(2-*cis*-pentenyl)-2-cyclopenten-1-one		1–10	0.0094	0.26
3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one$C_{11}H_{18}O$ CAS#: 1128-08-1 Log K_{ow} (calculated): 3.7 Molecular Weight: 184.0 Vapor Pressure: 0.01 mm Hg at 20 °C Water Solubility: 38.82 mg/l at 25 °C	2-Cyclopenten-1-one, 3-methyl-2-pentyl-; Dihydrojasmone; 3-Methyl-2-pentylcyclopent-2-en-1-one; 2-Pentyl-3-methyl-2-cyclopenten-1-one		10–100	0.0028	0.14
3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one$C_{11}H_{16}O$ CAS#: 488-10-8 Log K_{ow} (calculated): 3.55 Molecular Weight: 164.25 Vapor Pressure: 0.01 mm Hg at 20 °C Water Solubility: 60.54 mg/l at 25 °C	2-Cyclopenten-1-one, 3-methyl-2-(2-pentenyl)-, (*Z*)-; Jasmone; 3-Methyl-2-pent-2-en-1-ylcyclopent-2-en-1-one		1–10	0.0069	0.7

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure (mg/kg/day)[b]	Maximum skin level (%)[c,d]
3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one$C_{11}H_{18}O_2$ CAS#: 68922-13-4 Log K_{ow} (calculated): 3.01 Molecular Weight: 182.26 Vapor Pressure: 0.00875 mm Hg at 25 °C Water Solubility: 144.1 mg/l at 25 °C	2-Cyclopenten-1-one,3-methyl-2-(pentyloxy); 2-Cyclopenten-1-one, 2-(pentyloxy)-3-methyl-;3-Methyl-2-(pentyloxy) cyclopent-2-en-1-one		0.1–1	0.0025	0.02

[a] 2008 Volume of use survey (IFRA, 2008).
[b] Based on a 60 kg adult; upper 97.5 percentile levels of the fragrance ingredient in the fragrance mixture used in hydroalcoholic products, see Section 2.3, see FMRs (Scognamiglio et al., in press-a–y) for table.
[c] Percent concentration of the fragrance ingredient in the top 10 concentrations in fragrance mixtures that are used in hydroalcoholic products applied to the skin. It is then assumed that 20% of the fragrance mixture is in the fine fragrance consumer product. See Section 2.3.
[d] 2007 Use level survey (IFRA, 2007).
[e] A default value of 0.02% was used to calculate dermal systemic exposure.
[f] These materials belong to the Ketones Cyclopentanones and Cyclopentenones group; they are not being reviewed because there are not any reported use of these materials as fragrance ingredients.

ever, these approvals provide supportive information on the safety of the materials.

2.1. Rationale for grouping cyclopentanones and cyclopentenones together

The group consists of 25 cyclopentanones or cyclopentenones. The names, Chemical Abstracts Service Registration Number (CAS RN), synonyms and structures of the materials reviewed are shown in Table 1 (two materials, amylcyclopentenone and 2-pentylidenecylopentanone, belong to the group, but have no reported use in perfumery). The common characteristic structural element of the group members is a cyclopentanone or cyclopentenone ring with a straight or branched chain alkane or alkene substituent. 2-Cyclopentylcyclopentanone contains a cyclopentyl ring attached to the cyclopentanone ring and 2-(*p*-menth-1-ene-10-yl) cyclopentanone contains a cyclohexene ring. The pentyl group in 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one is attached to the ring via an ether bridge. Four of the group members are methyl esters which besides alkyl substituents possess an additional methyl carboxylate or a methyl acetate group attached to the cyclopentanone ring.

Due to their structural similarity, it is expected that the materials under review possess a similar toxicity, as their only functional groups are keto groups or double bonds. However, the eight materials in the α,β-unsaturated monocycle subgroup (3-methyl-2-(pentyloxy)-2-cyclopenten-1-one; dihydroisojasmone; 2-heptylidenecyclopentan-1-one; 2-hexylidene cylcopentanone; isojasmone; *cis*-jasmone; 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one; 3-methyl-2-(2-pentenyl)-2-cyclopenten-1-one), contain a conjugated double bound in alpha-position to the keto group. Due to this conjugation, a higher reactivity of these compounds may be expected and is expressed by the higher sensitization potency exhibited with two of the materials in this subgroup. Alkylating and thus mutagenic properties might be expected. However, mutagenicity tests on three of the materials (dihydroisojasmone, 2-hexylidene cyclopentanone, *cis*-jasmone,) were negative.

As to the four methyl esters (methyl dihydrojasmonate; methyl hexyl oxo cyclopentanone carboxylate; methyl jasmonate; and methyl 3-oxo-2-(pent-2-enyl) cyclopentaneacetate), alkyl esters are known to be hydrolyzed *in vivo* to their acids and the corresponding alcohol, in this case methanol. Since methanol is a systemically toxic compound, these four methyl esters, at least at high exposures, are expected to be more toxic than the rest of the group members and are treated separately in each chapter of this review.

Apart from conjugated double bonds and methyl ester groups, the structural differences of the group members are restricted to alkyl substituents attached to the 5-ring which are expected to be without great influence on the toxicity. This also applies for the materials containing cyclopentyl, cyclohexenyl and pentyloxy groups.

Data on metabolism of the substances under review are limited. In general, ketones are metabolized to the corresponding secondary alcohol.

From metabolism studies with other ketones it can be concluded that side-chain oxidation might be possible (JECFA, 2007). This reaction yields polar metabolites, which are conjugated and excreted. Reduction of endocyclic double bonds is more likely than that of exocyclic double bonds (JECFA, 2007). Supporting experimental data for these metabolism steps are not available for the materials under study. As already pointed out, the methyl esters will be hydrolyzed, yielding the corresponding acid and methanol as well as its metabolic products formaldehyde and formic acid, which is further metabolized to carbon dioxide.

The critical effect of these materials when used as fragrance ingredients is skin irritation and sensitization, especially for alpha, beta-unsaturated compounds, which can react with nucleophilic centers of proteins. Skin irritation studies in humans are available for 17 materials, and yield non-irritating concentrations ranging from 0.05% to 20%. Most of the compounds are irritants, when tested undiluted in animal experiments.

With the exception of 2 materials (2-cyclopentylcyclopentanone and methyl 3-oxo-2-(pent-2-enyl) cyclopentaneacetate) all compounds under review have been studied for their sensitization potential in humans or animals. The two untested materials are both very low volume of use materials and are not chemically reactive. Three of the materials are sensitizers in humans and/or animals. A no observed effect level (NOEL) for this endpoint has been determined for 2-hexylidene cyclopentanone and 2-heptylidenecyclopentan-1-one and 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one.

Genotoxicity tests in bacteria with nine of the materials, including three alpha, beta-unsaturated, yielded negative results. Methyl dihydrojasmonate was tested in mammalian cell systems *in vitro*, in the mouse bone marrow micronucleus test and an unscheduled DNA synthesis (UDS) test. Only one material, in one of three *in vitro* mammalian cell test systems, showed mutagenicity, but it was noted that no differentiation was made between large and small colonies.

The database for systemic toxicity studies is limited. Two cyclopentanones have been tested in repeated dose toxicity studies, one of them methyl dihydrojasmonate, a methyl ester. As outlined above, the compounds with highest expected systemic toxicity are the alpha, beta-unsaturated and the methyl esters. For both classes, no observed adverse effect levels (NOAELs) in rats are in the range of 40 to 500 mg/kg body weight/day with non-specific toxicity such as reduced body weight gain being the leading effect.

In conclusion, the similar structure, reactivity and metabolism justify the grouping the cylopentanones and cyclopentenones for the purpose of a risk assessment. It is believed that the materials in this group have similar metabolism and are detoxified in the same manner. Their toxicological profiles would, then, be expected to be similar. Skin irritation and sensitization are considered to be the predominant and most sensitive effects of this group of compounds, whereas systemic effects are expected, if at all, at higher doses only.

All data available are summarized in Tables 2-11. CAS RN, synonyms, structural formulas and exposure data are shown in Table 1.

2.2. Occurrence and use

Several fragrance ingredients in the cyclopentanones and cyclopentenones group of fragrance ingredients have been reported to occur in nature. Cyclopentanone (CAS RN 120–92-3) has been reported to occur in beef, cheese, chicken and species of allium plants. Methyl dihydrojasmonate (CAS RN 24851-98-7) and methyl 3-oxo-2-(pent-2-enyl) cyclopentaneacetate (CAS RN 39924-52-20) have been reported to occur in tea, with the latter also being found in citrus fruits and menthe oils (VCF, 1963–2009).

There are 27 materials belonging to this group (see Table 1). However, the industry has reported that two (amylcyclopentenone and its isomer, 2-pentylidenecyclopentanone) are not used as fragrance materials (IFRA, 2008), and are prohibited for use as fragrance materials by the International Fragrance Association (IFRA) (IFRA, 2007). They will not be discussed any further.

2.3. Estimated consumer exposure

Exposure data have been provided by the fragrance industry. Potential consumer exposure to fragrance materials occurs through the dermal and inhalation routes of exposure. Worst-case scenario calculations indicate that depositions on the surface of the skin following use of cosmetics represents the major route of exposure to fragrance ingredients when conservative estimates for evaporation, rinsing and other forms of product removal are employed (Cadby et al., 2002). Therefore, the dermal route was the major route in assessing the safety of these compounds.

The fragrance industry has developed three types of approaches to estimate potential exposure for consumers to fragrance materials. All three types of exposure are summarized in Table 1. The first is volume of use. The total worldwide volume of use for fragrance materials in the Cyclopentanones and Cyclopentenones group ranges from <0.01 to >1000 metric tons per year (IFRA, 2008). The reported volume is based on the use of the fragrance ingredient in all finished consumer product categories. The volume of use is determined by IFRA approximately every four years through a comprehensive survey of IFRA and RIFM member companies. As such the volume of use data from this survey provides volume of use of fragrance ingredients for the majority of the fragrance industry.

Table 2-1
Acute dermal toxicity studies.

Material	Species	No. animals/dose	LD_{50}/Clinical signs[a]	References
Cyclopentanone	Rabbit	4	5000 mg/kg body weight,	RIFM (1976a)
	Rabbit	4	>3160 mg/kg body weight, diarrhea, body weight loss, mortality in 1 animal: congestion of lung, liver, kidneys, fluid in cranial cavity	RIFM (1982a)
Dihydroisojasmone	Rabbit	10	>5000 mg/kg body weight, mortality in 1 animal	RIFM (1976b)
2-Heptylcyclopentanone	Rabbit	6	5000 mg/kg body weight	RIFM (1973a)
Hexenylcyclopentanone	Rabbit	10	>5000 mg/kg body weight	RIFM (1976b)
2-Hexylcyclopentanone	Rabbit	10 (5/sex)	>5000 mg/kg body weight, mortality in 1 animal: dilated heart, collapsed congested lungs, dark fluid in pleural cavity	RIFM (1980a)
2-Hexylidene cyclopentanone	Rabbit	10	>5000 mg/kg body weight, mortality in 1 animal	RIFM (1980a)
Isojasmone	Rabbit	10	>5000 mg/kg body weight	RIFM (1974a)
cis-Jasmone	Rabbit	10	>5000 mg/kg body weight, no mortalities, diarrhea, white spotted liver, marked kidneys	RIFM (1977a)
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	Rat	5	>2008 mg/kg body weight	RIFM (1989a)
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one	Rabbit	6	> 5000 mg/kg body weight, mortality in 1 animal	RIFM (1972a)
3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one	Rabbit	6 (3/sex)	> 2000 mg/kg body weight	RIFM (1981a)
2-Pentylcyclopentan-1-one	Rabbit	6 (3/sex)	>2000 mg/kg body weight	RIFM (1979a)
2,2,5-Trimethyl-5-pentylcyclopentanone	Rabbit	4 (2/sex)	>2025 mg/kg body weight	RIFM (1978a)
Methyl ester				
Methyl dihydrojasmonate	Rabbit	10	>5000 mg/kg body weight, mortality in 1 animal, diarrhea (4/10) at d 1	RIFM (1976b)
Methyl hexyl oxo cyclopentanone carboxylate	Rabbit	10	>5000 mg/kg body weight, mortality in 2 animals, diarrhea, adipsia, anorexia, lethargy, emaciation, mottled spleen, discolored liver, intestines, lungs	RIFM (1978b)
Methyl jasmonate	Rabbit	10 (5/sex)	>2000 mg/kg body weight	RIFM (1980b)

[a] Clinical signs are noted when LD_{50} > highest dose tested and negative effects were observed.

Table 2-2
Acute oral toxicity studies.

Material	Species	No. animals/ dose	LD_{50}/Clinical Signs[a]	References
Cyclopentanone	Rat	10	1.24 ml/kg body weight (95% C.I. 1.12–1.36 ml/kg body weight) (1179 mg/kg body weight, 95% C.I. 1065–1293 mg/kg body weight)	RIFM (1976a)
	Rat	5 males	2690 mg/kg body weight	RIFM (1982a)
Dihydroisojasmone	Rat	10	>5000 mg/kg body weight, no mortalities, transient diarrhea and lethargy	RIFM (1976b)
2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone	Rat	10 (5/sex)	> 5000 mg/kg body weight	RIFM (1991a)
2-Heptylcyclopentanone	Rat	10	>5000 mg/kg body weight	RIFM (1973a)
	Mouse	2 or 6*	5 ml/kg body weight (4420 mg/kg body weight),	RIFM (1980c)
2-Heptylidenecyclopentan-1-one	Mouse	2 or 6*	>5 ml/kg body weight (5000–10,000 mg/kg body weight) hypothermia; mortalities: labored breathing, cyanosis, gastrointestinal distension and irritation, pale liver and kidney; survivors: thickening and corrosion of the stomach with adhesion to spleen, liver and abdominal cavity wall	RIFM (1980d)
Hexenylcyclopentanone	Rat	10	>5000 mg/kg body weight, no mortalities, slight lethargy, some ataxia	RIFM (1976b)
2-Hexylcyclopentanone	Rat	10	>5000 mg/kg body weight, no mortalities, diarrhea	RIFM (1980a)
	Mouse	2 or 6*	5–10 ml/kg body weight (4450–8910 mg/kg body weight)	RIFM (1982b)
2-Hexylidene cyclopentanone	Rat	10	>5000 mg/kg body weight, no mortalities, lethargy, ataxia, ptosis, chromodacryorrhea	RIFM (1980a)
	Mouse	2 or 6*	Approx. 5 ml/kg body weight (4580 mg/kg body weight),	RIFM (1977b)
	Mouse	2 or 6*	>5 ml/kg body weight (4580 mg/kg body weight), transient hypothermia, labored breathing; mortalities: fluid distension and irritation of small intestine, intussusception of large intestine; survivors: adhesions of stomach, liver, spleen, peritoneum, distension and thickening of stomach, enlarged spleens	RIFM (1980e)
Isojasmone	Rat	10	>5000 mg/kg body weight, 1 mortality, slight lethargy	RIFM (1974a)
cis-Jasmone	Rat	10	5000 mg/kg body weight	RIFM (1977a)
	Rat	9	4300 mg/kg body weight	RIFM (1971a)
2-(*p*-Menth-1-ene-10-yl) cylopentanone	Rat	10	>2008 mg/kg body weight	RIFM (1989b)
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one	Rat	10	2500 mg/kg body weight (95% C.I. 1790–3500 mg/kg body weight)	RIFM (1972a)
	Mouse	10 males	>4000 mg/kg body weight, reduced breathing rate, ataxia	RIFM (1983a)
3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one	Rat	10 (5/sex)	>5000 mg/kg body weight, mortalities in 3 males and 1 female, depression or semi-comatose 6 h after dosing, poor health for 5–7 d	RIFM (1981b)
2-Pentylcyclopentan-1-one	Rat	10 (5/sex)	>5000 mg/kg body weight	RIFM (1979b)
2,2,5-Trimethyl-5-pentylcyclopentanone	Rat	4	>6834 mg/kg body weight, no mortalities, hypoactivity, muscular weakness, labored breathing, lacrimation, diuresis, prostration	RIFM (1978a)
Methyl ester				
Methyl dihydrojasmonate	Rat	10	>5000 mg/kg body weight	RIFM (1976b)
	Rat	4 (2/sex)**	>5000 mg/kg body weight	RIFM (1986a)
	Rat	10 (5/sex)	>5000 mg/kg body weight, no mortalities, piloerection, hunched posture, abnormal gait, diarrhea, increased salivation until day 4, no changes at necropsy	RIFM (1986a)
Methyl hexyl oxo cyclopentanone carboxylate	Rat	10 males	>5000 mg/kg body weight, no mortalities, lethargy, chromorhinorrhea, discolored liver, kidneys, intestines	RIFM (1978c)
Methyl jasmonate	Rat	10 (5/sex)	>5000 mg/kg body weight, mortality in 1 animal, central nervous system depression, ruffled	RIFM (1980f)

[a] Clinical signs are noted when LD_{50} > the highest dose tested, and negative effects were observed.
* Observation period = 7 days.
** Preliminary study, observation period = 5 days.

The second method estimates potential percutaneous (total human skin exposure) absorption from the entire body based on the use of multiple consumer personal care products containing the same fragrance ingredient. The dermal systemic exposure

Table 2-3
Acute inhalation and intraperitoneal toxicity studies in animals.

Material	Dose route	Species	No. animals/dose	$LD_{50}$and/or clinical signs	References
Cyclopentanone	Inhalation, 4 h Inhalation, 6 h, 15.6 mg/L	Rat Rat, mouse, guinea pig	10 males 10 females	>19.5 mg/l (mortality in 4/10 at 19.5 mg/l) All animals died during study, LT_{50} mice = 168 min, Rats died at the end of exposure, guinea pigs died within 24 h following exposure; dyspnea, ataxia (all species), loss of righting reflex (mice), ptosis, lacrimation (Rats, guinea pigs), slightly (guinea pig) or severely (mice) congested lungs, discoloration of the lungs (Rats)	RIFM (1982c) RIFM (1982a)
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one	Intraperitoneal	Mouse	10 males	500 mg/kg body weight, reduced breathing rate, ataxia	RIFM (1983a)
Methyl ester					
Methyl dihydrojasmonate	Intraperitoneal Intraperitoneal	Rat Mouse	4 (2/sex) 10 (5/sex)	1000–2000 mg/kg body weight 1397.2 mg/kg body weight	RIFM (2001b) RIFM (1998)

Table 3-1
Repeated dose toxicity studies – oral

Material	Method	Dose	Species (No./Dose)	Results	References
2-Hexylidene cyclopentanone	Diet, 13 weeks	0, 2.9 (m), 3.37 (f) mg/kg body weight/day	Charles River CD Rat (10–16/sex)	No effects were observed at 2.9 mg/kg body weight/day (males) or 3.37 mg/kg body weight/day (females)	Posternak et al. (1969)
Methyl ester					
Methyl dihydrojasmonate	Diet, 14 days, histopathological examination of liver (control + high-dose) (dose-finding study)	0, 10, 50, 100, 400 mg/kg body weight/day	Sprague Dawley derived CD Rat (Crl:CD (SD) IGS BR) (5/sex/dose)	400 mg/kg body weight: body weight gain ↓ (f), No effects (m)	RIFM (2000a)
	Diet, 13 weeks OECD TG 408	0, 10, 50, 100 mg/kg body weight/day	Sprague Dawley derived CD Rat (Crl:CD (SD) IGS BR) (10/sex/dose)	No effects were observed NOEL systemic: 100 mg/kg body weight/day	RIFM (2000b)

Table 3-2
Repeated dose toxicity studies – dermal

Material	Method	Dose	Species (No./Dose)	Results	Reference
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	28 day dermal toxicity	0, 50, 200 and 1,000 mg/kg body weight/day	Rats (10/dose; 5/sex)	NOEL 1000 mg/kg No mortalities. No changes to body weight gain or food consumption. No alterations in pathology or abnormalities at necropsy	RIFM (1989c)

Table 3-3
Repeated dose toxicity studies – inhalation

Material	Method	Dose	Species (No./Dose)	Results	Reference
Cyclopentanone	Inhalation, 6 h/day, 5 days/week, for 15 weeks	50, 100, 300 p.p.m. (172, 344, 1032 mg/m^3)	Wistar Rat (20)	Body weight, concentration of cyclopentanone in brain and perirenal fat, biochemical effects on liver cytosol and kidneys were the parameters measured. No mortalities; no reactions observed; no appreciable organ toxicity NOEL was not determined.	Elovaara et al. (1984)

from cosmetic products is calculated based on the concentrations in ten types of the most frequently used personal care and cosmetic products (anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap). The concentration of the fragrance ingredient in fine fragrances is obtained from examination of several thousand commercial formulations. The upper 97.5 percentile concentration is calculated from the data obtained. This upper 97.5 percentile concentration is then used for evaluation of all 10 consumer products. These concentrations are multiplied by the amount of product applied, the number of applications per day for each product type, and a "retention factor" (ranging from

Table 4-1
Genotoxicity in bacteria.

Material	Test system	Concentration	Results	References	
Cyclopentanone	Ames assay with and without S9 activation ("spot test")	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	TA100: 0.03, 0.3, 3, 30 μmol/plate (2.5–2524 μg/plate) TA98, TA1535, TA1537: 3 μmol/plate (252 μg/plate) vehicle: ethanol	Negative	Florin et al. (1980)
Dihydroisojasmone	Ames assay with and without S9 activation (standard plate assay) OECD TG 471	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537	5–1500 μg/plate in DMSO	Negative	RIFM (2004b)
	Ames assay with and without S9 activation (preincubation assay) OECD TG 471	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537	Up to 500 μg/plate in DMSO	Negative	RIFM (2004b)
2-Heptylcyclopentanone	Ames assay with and without S9 activation	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537	with S9: 5–1500 μg/plate without S9:1.5–1500 μg/plate	Negative	RIFM (2000c)
2-Hexylidene cyclopentanone	Ames assay with and without S9 activation (standard plate assay)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 concentrations, up to 3600 μg/plate	Negative	Wild et al. (1983)
cis-Jasmone	Ames assay with and without S9 activation (standard plate assay and preincubation assay) OECD TG 471	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537	3–2500 μg/plate in ethanol	Negative	RIFM (2003c)
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	Ames assay with and without S9 activation (standard plate assay) OECD TG 471	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.1–100 μg/plate in ethanol	Negative	RIFM (1989d)
	Ames assay with and without S9 activation	*Escherichia coli* WP2 uvrA	up to 5000 μg/plate in ethanol	Negative	RIFM (2006b)
2-Pentylcyclopentan-1-one	Ames assay with and without S9 activation OECD TG 471	*Salmonella typhimurium* TA 98, TA100, TA1535, TA 1537 and *E. coli* WP2uvrA^{-}	5–5000 μg/plate in DMSO	Negative	RIFM (2006a)
Methyl ester					
Methyl dihydrojasmonate	Ames assay with and without S9 activation (standard plate assay)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	10–3300 μg/plate	Negative	RIFM (1978d)
	Ames assay with and without S9 activation (standard plate assay) OECD TG 471	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, E.coli WP2 uvrA	100–5000 μg/plate in DMSO	Negative	RIFM (2000d)
	Ames assay with and without S9 activation (standard plate assay) OECD TG 471	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537	15–5000 μg/plate in DMSO	Negative	RIFM (2000e)
	Ames assay with and without S9 activation (preincubation assay)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	1.5–150 μg/plate in DMSO (all strains without S9 and TA100, TA1535 with S9) 1.5–1500 μg/plate (TA98, TA1537 with S9)	Negative	RIFM (1987a)
Methyl hexyl oxo cyclopentanone carboxylate	Ames assay with and without S9 activation OECD TG 471	*Salmonella typhimurium* TA98, TA100, TA 1535, TA1537 and *Escherichia coli* WP2uvrA	10–3300 μg/plate in ethanol	Negative	RIFM (2008a)

DMSO: dimethyl sulfoxide.

0.001 to 1.0) to account for the length of time a product may remain on the skin and/or the likelihood of the fragrance ingredient being removed by washing. The resultant calculation represents the total consumer exposure (mg/kg/day) (Cadby et al., 2002; Ford et al., 2000). In view of all of the above assumptions, the total calculated consumer exposure is conservative; it is unlikely that a consumer will consistently use a number of different consumer products which are all perfumed with the upper 97.5 percentile level of the fragrance ingredient from a fine fragrance type product (Cadby et al., 2002; Ford et al., 2000). The total consumer exposures to fragrance ingredients range from 0.0003 mg/kg body weight (bw)/day to 0.7122 mg/kg body weight (bw)/day for the cyclopentanones and cyclopentenones group of fragrance ingredients in high-end users of cosmetic products containing these materials. (see Table 1) (IFRA, 2007). The third method provides maximum skin levels. For consideration of potential adverse skin effects, e.g. sensitization, phototoxicity, etc., exposure is calculated as the percent concentration of the fragrance ingredient in the top 10 concentrations in fragrance mixtures that are used in hydroalcoholic products applied to the skin. It is then assumed that 20% of the fragrance mixture is in the fine fragrance consumer product (Ford et al., 2000). The maximum skin exposure levels of the cyclopentanone and cyclopentenone compounds that form part of the formulae of fine fragrances vary widely and have been reported to range from 0.002% to 15.16%. The maximum skin exposure for cyclopentanones and cyclopentenones in fine fragrance products are listed in Table 1 (IFRA, 2007).

The recently revised IFRA Standards on 2-hexylidene cyclopentanone (RIFM, 2008), 2-heptylidenecyclopentan-1-one (IFRA, 2011) and 3-methyl-2-(penyloxy)-2-cyclopenten-1-one are based on the dermal sensitization quantitative risk assessment (QRA) approach for fragrance ingredients (Api and Vey, 2008). The details of the Standards can be found in Sections 5.8.1 and 5.8.2 of this fragrance review. The zero-use material amylcyclopentenone has an IFRA Standard prohibiting its use as a fragrance ingredient (IFRA, 2008) based on the presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000), and/or adverse data on the material itself, and/or adverse data for a structurally related material (IFRA, 2008).

Table 4-2
Genotoxicity in mammalian cells

Material	Test system		Concentration	Results	References
3-Ethyl-2-hydroxy-2-cyclopenten-1-one	Sister chromatid exchange	Human peripheral lymphocytes from non-smoking volunteers	Up to 2 mM	Negative	Jansson et al. (1986)
cis-Jasmone	Sister chromatid exchange	Chinese hamster ovary cells (CHO) K-1	3.3–1000 μM	Negative	Sasaki et al. (1989)
Methyl ester					
Methyl dihydrojasmonate	Mammalian cell mutation with and without S9 activation[a]	Mouse Lymphoma L5178Y $TK^{+/-}$ expression time 3 days	58–300 μg/ml in DMSO	positive without S9: ⩾200 μg/ml with S9: 300 μg/ml	RIFM (1979c)
	Forward mutation assay with and without S9 activation[b] OECD TG 476	Mouse Lymphoma L5178Y $TK^{+/-}$ expression time 2 days	100, 150, 200, 225, 250, 275, 300, 325 μg/ml	Negative	RIFM (2001c)
	Chromosomal aberration assay with and without S9 activation OECD TG 473	Chinese hamster ovary cells (CHO)	without S9: 5.7–180 μg/ml with S9: 1.3–40 μg/ml vehicle: DMSO	Negative	RIFM (1988)

DMSO: dimethyl sulfoxide.
[a] No differentiation between small and large colonies; concentrations which gave positive results were also cytotoxic, positive result may be an artifact.
[b] Differentiation between small and large colonies.

Table 4-3
Genotoxicity in animals.

Material	Test system	Species (No./dose)	Dose	Results	References
2-Hexylidene cyclopentanone	Bone marrow micronucleus assay, intraperitoneal, sampling time: 30 h after treatment	NMRI Mouse (4/dose)	0, 166, 333, 500 mg/kg body weight in olive oil	Negative	Wild et al. (1983)
				No mortality was observed, no information on toxicity	
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	Mouse Micronucleus test	Mice (5/sex/sampling time)	4800 mg/kg body weight	Negative	RIFM (1989e)
				2/10 mortalities in 48 and 72 h sampling groups. No increase in frequency of micronucleated polychromatic erythrocytes.	
Methyl ester					
Methyl dihydrojasmonate	Unscheduled DNA synthesis (UDS) in hepatocytes, intraperitoneal, (1) perfusion started 16 h after dosing; (2) perfusion started 2 h after dosing OECD TG 486	Male Sprague–Dawley CD (Crl:CD® (SD) IGS BR) rat (control: 6, test group and positive control: 4/dose)	0, 333.3, 1000 mg/kg body weight in arachis oil	Negative	RIFM (2001b)
	Bone marrow micronucleus test, intraperitoneal, sampling time: control and high dose 24 and 48, low and mid dose: 24 h after treatment OECD TG 474	ICR Mouse (control: 10/sex; low and mid dose: 5/sex; high dose: 15/sex, 5/sex = replacement group)	0, 280, 560, 1120 mg/kg body weight in corn oil	Negative	RIFM (1998)
				1120 mg/kg: mortality in 4/15 (m) and 1/15 (f)	

Exposure data for nine fragrance materials (cyclopentanone; 2-cyclopentylcyclopentanone; cyclotene propionate; 2-(3,7-dimethyl-2, 6-octadienyl) cyclopentanone; 3-ethyl-2-hydroxy-2-cyclopenten-1-one; hexenylcyclopentanone; 2-hydroxy-3,4-dimethyl-2-cyclopenten-1-one; 3-methyl-2-pentylcyclopentan-1-one; 2-heptylidenecyclopentan-1-one) were not reported. A default value of 0.02% is used to calculate the maximum daily exposure on the skin which is 0.0005 mg/kg bw for high end users of these products.

In assessing safety, the calculated dermal systemic exposure in cosmetic products can be compared to the indices of systemic toxicity such as NOAEL and lowest observed adverse effect level (LOAEL) that are obtained from the repeat dose sub-chronic, chronic and reproductive toxicity studies to derive a margin of exposure (MOE). Systemic exposures (i.e., the dose absorbed through the skin and available to the systemic circulation) were estimated based on dermal absorption rates. Where such data were lacking, as a conservative measure, dermal absorption was considered to be 100% (i.e., the maximum skin exposure value was considered as the estimate of systemic exposure). All exposure data were provided by the fragrance industry. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).

2.4. Experimental exposure studies

Results from a study by Behan et al. (1996) show that after dermal application of 75 μL of a model cologne perfume with a ten-ingredient mixture the residual quantity of *cis*-jasmone on the skin after 60 min of free evaporation was 2274 ng.

With regard to potential inhalation exposure, data from studies using different surrogate products (pressurized aerosol and heated oil plug-in air fresheners, a fragrance in an atomizer, and a fine fragrance) are available showing that product type and volatility of each fragrance material affect its air concentration

Table 5
Developmental toxicity studies.

Material	Method	Dose	Species (No./Dose)	Results	References
Cyclopentanone	female Rats were dosed daily on gestational days 6 through 15 via gavage	0 (vehicle), 50, 300 mg/kg body weight in corn oil	COBS® CD® female rats (25/dose)	*Maternal:* No effects *Offspring:* 300 mg/kg body weight/day: fetal body weight ↓ NOEL not determined NOAEL maternal = 300 mg/kg body weight NOAEL developmental = 50 mg/kg body weight	Rusch et al. (1988)
Methyl ester Methyl dihydrojasmonate	presumed pregnant rats were dosed daily on gestational days 7 through 20 via gavage (dose-finding study)	0 (vehicle), 125, 250, 500, 1000 mg/kg body weight/day in corn oil	Crl:CD (SD) female rats (8/dose)	*Maternal:* ⩾125 mg/kg body weight: body weight gain ↓, feed consumption ↓ (most pronounced effects on the first 3 days of treatment) ⩾250 mg/kg body weight/day: excessive salivation 1000 mg/kg body weight: dehydration, ungroomed appearance *Offspring:* ⩾125 mg/kg body weight/day: fetal body weight ↓ (total, male and female)	RIFM (2007)
	Presumed pregnant Rats were dosed daily on gestational days 7 through 20 via gavage according to OECD TG 414	0 (vehicle), 40, 80, 120 mg/kg body weight/day in corn oil	Crl:CD (SD) female Rats (25/dose)	*Maternal:* 120 mg/kg body weight/day: sparse hair coat, ungroomed appearance, body weight gains ↓, body weights ↓, abs. and rel. feed consumption ↓ (entire dosage period), tan areas in the liver (2), pale spleen (2) *Offspring*: 120 mg/kg body weight/day: no gross external, soft tissue, or skeletal fetal alterations, no difference in ossification NOAEL maternal: 80 mg/kg body weight/day NOAEL developmental: 120 mg/kg body weight	RIFM (2007)

(RIFM, 2003a,b, 2004a). Each surrogate product contained nine common fragrance materials at 0.06% each for the aerosol, 8.89% each for the plug-in air freshener, and 2.2% each for the fine fragrance.

In the aerosol study, a typical application scenario in a bathroom was simulated in triplicate experiments. Aerosol spray was released for approximately 5 s, 4–4.5 ft above the floor with a slight sweeping motion at a rate of 1–1.2 g/s. The room had a volume of 14.5 m^3 with 0.6 air changes per hour, similar to the typical residential air exchange rate in North America. Airborne fragrances were sampled from the time of application to 2 h post-application at breathing zone heights for adults (5 ft) and children (1.5 ft). The peak air concentration of methyl dihydrojasmonate at the adult breathing height was 114 μg/m^3, and it was 118 μg/m^3 at the child breathing height immediately after application. After 2 h, the concentrations were 4.3 and 4.2 μg/m^3 at the adult and child heights, respectively. The mean aerodynamic diameter (MAD) of the airborne particles ranged between 0.89 and 1.15 μm (RIFM, 2003a; Rogers et al., 2005).

The potential human inhalation exposure to a surrogate fine fragrance was characterized in triplicate experiments. The fine fragrance was applied with 6 pumps of fragrance spray around a mannequin's neck region 3.5 inches away from the neck (0.6 g application mass). Air was sampled at adult and child breathing zone heights (see above) for up to 5 h. The maximum concentrations of methyl dihdrojasmonate were 17 μg/m^3 for adult breathing height and 22 μg/m^3 for child breathing height. The concentrations decayed with time. Maximum mean aerodynamic diameters were 1.3 to 1.9 μm (RIFM, 2004a).

In the plug-in air freshener study, the emissions released into an environmental chamber of 5.5 or 5.9 m^3 volume were measured in three experiments for up to 701 h. The peak concentration of methyl dihydrojasmonate was 14.1 μg/m^3 at 125 h and declined to 8.6 μg/m^3 after 701 h. Due to the low volatility of methyl dihydrojasmonate many samples were below the reporting limit of 4.1 μg/m^3 (RIFM, 2003b).

3. Metabolism

Based on studies with a number of related compounds (cyclohexanone, isophorone and carvone, among others), the major metabolic pathway for cyclopentanones and cyclopentenones involves reduction of the ketone to the corresponding secondary alcohol followed by conjugation of the alcohol with glucuronic acid. Studies with cyclopentanone in rabbits provide direct evidence for this pathway. Following oral gavage with 2.3 mmole of cyclopentanone/kg body weight (193 mg/kg body weight), about 47% of the dose was excreted in the urine of rabbits as the glucuronide of cyclopentanol. Sulfur containing metabolites were also detected in the urine, but, *in toto*, represented only around 5% of the administered dose. These were reported as unidentified sulfur-containing metabolite (probably the sulfate ester of hydroxycycloalkylmercapturic acid), an ethereal sulfate and traces of *cis*- and *trans*-2-hydroxycyclopentylmercapturic acid in the urine. The unidentified sulfur-containing metabolite and 2-hydroxycyclopentylmercapturic acid were also detected in a similar study with rats (dose not given), but no glucuronide was found. In rats,

Table 6-1
Skin irritation studies in humans.

Material	Method	Concentration	Subjects	Reactions	References
Cyclopentanone	Maximization study (pre-test): 48 h, volume not stated, occlusive	10% in petrolatum	25	0/25	RIFM (1976c)
Dihydroisojasmone	Maximization study (pre-test): 48 h, volume not stated, occlusive	4% in petrolatum	35	0/35	RIFM (1976d)
3-Ethyl-2-hydroxy-2-cyclopenten-1-one	HRIPT (induction phase): 0.02 ml, occlusive	0.5% in alcohol SDA 39C	101	0/101	RIFM (2000g)
2-Heptylcyclopentanone	HRIPT (induction phase): 0.5 ml, semi-occlusive	1.25% in ethanol	40[a] (12 males, 28 females)	0/40[b]	RIFM (1964a)
	Maximization study (pre-test): 48 h, 1 ml, occlusive	10% in petrolatum	5 males	0/5	RIFM (1973b)
Hexenylcyclopentanone	Maximization study (pre-test): 48 h, volume not stated, occlusive	10% in petrolatum	25	0/25	RIFM (1976c)
2-Hexylcyclopentanone	Maximization study (pre-test): 48 h, volume not stated, occlusive	10% in petrolatum	45	0/45	RIFM (1980h)
2-Hexylidene cyclopentanone	HRIPT (induction phase): 0.2 ml, occlusive	1% in alcohol SDA 39C	51	3/51	RIFM (1982d)
	HRIPT (induction phase): 0.2 ml, occlusive	0.6% in DEP/ethanol (3:1)	103	0/103	RIFM (2005a)
	Maximization study (pre-test): 48 h, volume not stated, occlusive	5% in petrolatum	27	0/27	RIFM (1981c)
Isojasmone	HRIPT (induction phase): 0.5 ml, semi-occlusive	0.5% in ethanol	38 (6 males, 32 females)	6/38 slight to marked erythema (5), erythema with papules (1)	RIFM (1964b)
	Maximization study (pre-test): 48 h, volume not stated, occlusive	8% in petrolatum	5	0/5	RIFM (1974b)
	Patch test: 24–48h, amount not stated, occlusive	0.05–0.5% in a base cream or in 99% ethanol (exact concentration not stated)	60	0/60	Takenaka et al. (1968)
cis-Jasmone	HRIPT (induction phase): 0.5 ml, occlusive	2% in DMP	54	0/54	RIFM (1972b)
	Maximization study (pre-test): 48 h, volume not stated, occlusive	8% in petrolatum	35	0/35	RIFM (1977c)
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	HRIPT (induction phase): 0.2 ml, occlusive	5% in DMP	53	0/53	RIFM (1996)
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one	HRIPT (induction phase): 0.5 ml, semi-occlusive	1% in alcohol SDA 39C	38 (12 males, 26 females)	0/38	RIFM (1972c)
	Maximization study (pre-test): 48 h, volume not stated, occlusive	4% in petrolatum	5	0/5	RIFM (1972d)
3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one	HRIPT (induction phase): 0.2 g, semi-occlusive	10% in white petrolatum	50 (9 males, 41 females)	0/50	RIFM (1981d)
2-Pentylcyclopentan-1-one	HRIPT (induction phase): 0.5 g, occlusive	10% in petrolatum	50 (15 males, 35 females)	0/50	RIFM (1978e)
2,2,5-Trimethyl-5-pentylcyclopentanone	HRIPT (induction phase): 0.2 ml, occlusive	10% in petrolatum	50	0/50	RIFM (1978f)
Methyl ester					
Methyl dihydrojasmonate	HRIPT (induction phase): 0.2 ml, occlusive	20% in DEP/ethanol (3:1)	112	0/112	RIFM (2005b)
	HRIPT (induction phase): 0.2 ml, occlusive	20% in DEP	100	0/100	RIFM (2003d)
	HRIPT (induction phase): 0.5 ml, semi-occlusive	10% in alcohol SDA 39C	23 (5 males, 18 females)	1/23	RIFM (1971b)
	HRIPT (induction phase): 0.5 ml, semi-occlusive	2.42% in alcohol SDA 39C	23 females	0/23	RIFM (1971c)
	Maximization study (pre-test): 48 h, volume not stated, occlusive	20% in petrolatum	25	0/25	RIFM (1976c)
Methyl hexyl oxo cyclopentanone carboxylate	Maximization study (pre-test): 48 h, volume not stated, occlusive	2% in petrolatum	5 males	0/5	RIFM (1972e)
Methyl jasmonate	HRIPT (induction phase): semi-occlusive, amount not stated	10%, vehicle not stated	50 (9 males, 41 females)	0/50	RIFM (1980i)
	HRIPT (induction phase): 0.4 ml, occlusive	1% in alcohol SDA 39C	44 (10 males, 34 females)	0/44	RIFM (1978g)

DEP: diethyl phthalate.
DMP: dimethyl phthalate.
HRIPT: Human Repeat Insult Patch Test (induction phase: 9 applications, 24 h each, within a 3-week period).
[a] Number of persons who finished irritation test (induction phase of HRIPT).
[b] Number with significant positive reactions/persons tested without pre-sensitized persons.

cyclopentanone caused a slight reduction in the level of glutathione in the liver (James and Waring, 1971). This reduction may relate to the consumption of glutathione in the formation of 2-hydroxycyclopentylmercapturic acid.

The rate of addition of the nucleophile, glutathione, to several alpha, beta-unsaturated carbonyl compounds used as flavoring substances/fragrance ingredients was investigated *in vitro*. The cyclopentanone compound, 2-hexylidene cyclopentanone, was included in this group (Portoghese et al., 1989). A molar ratio of glutathione to ketone of 38:1 was used. Under these conditions, 2-hexylidene cyclopentanone showed a half-life of 17 ± 4 min in the *in vitro* system. The relative rate of reaction with glutathione was 21% as compared to deithylmaleate, a common glutathione depletory. Methyl substitution at the endocyclic double bond in the β-position significantly slowed glutathione addition (Portoghese et al., 1989). Consequently, a low reactivity towards nucleophiles like glutathione would be expected for isojasmone, *cis*-jasmone and 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one, fragrance materials with an alkyl substituent in the beta-position.

As to the methyl esters under review, it is expected that the ester bond is hydrolyzed by carboxylesterases to methanol and the corresponding acid. Methanol is subsequently oxidized to formaldehyde and formic acid in the organism; the acid may be conjugated and excreted.

4. Toxicokinetics

4.1. Dermal route of exposure

No percutaneous absorption studies in humans and experimental animals are available for the cyclopentanones and cyclopentenones. Therefore, for the purpose of exposure and safety assessment 100% dermal absorption has to be assumed (see Section 2.3).

4.1.1. In vitro

In an *in vitro* test using human epidermal membranes from full-thickness skin, 45.9% of the applied dose (200 μg/cm^2) of a 1% ethanolic solution of methyl dihydrojasmonate was found in the receptor fluid after open exposure for 48 h. The overall recovery was 65.8% indicating significant loss by evaporation. The membrane integrity was confirmed before application of the test substance (Isola and Api, 2002; RIFM, 2001a). From the data presented in the report, a penetration rate of 3 μg/cm^2 per hour can be calculated for the first 8 h of exposure.

4.2. Oral route

No data are available.

4.3. Respiratory route of exposure

No data are available.

5. Toxicological studies

5.1. Acute toxicity

Acute dermal toxicity studies have been performed with thirteen cyclopentanones and cyclopentenones and three methyl esters of cyclopentanones. The dermal LD_{50} values in rats and rabbits are greater than 2000 mg/kg body weight with 11 studies showing values greater than 5000 mg/kg body weight. In summary, all compounds tested are of low acute toxicity by the dermal route (Table 2-1).

Fifteen cyclopentanones and cyclopentenones and three methyl esters of cyclopentanones have been tested for oral acute toxicity. The oral LD_{50} values in rats and mice are greater than 2000 mg/kg body weight. The only exception is cyclopentanone, which, in one study, had an LD_{50} value in rats of 1.24 ml/kg body weight (1179 mg/kg body weight). In general, the compounds exhibit a low toxicity when administered orally (Table 2-2).

Inhalation studies are available for cyclopentanone showing a LC_{50} value after 4 h inhalation of > 19.5 mg/l in rats (RIFM, 1982c). A 6-h inhalation of 15.6 mg/l caused death in all rats, mice and guinea pigs tested (RIFM, 1982a), see Table 2-3.

Acute toxicity data obtained from inhalation and intraperitoneal studies are summarized in Table 2-3. Although intraperitoneal exposure is not a primary route of exposure to fragrance ingredients, the data presented are supportive to assessing safety.

5.2. Repeated dose toxicity

Only three cyclopentanones have been tested in repeated dose toxicity studies, one of them being a methyl ester. The studies are summarized in Tables 3-1, 3-2 and 3-3.

5.2.1. Dermal studies

A 28-day dermal toxicity study was performed with 2-(*p*-menth-1-ene-10-yl) cyclopentanone. Rats (10/dose, 5 of each sex) were exposed to 0, 50, 200 or 1,000 mg/kg body weight of the test material for 5.4 to 8 h each day for 28 days. Animals were observed daily and full clinical examinations were performed weekly. No changes in body weight gain or food consumption were noted, and no mortalities occurred. At necropsy there were no alterations or abnormalities (RIFM, 1989c). The authors concluded a no observed toxic effect level of 1000 mg/kg body weight. Results of this study are summarized in Table 3-2.

5.2.2. Oral studies

Oral studies with cyclopentanones are summarized in Table 3-1.

Charles River Sprague–Dawley CD rats (10–16 animals per sex and group) were fed a diet containing 2-hexylidene cyclopentanone (males/females: 2.9/3.37 mg/kg body weight/day) for 13 weeks. Observations included body weight, food consumption, hematology and blood urea determination, liver and kidney weight, histological examination of a "wide range of organs" (no further information). No effects were observed in male or female rats (Posternak et al., 1969) at the given dose. The systemic NOAEL could not be determined as only one dose level was administered.

In a dose-finding study groups of 5 male and 5 female Sprague–Dawley CD-derived rats (Crl:CD (SD) IGS BR) rats were fed a diet containing the methyl ester methyl dihydrojasmonate (98.5% purity) at dose levels of 0, 10, 50, 100 or 400 mg/kg body weight/day for 14 days. Observations included body weight and food consumption, hematology, blood coagulation and clinical chemistry, weight of selected organs, and complete macroscopic examinations were conducted in all animals. Histopathological examination of the liver was performed for the control and high-dose-animals. No effects were noted in females at the two lowest doses. No treatment-related effects were observed in males at any dose. Treatment with 100 mg/kg body weight/day and above resulted in a dose-dependent incidence of feed spillage in the females, suggesting that the animals sought to avoid the test article due to poor palatability or unpleasant taste. At 400 mg/kg body weight/day, there was an approximate 8% decrease in body weight gain, relative to controls (RIFM, 2000a).

In the main study according to Organization for Economic Cooperation and Development Testing Guideline (OECD TG) 408 methyl

Table 6-2a
Skin irritation in animals, single application

Material	Method	Concentration	Species	Reactions	References
Cyclopentanone	4 h, 0.5 ml, semi-occlusive, intact skin, observations after 1, 24, 48 h and 72 h OECD TG 404	Undiluted	Rabbit (n = 6)	PCI (Primary cutaneous irritation index) = 0.31 Not irritating	Guillot et al. (1982a)
	4 h, 0.5 ml, occlusive, abraded and intact skin, observations after 1, 24 and 48 h [a]	Undiluted	Rabbit (n = 6)	PCI (Primary cutaneous irritation index) = 2.75 slightly irritant according to employed method	Guillot et al. (1982a)
	4 h, 0.5 ml, occlusive, intact skin, observations after 1, 24, 48 and 72 h	Undiluted	Rabbit (n = 6)	PCI (Primary cutaneous irritation index) = 3.00 slightly irritant according to author	Guillot et al. (1982a)
	23 h, 0.5 ml, occlusive, abraded and intact skin, observations after 1 and 48 h [b]	Undiluted	Rabbit (n = 6)	PCI (Primary cutaneous irritation index) = 2.21 Moderately irritant according to employed method	Guillot et al. (1982a)
	24 h, 5000 mg/kg body weight, occlusive, observation period 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 4)	erythema, n.f.i.	RIFM (1976a)
	24 h, up to 3160 mg/kg body weight, occlusive, intact skin, observation period 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 4/group)	50, 200 mg/kg body weight: slight transient erythema and desquamation 794 mg/kg body weight: transient slight erythema and atonie, persistent slight desquamation 3160 mg/kg body weight: slight to severe erythema, moderate edema, transient slight to moderate atonia, persistent slight to severe desquamation, fissuring, necrosis	RIFM (1982a)
Dihydroisojasmone	24 h, 5000 mg/kg body weight, occlusive, observation period 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 10)	slight (2/10) or moderate (8/10) redness, slight (4/10) or moderate (6/10) edema	RIFM (1976b)
2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone	24 h, 0.4 ml, occlusive, (*p*re-test for modified Buehler test), observations 24 and 48 h after application, n.f.i.	10, 25, 50, 75, 100% in white mineral oil	Guinea pig (n = 4/group)	up to 100%: not irritating	RIFM (1991b)
	24 h, 0.5 ml, occlusive, abraded and intact skin, observations 24 and 72 h, 7 and 14 days after application	Undiluted	Rabbit (n = 6; intact and abraded skin)	Primary irritation index (24 and 72 h, abraded and intact skin): 4.12 well-defined to moderate erythema for up to 3 days, progressed to exfoliation, eschar, denuded skin Irritating	RIFM (1991c)
2-Heptylcyclopentanone	4 h, 0.5 ml, semi-occlusive, observations immediately after patch removal and after 24, 48, 72 h	Undiluted	Rabbit (n = 8)	9-point score scale: slight to well-defined erythema and edema, slight cracking and scaling starting at the 24 h observation and intensifying to end of observation time	RIFM (1980j)
	24 h, saturated filter paper, occlusive, (*p*re-test for Maximization test), observations 24 h, 48 h after patch removal	0, 0.5, 1, 2.5, 5, 10, 25% in ethanol	Guinea pig (4 females/group)	0.5, 1%: no reaction 2.5%: barely perceptible erythema $\geqslant$ 5%: barely perceptible erythema to scattered, mild erythema	RIFM (1980k)
	exposure duration not stated, 0.1 ml, open, (*p*re-test for phototoxicity study), observations 3, 6, 24, 48, 72 h after application	0, 10, 30, 100% in ethanol	Rat (5/group)	9-point score scale: 0, 10%: very slight erythema and edema, very slight cracking starting at 24 h and scaling starting at 48 h 30%: very slight to slight erythema, very slight to distinct edema, very slight to distinct cracking and scaling starting at 24 h 100%: animals were euthanized after 3 h score (n.f.i.)	RIFM (1982e)
	exposure duration not stated, 0.1 ml, open, (*p*hototoxicity study, dermal application phase), 0.1 ml, open, observations 3, 6, 24, 48, 72 h after application	10% in ethanol	Rat (10/group)	very slight erythema, very slight to slight edema, very slight cracking starting at 24 h, very slight to slight scaling starting at 48 h	RIFM (1982e)
	24 h, 5000 mg/kg body weight, occlusive, observation period of 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 6)	progressive drying and cracking, developing into shedding of skin, continued up to end of 14 d	RIFM (1973a)
2-Heptylidenecyclopentan-1-one	4 h, 0.5 ml, semi-occlusive, observations immediately after patch	undiluted	Rabbit (n = 8)	9-point score scale: slight to well-defined erythema and edema, slight	RIFM (1980j)

(*continued on next page*)

Table 6-2a (*continued*)

Material	Method	Concentration	Species	Reactions	References
	removal and at 24, 48, 72 h			cracking and scaling starting at the 48 h observation and intensifying to end of observation time	
	24 h, saturated filter paper, occlusive, (*p*re-test for Maximization test), observations 24 and 48 h after patch removal	0.5, 1, 2.5% in ethanol	Guinea pig (n = 4 females)	No irritation	RIFM (1980l)
Hexenylcyclopentanone	24 h, 5000 mg/kg body weight, occlusive, observation period of 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 10)	slight (2/10) or moderate (8/10) redness, slight (7/10) or moderate (3/10) edema	RIFM (1976b)
2-Hexylcyclopentanone	4 h, 0.5 ml, semi-occlusive, observations immediately after patch removal and at 24, 48, 72 h	Undiluted	Rabbit (n = 8)	9-point score scale: well-defined to moderate erythema, mild edema (effects are milder 72 h), slight cracking and scaling starting at the 48 h observation moderately irritating	RIFM (1982f)
	24 h, saturated filter paper, occlusive, (*p*re-test for Maximization test), observations 24 h, 48 h after patch removal	0, 2.5, 5, 10, 25, 50, 75% in acetone/PEG	Guinea pig (4 males/group)	$\leqslant$ 25%: no reaction $\geqslant$ 50%: very slight erythema (1/4)	RIFM (1982g)
	exposure duration not stated, 0.1 ml, open, (*p*re-test for phototoxicity study), observations 3, 6, 24, 48, 72 h after application	10, 30, 100% in ethanol	Rat (5/group)	9-point score scale: 10%: very slight erythema and edema, very slight cracking and scaling at 72 h 30%: very slight erythema, very slight to slight edema, very slight cracking and scaling starting at 24 h 100%: well-defined erythema, edema, cracking and scaling (more serious at 48 and 72 h), scabbing at 48 and 72 h	RIFM (1982h)
	exposure duration not stated, 0.1 ml, open, (*p*hototoxicity study, dermal application phase), observations 3, 6, 24, 48, 72 h after end of treatment	30% in ethanol	Rat (10/group)	30%: very slight to slight erythema, cracking and scaling	RIFM (1982h)
	24 h, 5000 mg/kg body weight, occlusive, abraded and intact skin, observation period of 14 days	Undiluted	Rabbit (n = 10)	slight to well-defined erythema, very slight to slight edema (cleared in all but 1), moderate to severe eschar, ulceration in 1 animal	RIFM (1980a)
2-Hexylidene cyclopentanone	4 h, 0.5 ml, semi-occlusive, observations immediately after patch removal and at 24, 48, 72 h	Undiluted	Rabbit (n = 8)	9-point score scale: well-defined to moderate erythema, well-defined edema, well-defined cracking and scaling at 72 h	RIFM (1977d)
	4 h, 0.5 ml, semi-occlusive, observations immediately after patch removal and at 24, 48, 72 h	Undiluted	Rabbit (n = 8)	9-point score scale: moderate erythema and edema, suspected necrosis in 3/8	RIFM (1980m)
	24 h, saturated filter paper, occlusive, (*p*re-test for Maximization test), observations 24 h, 48 h after patch removal	1, 2.5, 5% in ethanol	Guinea pig (4/group)	1%: barely perceptible erythema (24 h)$\geqslant$2.5%: barely perceptible to mild erythema (24, 48 h)	RIFM (1980n)
		0.5, 1, 2.5% in ethanol		0.5%: no reaction 1%: barely perceptible erythema (24 h) 2.5%: mild erythema (24, 48 h)	
	24 h, saturated filter paper, occlusive, (*p*re-test for Maximization test), observations 24 h, 48 h after patch removal	2.5, 5% in acetone/PEG	Guinea pig (6 males/group)	2.5%: no reaction	RIFM (1982j)
	24 h, saturated filter paper, occlusive, (*p*re-test for Maximization test), observations 24 h, 48 h after patch removal	0.5, 1, 2.5, 5% in acetone/PEG	Guinea pig (6 males/group)	5%: very slight to slight erythema $\leqslant$ 2.5%: no reaction	RIFM (1982i)
	24 h, saturated filter paper, occlusive, (*p*re-test for Maximization test), observations 24 h, 48 h after patch removal	0.5, 1, 2.5, 5, 10, 25% in ethanol	Guinea pig (4 females/group)	5%: very slight to slight erythema 0.5%: no reaction 1%: barely perceptible erythema (1/4, 24 h) 2.5%: mild erythema (2/4, 24 and 48 h) 5%: barely perceptible to mild erythema 10, 25%: barely perceptible to moderate erythema	RIFM (1981e)

Table 6-2a (*continued*)

Material	Method	Concentration	Species	Reactions	References
	24 h, 0.1 ml, occlusive, (*p*re-test for modified Buehler-test), n.f.i.	10% in PEG	Guinea pig ($n = 11$)	Not irritating	RIFM (1971d)
	24 h, 0.025 ml, open (*p*re-test for OET), observations at 24 h and 48 h	0, 3, 10, 30, 100% in ethanol	Guinea pig (6/group)	30%: maximal non-irritating concentration 100%: minimal irritating concentration	RIFM (1985a)
	24 h, 0.1 ml, open (*p*re-test for modified Draize test)	5%, vehicle not stated	Guinea pig ($n = 4$)	Not irritating	Sharp (1978)
	6 h, 0.3 ml, occlusive, (*p*re-test for Buehler test), observations 24 and 48 h after application	0.5, 1, 2.5, 5, 10, 25, 50, 100% in 80% ethanol	Guinea pig (4/group)	vehicle: ethanol $\leqslant$ 1%: very slight erythema 2.5, 5%: slight or moderate patchy erythema 10–50%: necrosis 100%: slight or moderate patchy erythema	RIFM (1986b)
		0.25, 0.5, 1, 2.5, 5, 10, 25, 50% in DEP		vehicle: DEP $\leqslant$ 25%: very slight erythema 50% slight or moderate patchy erythema	
	6 h, 0.3 ml, occlusive, (*p*re-test for Buehler test), observations 24 and 48 h after application	0.5, 1, 2.5, 5, 10, 25, 50, 100% in 80% aqueous ethanol or in acetone	Guinea pig (4/group)	vehicle: ethanol $\leqslant$ 1%: very slight erythema 2.5%: slight or moderate patchy erythema 5–50%: necrosis 100%: very slight to slight or moderate patchy erythema, desquamation vehicle: acetone 0.5, 1%: no erythema 2.5–25%: very slight erythema $\geqslant$10%: desquamation 50% very slight to slight or moderate patchy erythema	RIFM (1985b)
	48 h, 0.021 g, occlusive (3 pre-test for closed epicutaneous sensitization study, 2nd and 3rd with additional wrapping), observations 24 and 48 h after removal of test substance	1st: 1, 3, 10% 2nd and 3rd: 0.3, 1, 3% vehicle: 1st and 2nd: petrolatum 3rd: petrolatum at room tempeRature ($n = 5$) or molten ($n = 5$)	Guinea pig (1stand 3rd: 10/group, 2nd: 5/group)	1st: up to 10%: mild to well-defined erythema (24 h), desquamation, mild erythema (48 h) 2nd: up to 3%: mild to well-defined erythema 3rd (petrolatum at room tempeRature): mild to well-defined erythema (molten petrolatum): mild erythema	RIFM (1985c)
	48 h, 0.15 or 0.2 ml, occlusive (*p*re-test for closed epicutaneous sensitization study), observations 24 and 48 h after removal of test substance	0.3, 1, 3% in petrolatum	Guinea pig (5/group)	0.3%: mild erythema 1, 3%: well-defined erythema	RIFM (1985d)
	Not wiped after application, 0.1 ml, open, (*p*re-test for phototoxicity study), observations 3, 6, 24, 48 and 72 h after application	0, 5, 10, 30% in ethanol	Rat (5/group)	9-point score scale: 0, 5, 10%: very slight to slight erythema and edema, very slight to slight cracking and scaling at 48 and 72 h 30%: very slight to well-defined erythema and edema, strongest reactions at 48 h, very slight to slight cracking and scaling at 48 and 72 h	RIFM (1980o)
	Not wiped after application, 0.1 ml, open, (*p*hototoxicity study, dermal application phase), observations 3, 6, 24, 48 and 72 h after application	10% in ethanol	Rat (10/group)	10%: very slight to slight erythema and edema, cracking and scaling at 48 and 72 h	RIFM (1980o)
	24 h, 5000 mg/kg body weight, occlusive, observation period of 14 days, acute dermal LD_{50}	Undiluted	Rabbit ($n = 10$)	slight to severe skin reactions, n.f.i.	RIFM (1980a)
Isojasmone	24 h, 0.5 ml, occlusive, intact skin, observations after 2 and 24 h	Undiluted	Rabbit ($n = 9$)	PII: 0.28 (max. 4) Not irritating	Troy (1977)
	48 h, occlusive, (induction phase of maximization test), observations immediately, 24, 48 h after patch removal	25% in petrolatum	Guinea pig (control: 5, test group: 10)	slight to well-defined erythema in 5/10	RIFM (1982k)
	24 h, 5000 mg/kg body weight, occlusive, observation period of 14 days, acute dermal LD_{50}	Undiluted	Rabbit ($n = 10$)	slight (4/10), moderate (4/10) or marked (2/10) redness, moderate edema (10/10)	RIFM (1974a)
cis-Jasmone	4 h, 0.5 ml, semi-occlusive, observations 1 h after patch removal and 24, 48 and 72 h, 7 d, according to OECD TG 404	undiluted	Rabbit ($n = 4$)	very slight to well-defined erythema, very slight to slight edema, still present after 7 days, desquamation in all animals (7 d) RIFM (1987b) average irritation score for erythema: 1.8 for edema: 0.8 Mildly irritating	
	24 h, 5000 mg/kg body weight,	Undiluted	Rabbit ($n = 10$)	Moderate (1/10) or severe (9/10)	RIFM

(*continued on next page*)

Table 6-2a (*continued*)

Material	Method	Concentration	Species	Reactions	References
	occlusive, observation period of 14 days, acute dermal LD_{50}			redness, moderate edema (10/10), slight (2/10) or severe (1/10) eschar	(1977a)
	0.5 ml, semi-occlusive, abraded and intact skin, observations after 24 and 48 h	1% in alcohol SDA 39C	Rabbit (n = 3)	Not irritating	RIFM (1972f)
	24 h, 0.1 ml, occlusive, (*pre*-test for modified Buehler-test), n.f.i.	10% in PEG	Guinea pig (n = 11)	Not irritating	RIFM (1971d)
2-(p-Menth-1-ene-10-yl) cyclopentanone	4 h, 0.5 ml, semi-occlusive, observations after 1, 24, 48 and 72 h	Undiluted	Rabbit (n = 6)	very slight erythema; no edema not irritating	RIFM (1989f)
3-Methyl-2-(n-pentanyl)- 2-cyclopenten-1-one	24 h, 0.5 ml, occlusive, abraded and intact skin, observations 24 and 72 h after application	1% in alcohol SDA 39C	Rabbit (n = 3)	Not irritating	RIFM (1972g)
	24 h, 5000 mg/kg body weight, occlusive, observation period of 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 6)	Dermal irritation (n.f.i.)	RIFM (1972a)
3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one	24 h, 0.5 ml, occlusive, abraded and intact skin, 24 and 72 h after application	Undiluted	Rabbit (n = 6; intact and abraded skin)	Primary irritation index (24 and 72 h, abraded and intact skin): 2.95 Not a primary irritant	RIFM (1981f)
2-Pentylcyclopentan-1-one	24 h, 0.5 g, occlusive, abraded and intact skin, observations 24 h and 72 h after application	Undiluted	Rabbit (n = 6)	Primary irritation index (24 and 72 h, abraded and intact skin): 1.09 Not a primary irritant	RIFM (1979d)
2,2,5-Trimethyl-5-pentylcyclopentanone	4 h, 0.5 ml, semi-occlusive, observations 1 h after patch removal and 24, 48 and 72 h, daily up to 10 days OECD TG 404	Undiluted	Rabbit (n = 3)	Mean irritation score over 24, 48, 72 h for each animal: 2.0, 1.0, 1.0 for erythema, 0.3, 0, 0 for edema) dryness at 72 h and above, crusts at day 5 and 6 Not irritating	RIFM (2001d,e)
	24 h, 2025 mg/kg body weight, occlusive, intact and abraded skin, observation period of 14 days	Undiluted	Rabbit (n = 4)	severely irritating: beet red erythema, second degree burns, severe edema at 24 h, escharosis at day 7 and 14; moderate desquamation, superficial escharosis at necropsy	RIFM (1978a)
Methyl ester					
Methyl dihydrojasmonate	4 h, 0.5 ml, semi-occlusive, observations immediately after patch removal and at 24, 48, 72 h	Undiluted	Rabbit (n = 7)	9-point score scale: very slight to well-defined erythema and edema at 24 h and later, slight cracking at 48 and 72 h slight to moderate irritant	RIFM (1979e)
	4 h, 0.5 ml, semi-occlusive, observations immediately after patch removal and at 24, 48, 72 h	Undiluted	Rabbit (n = 8)	9-point score scale: very slight to well-defined erythema at 24 h, very slight erythema at 72 h, very slight to slight edema throughout the study, very slight cracking and scaling at 72 h slight irritant	RIFM (1986d)
	24 h, 0.5 ml, occlusive, abraded and intact skin, observations 24 and 72 h after application	10% in alcohol SDA 39C	Rabbit (n = 3)	Primary irritation index (24 and 72 h, abraded and intact skin): 0 Not irritating	RIFM (1971e)
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 and 48 h after patch removal	40, 70, 100%	guinea pig (4/group)	40%: barely perceptible erythema (4/4 resp. 3/4, 24, 48 h) 70%: barely perceptible erythema (1/4, 48 h) 100%: barely perceptible erythema (3/4, 24 h)	RIFM (1981g)
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 and 48 h after patch removal	5, 10, 20, 40, 60, 80% in ethanol	Guinea pig (5/group)	5–40%: no to barely perceptible erythema (1/5, 24 and 48 h) 60%: barely perceptible erythema (2/5 resp. 1/5, 24 and 48 h) 80%: barely perceptible erythema (3/5, 24 and 48 h)	RIFM (1979f)
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 and 48 h after patch removal	40, 60, 100% in acetone/PEG	Guinea pig (4/group)	40–100%: no reaction	RIFM (1982l)

Table 6-2a (*continued*)

Material	Method	Concentration	Species	Reactions	References
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 h, 48 h after patch removal	25, 50, 100% in ethanol	Guinea pig (4/group)	25, 50%: no reaction 100%: barely perceptible erythema (1/4, 24 and 48 h)	RIFM (1981h)
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 and 48 h after patch removal	25, 50, 100% in ethanol	Guinea pig (4/group)	25–100%: barely perceptible erythema (1/4)	RIFM (1981i)
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 and 48 h after patch removal	50, 100% in acetone/PEG	Guinea pig (4/group)	50, 100%: no reaction	RIFM (1982m)
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 and 48 h after patch removal	40, 60, 100% in acetone/PEG	Guinea pig (4/group)	40–100%: no reaction	RIFM (1982n)
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 and 48 h after patch removal	50, 100% in acetone/PEG	Guinea pig (4/group)	50, 100%: no reaction	RIFM (1986c)
	24 h, saturated filter paper, occlusive, (*pre*-test for Maximization test), observations 24 and 48 h after patch removal	20, 40, 60% in ethanol	Guinea pig (4/group)	20%: no reaction 40%: barely perceptible erythema (1/4, 24 h) 60%: barely perceptible erythema (3/4, 24 and 48 h)	RIFM (1980p)
	24 h, 5000 mg/kg body weight, occlusive, observation period of 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 10)	slight (3/10) or moderate (7/10) redness, slight (6/10) or moderate edema (3/10)	RIFM (1976b)
	24 h, 0.1 ml, occlusive, (*pre*-test for modified Buehler-test), n.f.i.	10% in PEG	Guinea pig (n = 11)	Not irritating	RIFM (1971d)
Methyl hexyl oxo cyclopentanone carboxylate	24 h, 5000 mg/kg body weight, occlusive, intact and abraded skin, observation period of 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 10)	Intact: very slight (4/5) or slight (1/5) erythema, very slight edema (1/5) at day 1 abraded: very slight (2/5) or slight (3/5) erythema, very slight (1/5) or slight edema (1/5) at day 1	RIFM (1978b)
Methyl jasmonate	24 h, 0.5 ml, occlusive, abraded and intact skin, observations 24 and 72 h after application	1% in alcohol SDA 39C	Rabbit (n = 6)	Primary irritation index: 0.9 None to well-defined erythema and very slight edema Not irritating	RIFM (1978h)
	24 h, 0.5 ml, occlusive, abraded and intact skin, observations 24 and 72 h after application	Undiluted	Rabbit (n = 6)	Primary irritation index: 0 Not irritating	RIFM (1980q)
	24 h, 2000 mg/kg body weight, occlusive, observation period of 14 days, acute dermal LD_{50}	Undiluted	Rabbit (n = 10)	Not irritating	RIFM (1980b)
	24 h, 0.15 ml, occlusive, (*pre*-test for Maximization test), observations 2 h after patch removal	2.5, 5, 10 and 20% in alcohol SDA 39C	Guinea pig (n = 4)	Not irritating	RIFM (1980g)

DEP: diethyl phthalate.
PEG: polyethylene glycol.
n.f.i.: no further information.
[a] Method published by the Association Francaise de Normalisation (AFNOR), 1982.
[b] Method published by the French authorities for the testing of cosmetics and toiletries (Journal Officiel de la République Francaise (1971, 1973)).

dihydrojasmonate (98.5% purity) was fed to 10 male and 10 female Sprague–Dawley CD-derived (Crl:CD (SD) IGS BR) rats per dose and group in doses of 0, 10, 50, or 100 mg/kg body weight/day for 90 consecutive days. There were no clinical signs of toxicity or mortalities, and no changes in clinical chemistry or hematology parameters were observed. Organ weights, body weights and food consumption were similar to controls. The findings in the ophthalmology examination, the functional observational battery and the motor activity were normal. There were no treatment-related adverse findings in gross or microscopic examinations. The authors concluded a NOEL of 100 mg/kg body weight/day (RIFM, 2000b).

5.2.3. Inhalation studies

Cyclopentanone was tested for repeat dose toxicity in an inhalation study. Wistar rats (20 per dose) were administered the test material at doses of 0, 50, 100 and 300 p.p.m. 6 h/day for 5 days/week for 15 weeks. No reactions were observed and no mortalities

Table 6-2b
Skin irritation studies in animals, repeated application

Material	Method	Concentration	Species	Reactions	References
2-Heptylidenecyclopentan-1-one	0.05 ml, open, 2 consecutive days, observation 2 and 3 days after first application	Undiluted	Rat (n = 10)	9-point score scale: well-defined and moderate edema, necrosis in 5/10	RIFM (1980r)
2-Hexylidene cyclopentanone	OET, 0.1 ml, irritation phase, 5 times per week for 4 weeks, clipped skin, observations 24 h after each application	0, 3, 10, 30, 100% in ethanol	Guinea pig (3/sex/dose)	10%: slight skin irritation on day 7 (3/6) No other skin reactions at any other concentration	RIFM (1985a)
Methyl ester					
Methyl jasmonate	Maximization test (induction phase), 0.15 ml, animals treated 3x/week for 3 weeks	10% in alcohol SDA 39C	Guinea pig (n = 10)	No reactions	RIFM (1980g)

OET: Open Epicutaneous Test.

were seen. At necropsy there was no appreciable organ toxicity (Elovaara et al., 1984), see Table 3-3.

5.3. Genotoxicity studies

5.3.1. Bacteria

Nine materials have been tested for genotoxicity in bacteria in 14 Ames assays. The available studies are summarized in Table 4-1.

Dihydroisojasmone (RIFM, 2004b), 2-heptylcyclopentanone (RIFM, 2000c), 2-hexylidene cyclopentanone (Wild et al., 1983), *cis*-jasmone (RIFM, 2003c), 2-(*p*-menth-1-ene-10-yl) cyclopentanone (RIFM, 1989d, 2006b), and the methyl esters methyl dihydrojasmonate (RIFM, 1978d, 1987a, 2000d,e) and methyl hexyl oxo cyclopentanone carboxylate (RIFM, 2008a), were inactive in Ames tests performed mostly according to OECD TG 471. Cytotoxic concentrations were not reached in an Ames test with 2-hexylidene cyclopentanone (Wild et al., 1983). However, the maximum concentration tested was close to the maximum concentration required by OECD TG 471. Therefore, the negative result can be regarded as reliable. Using the spot test method, an Ames test with cyclopentanone was negative, but cytotoxic concentrations were not reached. The highest concentration was about half of the maximum concentration required by OECD TG 471 (Florin et al., 1980). As there is no structural alert, the negative result for cyclopentanone is plausible.

5.3.2. Mammalian cell lines

Three materials were tested for genotoxicity in mammalian cell lines in two sister chromatid exchanges, one chromosomal aberration assay and two mouse lymphoma tests. The data from these studies are summarized in Table 4-2.

Methyl dihydrojasmonate was inactive with and without metabolic activation in a mouse lymphoma test according to OECD TG 476. The negative result was repeated in a second assay and in a third assay with a longer exposure period (RIFM, 2001c). In a second pre-guideline test using similar concentrations methyl dihydrojasmonate showed positive results with and without metabolic activation (RIFM, 1979c). There was no differentiation between large and small colonies in the positive test. Therefore, it cannot be concluded whether clastogenic or mutagenic effects were induced. As the concentrations which gave positive results were cytotoxic as well, it is possible that the positive result is an artifact.

In indicator studies, 3-ethyl-2-hydroxy-2-cyclopenten-1-one did not induce sister chromatid exchange in human peripheral lymphocytes from non-smoking volunteers (Jansson et al., 1986) and *cis*-jasmone did not induce sister chromatid exchange in Chinese hamster ovary cells (Sasaki et al., 1989).

The methyl ester methyl dihydrojasmonate did not induce chromosomal aberrations *in vitro* according to OECD TG 473 when incubated with Chinese hamster ovary cells (RIFM, 1988).

5.3.3. Animals

Three materials have been tested for genotoxicity *in vivo*. The available studies (one mouse micronucleus assay, two bone marrow micronucleus assays and one unscheduled DNA synthesis assay) are summarized in Table 4-3.

2-Hexylidene cyclopentanone was negative in the mouse bone marrow micronucleus test but no information is given on toxicity in the assay (Wild et al., 1983). The micronucleus test was conducted with only one sampling time, and no positive controls were used; therefore, the negative result is not reliable. 2-(*p*-Menth-1-ene-10-yl) cyclopentanone was negative in a mouse bone marrow micronucleus test at a dose of 4800 mg/kg body weight (RIFM, 1989e). The methyl ester methyl dihydrojasmonate was not genotoxic in the mouse bone marrow micronucleus test (OECD TG 474) (RIFM, 1998) and did not induce unscheduled DNA synthesis in hepatocytes of rats (OECD TG 486) (RIFM, 2001b).

5.4. Carcinogenicity

There are no data available for the cyclopentanones and cyclopentenones under review.

5.5. Developmental toxicity

No true fertility studies are available for the cyclopentanone and cyclopentenone group of fragrance ingredients. In a previously discussed repeat dose toxicity study (see Section 5.2.2), the reproductive organs of male and female rats showed no histopathological effects after being fed a diet with up to 100 mg/kg body weight/day of the methyl ester methyl dihydrojasmonate for 90 days (RIFM, 2000b).

Developmental toxicity data are available for two of the materials under review; these studies are discussed below and summarized in Table 5.

5.5.1. Oral

In a developmental study, which is only available as an abstract, 25 COBS® CD® female rats per dose were given cyclopentanone in corn oil by gavage at 0, 50 or 300 mg/kg body weight/day on gestation days 6 to 15. The highest dose was selected due to a dose-range finding study, where it caused reduced maternal body weight gain. In the main study, no maternal, embryotoxic or teratologic effects were observed at either dose level. At 300 mg/kg body weight, the mean fetal body weight was slightly decreased (no information on statistical significance). The maternal NOAEL

was considered, by the panel, to be 300 mg/kg body weight. The authors of the study considered the no effect level for developmental toxicity to be 50 mg/kg body weight. Neither the statistical findings, nor the biological relevance of the effects leading to the establishment of the NOAEL can be assessed (Rusch et al., 1988).

In a dose-range finding study 8 presumed pregnant female Crl:CD (SD) rats per group were treated per gavage with methyl dihydrojasmonate in doses of 0, 125, 250, 500, or 1000 mg/kg body weight/day on gestation days 7 to 20. Maternal body weight gain, absolute and relative feed consumption and fetal body weights were reduced at doses of 125 mg/kg body weight/day and above. Excess salivation occurred at 250 mg/kg body weight/day and above, dehydration and ungroomed appearance were noted at 1000 mg/kg body weight (Politano et al., 2008; RIFM, 2007).

The developmental toxicity of methyl dihydrojasmonate was investigated in presumed pregnant female Crl:CD (SD) rats according to OECD TG 414. 25 rats/dose group were gavaged from gestation day 7 through 20 with doses of 0, 40, 80 or 120 mg/kg body weight/day in corn oil. Doses of up to 80 mg/kg body weight/day showed no effects on dams. No developmental toxicity was observed. The authors considered maternal NOAEL for systemic toxicity to be 80 mg/kg body weight/day based on reduced body weight at 120 mg/kg body weight/day. The authors considered the NOAEL for developmental toxicity to be the highest tested dose of 120 mg/kg body weight/day (Politano et al., 2008; RIFM, 2007).

5.5.2. Inhalation

No data available.

5.6. Skin irritation

5.6.1. Human studies

Fourteen cyclopentanones and cyclopentenones and three methyl esters of cyclopentanones under review have been studied for their potential to produce dermal irritation in humans (see Table 6-1).

Eight substances did not induce skin irritation during the induction phase of human repeat insult patch tests (HRIPT) when applied in the following concentrations: 0.5% 3-ethyl-2-hydroxy-2-cyclopenten-1-one (RIFM, 2000g), 1.25% 2-heptylcyclopentanone (RIFM, 1964a), 0.6% 2-hexylidene cyclopentanone (RIFM, 2005a), 2% *cis*-jasmone (RIFM, 1972b), 5% 2-(*p*-menth-1-ene-10-yl) cyclopentanone, 1% 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one (RIFM, 1972c), 10% 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one (RIFM, 1981d), 10% 2-pentylcyclopentan-1-one (RIFM, 1978e), 10% 2,2,5-trimethyl-5-pentylcyclopentanone (RIFM, 1978f), 20% or 2.42% of the methyl ester methyl dihydrojasmonate (RIFM, 1976c, 2003d, 2005b, respectively) and 10% or 1% methyl jasmonate (RIFM, 1978g, 1980i, respectively).

No skin irritation was observed in pre-tests for maximization studies in which sometimes only a limited number of volunteers were tested with a single occlusive application for 48 h with 11 materials in the following concentrations: 10% cyclopentanone (RIFM, 1976c), 4% dihydroisojasmone (RIFM, 1976d), 10% 2-heptylcyclopentanone (RIFM, 1973b), 10% hexenylcyclopentanone (RIFM, 1976c), 10% 2-hexylcyclopentanone (RIFM, 1980h), 5% 2-hexylidene cyclopentanone (RIFM, 1981c), 8% isojasmone (RIFM, 1974b), 8% *cis*-jasmone (RIFM, 1977c), 4% 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one (RIFM, 1972d). Corresponding non-irritating concentrations for the methyl esters were 20% methyl dihydrojasmonate (RIFM, 1976c) and 2% methyl hexyl oxo cyclopentanone carboxylate (RIFM, 1972e).

5.6.2. Animal studies

Fifteen of the cyclopentanones and cyclopentenones and three of the methyl esters under review have been tested in animal models of skin irritation using rabbits, rats, or guinea pigs. Studies with single application are summarized in Table 6-2a and studies with repeated application are shown in Table 6-2b.

5.6.2.1. Single application. Most irritation studies have been performed with 24 h occlusive application before the introduction of the OECD TG 404, which prescribes a semi-occlusive application of 4 h only. Additionally, results from acute dermal toxicity testing in rabbits have been included.

If applied undiluted semi-occluded or occluded once for 24 h in skin irritation or dermal LD_{50} tests with rats, rabbits or guinea pigs, irritation to a varying degree was induced by cyclopentanone (Guillot et al., 1982a), dihydroisojasmone (RIFM, 1976b), 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone (RIFM, 1991c), 2-heptylcyclopentanone (RIFM, 1973a), hexenylcyclopentanone (RIFM, 1976b), 2-hexylidene cyclopentanone (RIFM, 1980a), isojasmone (RIFM, 1974a; Troy, 1977), *cis*-jasmone (RIFM, 1977a), 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one (RIFM, 1972a), 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one (RIFM, 1981f), and 2-pentylcyclopentan-1-one (RIFM, 1979d). With the methyl esters the following results were obtained: no irritation with undiluted methyl jasmonate (RIFM, 1981h,i), no to slight irritation with methyl hexyl oxo cyclopentanone carboxylate (RIFM, 1978b), and no to moderate irritation with undiluted methyl dihydrojasmonate (RIFM, 1976b, 1981g,h,i, 1982l,m,n, 1986c).

In some dermal LD_{50} tests, severe irritation or necrosis were observed: necrosis occurred after application of cyclopentanone (RIFM, 1982a), eschar and ulceration occurred with 2-hexylcyclopentanone (RIFM, 1980a), severe erythema and edema, escharosis and second degree burns after application of 2,2,5-trimethyl-5-pentylcyclopentanone (RIFM, 1978a).

Undiluted 2-hexylidene cyclopentanone did induce skin irritation in guinea pigs after 6 h occlusive contact. Necrosis was observed when 2-hexylidene cyclopentanone was diluted with 80% aqueous ethanol to concentrations between 5% and 50% (RIFM, 1985b, 1986b). When 2-hexylidene cyclopentanone was diluted to the same concentrations with acetone (RIFM, 1985b) or diethyl phthalate (RIFM, 1986b), necrosis was not observed, suggesting it may have been due to the vehicle and not the test material.

As opposed to results in dermal LD_{50} tests, undiluted cyclopentanone (Guillot et al., 1982a) and 2,2,5-trimethyl-5-pentylcyclopentanone (RIFM, 2001d,e) were not skin irritants in rabbits when tested according to OECD TG 404 for 4 h. A 4 h semi-occlusive application of undiluted *cis*-jasmone (RIFM, 1987b) was considered mildly irritating to the skin of rabbits. 2-Heptylcyclopentanone and 2-heptylidenecyclopentan-1-one (RIFM, 1980j), tested under the same conditions, resulted in moderate to well-developed reactions. Undiluted 2-hexylcyclopentanone, after 4 h semi-occlusive application, was judged to be a moderate irritant (RIFM, 1982f). In identical protocols, 2-hexylidene cyclopentanone produced a well developed reactions and was considered moderately irritating to rabbit skin (RIFM, 1977d, 1980m). The undiluted methyl ester methyl dihydrojasmonate was considered a slight to moderate irritant in one study (RIFM, 1979e) and a slight irritant in another (RIFM, 1986d), after 4 h semi-occlusive application. With diluted materials or open application (pre-test for open epicutaneous test or phototoxicity studies), the irritation reactions produced were in most cases reduced and led to no or only slight effects in rabbits or guinea pigs: 75% 2-hexylcyclopentanone (RIFM, 1982g), 30% 2-heptylcyclopentanone (open) (RIFM, 1982e), 25% 2-heptylcyclopentanone (RIFM, 1980k), 25% isojasmone (RIFM, 1982k), 10% *cis*-jasmone (RIFM, 1971d), 2.5% 2-heptylidenecyclopentan-1-one (RIFM, 1980l), 1% 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one (RIFM, 1972g), 0.5% 2-hexylidene cyclopentanone (RIFM, 1981e).

Table 7
Eye irritation studies in rabbits.

Material	Method	Concentration	Reactions	References
Cyclopentanone	0.1 ml, observations after 1, 4, 24 h, 2, 3, 4, 7, 10 and 14 days, 6 rabbits	Undiluted	Moderate or marked erythema, chemosis, discharge, slight iritis, corneal opacity, vascularization, sloughing, apparent blistering of the lower lid, corneal lesions (4/6 on day 7), still present in 3/6 on day 14 Irritating	RIFM (1982a)
	0.1 ml, observations after 1 h, 1, 2, 3, 4 and 7 days, 6 rabbits			
	No rinsing resp. rinsing 4 or 30 s after instillation	Undiluted	according to author's evaluation severely irritating without and with rinsing, effects still present at the end of the study on day 7 Irritating	Guillot et al. (1982b)
2-Heptylcyclopentanone	0.1 ml, observations after 15 min, 1, 2, 3 and 4 days, 3 rabbits	Undiluted	No effects on iris, conjunctival irritation in all rabbits with redness and chemosis (0/3 rabbits were positive), slight ("grade 0.5" in two animals) or moderate corneal opacities (grade 1 in one animal at day 1) associated with slight or moderate corneal swelling in all rabbits, conjunctival swelling (2/3), effects cleared by day 3[a,b] Not irritating	RIFM (1980s)
	0.1 ml, observations after 15 min, 1, 2, 3 up to 22 days, 3 rabbits	50% in Tween80	Moderate conjunctival irritation, slight to moderate discharge and chemosis, iritis (1/3, grade 1 at day 1), moderate (2/3) or severe (1/3) corneal opacities (effect persistent in 1/3 at day 22), corneal swelling, pannus (3/3), one animal being euthanized on day 15 due to the severity of the reaction[b]	RIFM (1980t)
	0.1 ml, observations after 15 min, 1, 2, 3 and 4 days, 3 rabbits	10% in Tween80	No effects on iris, slight conjunctival irritation in all rabbits, "slight corneal opacity" in all rabbits, effects cleared by day 4, one animal was found dead at day 4 (n.f.i.)[b]	RIFM (1980u)
	0.1 ml, observations after 24 h, 2, 3, 4 and 7 days, 3 rabbits	1.25%	No effects on iris or cornea, conjunctival irritation with redness and chemosis in all rabbits (average Draize scores after 1, 2, 3 days: 6, 4, 2 (maximum 110), effects cleared by day 7 Not irritating	RIFM (1963a)
2-Heptylidenecyclopentan-1-one	0.1 ml, observations after 15 min, 1, 2 and 3 days, 3 rabbits	Undiluted	No effects on iris or conjunctiva, slight ("grade 0.5" in two animals) corneal opacities, effects cleared by day 3[b] Not irritating	RIFM (1980v)
	0.1 ml, observations after 15 min, 1, 2, 3, 4 up to 22 days, 3 Rabbits	50% in Tween80	Slight or moderate conjunctival irritation with redness and chemosis and slight or moderate discharge in all animals, conjunctival hemorrhage (2/3), iritis (2/3), pannus in all animals (associated with two persistent opacities), moderate (2/3) or severe (1/3) corneal opacities associated with moderate corneal swelling, opacity still present at the end of the study on day 22 (2/3)[b]	RIFM (1980w)
	0.1 ml, observations after 15 min, 1, 2, 3 and 4 days, 3 rabbits	10% in Tween80	No effects on iris, slight conjunctival irritation with redness and chemosis, slight corneal opacities in all rabbits, effects cleared by day 4[b]	RIFM (1980x)
2-Hexylcyclopentanone	0.01 ml, observations after 15 min, 1, 2, 3 and 4 days, 2 rabbits	Undiluted	No effects on iris, mild conjunctival irritation in 1/2 with redness and discharge, slight corneal opacity ("grade 0.5" in both animals), cornea effects cleared by day 4[a,b] test not according to OECD TG 405, because sample volume only 0.01 ml	RIFM (1982o)
	0.1 ml, observations after 15 min, 1, 2, 3, 4, 7 and 9 days, 1 rabbit	undiluted	No effects on iris, mild conjunctival irritation (grades on day 1, 2, 3 for redness: 1, 1, 1 and for chemosis: 1, 1, 0), corneal opacity (grades on day 1, 2, 3: 2, 1, 1) with slight corneal swelling, cornea effects cleared by day 9[a,b] Irritating	RIFM (1982p)
	0.1 ml, observations after 15 min, 1, 2, 3, 4 up to 22 days, 2 Rabbits	50% in Tween80	No effects on iris, moderate conjunctival irritation with discharge, corneal opacity, swelling and epithelial damage, effects cleared by day 8 for one Rabbit, the other developed pannus on day 5, persisted along with corneal opacity until the end of the study on day 22[b]	RIFM (1982o)
	0.1 ml, observations after 15 min, 1, 2, 3, 4 and 7 days, 3 rabbits	10% in Tween80	No effects on iris, slight to moderate conjunctival irritation with redness, chemosis and discharge, loss of epithelium from a small area of the cornea (2/3), superficial epithelial damage over the whole corneal area (1/3), effects cleared by day 7[b]	RIFM (1982p)
2-Hexylidene cyclopentanone	0.1 ml, observations after 15 min, 1, 2, 3, 4, 8 up to 21 days, 6 rabbits	Undiluted	Slight conjunctival irritation with slight or moderate chemosis (mean score for redness and chemosis in 3/6 $\geqslant$ 1), iritis (2/6) (mean score in 2/6 = 0.7) conjunctival and iris effects cleared by day 8, "slight or moderate" corneal lesions (mean score for opacity in 2/6 = 1), slight to moderate corneal swelling in all animals, cornea opacity returned to grade 0.5 in two animals by day 8 and cleared by day 21[a,b] Moderately irritating	RIFM (1978i)
	0.1 ml, observations after 15 min, 1, 2, 3, 4 and 6 days, 3 rabbits	undiluted	Slight conjunctival irritation with redness and chemosis (mean score for redness in 2/3 = 1), moderate discharge (1/3), iritis (grade 1 in 2/3 at day 1), "slight to moderate" corneal lesions (mean score in 3/3 $\leqslant$ 0.7), slight or moderate corneal swelling in all Rabbits, cornea opacity returned to grade 0.5 by day 3 (2/3) resp. day 4 (1/3) and cleared by day 4 resp. 5[a,b] Moderately irritating	RIFM (1980y)

Table 7 (*continued*)

Material	Method	Concentration	Reactions	References
	0.1 ml, observations after 15 min, 1, 2, 3, 4, 7 up to 21 days, 3 Rabbits	50% in Tween80	Slight to moderate conjunctival irritation in all rabbits, discharge (2/3), iritis (2/3 at day 1), moderate corneal opacity (mean score in 3/3 = 1) associated with moderate or severe corneal swelling, one animal being euthanized on day 7 due to the severity of the reaction, the remaining two animals developed pannus, persisted along with corneal opacity until the end of the study on day 21[a,b]	RIFM (1980z)
	0.1 ml, observations after 15 min, 1, 2, 3, and 7 until 11 days, 6 Rabbits	10% in Tween80	Slight to moderate conjunctival irritation in all animals, slight to moderate discharge (3/6), iritis in all animals (mean score in 3/3 = 1)), moderate corneal opacity in all animals (mean score in 6/6 $\geqslant$ 1), moderate corneal edema, effects cleared by day 11[a,b]	RIFM (1977e)
	0.1 ml, observations after 15 min, 1, 2, 3, 4 and 7 days, 3 rabbits	10% in Tween80	Slight conjunctival irritation in all rabbits, iritis (1/3) (grade 1), moderate corneal opacity (mean score in 1/3 = 1), slight or moderate corneal swelling in all rabbits, effects cleared by day 7[a,b]	RIFM (1980aa)
	0.1 ml, observations after 15 min, 1, 2, and 3 days, 6 rabbits	1% in Tween80	No effects on iris or cornea, slight conjunctival irritation in 5 rabbits (mean score in 6/6 $\leqslant$ 0.7), effects cleared by day 3[a]	RIFM (1977f)
Isojasmone	0.1 ml, observations after 1, 2, 3, 4 and 7 days, 6 rabbits	undiluted	Draize scores after 1, 2, 3 days: 9, 5, 2 (maximum 110) (n.f.i.) Not irritating	Troy (1977)
	0.1 ml, observations after 1, 2, 3, 4 and 7 days, 3 rabbits	0.5% in ethanol	No effects on iris or cornea, conjunctival irritation in all Rabbits (average Draize scores after 1, 2, 3 days: 14.7, 12, 9.3 (maximum 110)), (mean score in 3/3 for redness = 2.7, mean score in 2/3 for chemosis $\geqslant$ 2), effects still present at the end of the study on day 7[a] Irritating	RIFM (1963b)
cis-Jasmone	0.1 ml, observations every 24 h for 7 days, n.f.i.	100%, 30%, 10%, 3%, 1% in neantine	Strong redness, strong secretion and edema at 100%; slight to moderate effects at lower concentrations Not irritating	RIFM (1971f)
	0.1 ml, observations after 1, 2, 3, 4 and 7 days, 3 rabbits	1% in alcohol SDA 39C	No effects on iris or cornea, conjunctival irritation in all rabbits (average Draize scores after 1, 2, 3 days: 2, 0, 0 (maximum 110)), (mean score in 3/3 for redness = 0.3), effects cleared by day 2[a] Not irritating	RIFM (1972h)
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	0.1 ml, observations after 1, 2, 3, 4 and 7 days, 6 rabbits	100%	Grade 1 iritis, grade 2 conjunctivitis; corneal opacity and ulceration mostly resolved by 72 h Not irritating	RIFM (1989f)
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one	0.1 ml, observations after 1, 2, 3, 4 and 7 days, 3 rabbits	1% in alcohol SDA 39C	No effects on iris or cornea, slight conjunctival irritation in all rabbits (average Draize scores after 1, 2, 3 days 4.7, 2, 2 (maximum 110)), (mean scores in 3/3 for redness = 1, for chemosis in 2/3 = 0.3), discharge in 2/3, effects cleared by day 4[a] effects in control Rabbits (0.1 ml alcohol SDA 39) similar, cleared by day 7	RIFM (1972i)
3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one	0.1 ml, observations after 1, 2, 3, 5 and 7 days, 6 rabbits	Undiluted	No effects on iris or cornea, conjunctival irritation in all rabbits (average Draize scores after 1, 2, 3 days: 6.7, 2, 0 (maximum 110)), effects cleared by day 3 Not irritating	RIFM (1981j)
2-Pentylcyclopentan-1-one	0.1 mg, observations after 1, 24, 48, 72 h, 5 and 7 days, 6 rabbits	Undiluted	No effects on iris or cornea, conjunctival irritation in all rabbits (mean scores for redness in 2/6 = 2, mean scores for chemosis in 3/6 $\geqslant$ 2), discharge in all Rabbits, effects cleared by day 7[a] Irritating	RIFM (1979g)
	0.1 mg, observations after 1, 24, 48, 72 h, 5 and 7 days, 6 Rabbits	20% in corn oil	No effects on iris or cornea, slight conjunctival irritation in all rabbits (mean scores for redness in 6/6 = 0.3), effects cleared by 48 h[a]	RIFM (1979g)
2,2,5-Trimethyl-5-pentylcyclopentanone	0.1 ml, observations after 24, 48, 72 h, 6 rabbits	Undiluted	No effects on iris or cornea, slight conjunctival irritation in 5/6 rabbits (mean scores for redness and chemosis in 6/6 $\leqslant$ 0.7), effects cleared by 48 h[a] Not irritating	RIFM (1979h)
Methyl ester				
Methyl dihydrojasmonate	0.1 ml, observations after 1, 24, 48, 72 h, 3 rabbits	Undiluted	No effects on iris or cornea, slight conjunctival irritation in all rabbits (mean scores for redness in 2/3 Rabbits = 0.3), effects cleared by 48 h[a]	RIFM (2000f)
	OECD TG 405	Not irritating undiluted		
	0.1 ml, observations after 15 min, 4 h, 1, 2, and 3 days, 3 rabbits		No effects on iris or conjunctiva, "slight" corneal opacity (grade 0.5 in all animals), effects cleared by day 3[b] Not irritating	RIFM (1979i)
	0.01 ml, observations after 15 min, 1 day, 2 rabbits	Undiluted	No effects on iris or cornea, slight transient conjunctival irritation in all rabbits (15 min), effects cleared by day 1 Not irritating	RIFM (1986e)
	0.1 ml, observations after 15 min, 1 day, 1 rabbit	Undiluted	No effects on iris or cornea, slight transient conjunctival irritation (15 min), effects cleared by day 1 Not irritating	RIFM (1986f)
	0.1 ml, observations after	50% in	No effects on iris, slight conjunctival irritation in all rabbits (mean	RIFM (1979j)

(*continued on next page*)

Table 7 (*continued*)

Material	Method	Concentration	Reactions	References
	15 min, 4 h, 1, 2, 3 and 4 days, 3 rabbits	Tween80	score for redness in 3/3 $\leqslant$ 1), "slight" corneal opacity (grade 0.5 in all animals), effects cleared by day 4[a,b] Not irritating	
	0.1 ml, observations after 15 min, 1 day, 1 rabbit	50% in Tween80	no effects on iris or cornea, slight transient conjunctival irritation (15 min), effects cleared by day 1 Not irritating	RIFM (1986f)
	0.01 ml, observations after 15 min, 1 day, 2 rabbits	50% in Tween80	no effects on iris or cornea, slight transient conjunctival irritation in all rabbits (15 min), effects cleared by day 1 Not irritating	RIFM (1986e)
	0.1 ml, observations after 15 min, 1 day, 3 rabbits	10% in Tween80	no effects on iris or cornea, no conjunctival irritation	RIFM (1979k)
	0.1 ml, observations after 15 min, 1 and 2 days, 3 rabbits	10% in Tween80	No effects on iris or cornea, slight transient conjunctival irritation in two Rabbits, effects cleared by day 2	RIFM (1986f)
	0.1 ml, observations after 1, 2, 3, 4 and 7 days, 3 rabbits	10% in alcohol SDA 39C	No effects on iris or cornea, conjunctival irritation (mean scores for redness in 3/3 $\geqslant$ 2, mean scores for chemosis in 3/3 = 1.7), discharge, effects cleared by day 7[a] effects in control Rabbits (0.1 ml alcohol SDA 39) similar, cleared by day 7	RIFM (1971g)
Methyl jasmonate	0.1 ml, observations after 1, 2, 3, 5 and 7 days, 6 Rabbits	Undiluted	No effects on iris or cornea, no conjunctival irritation Not irritating	RIFM (1980b)bb
	0.1 ml, observations after 1, 2, 3, 4, 7 and 10 days, 6 rabbits	1% in alcohol SDA 39C	conjunctival irritation (mean scores for redness in 4/6 $\geqslant$ 2, mean scores for chemosis in 2/6 = 2), iritis (mean scores in 3/6 = 1), corneal opacity (mean score in 1/6 = 1), pannus in one Rabbit at day 7, effects still present at day 10 in one Rabbit[a] the vehicle alcohol SDA 39C itself is irritating (note of the test laboRatory) (n.f.i.)	RIFM (1978j)
	0.1 ml, observations after 1, 2, 3, 4, 7 and 10 days, 6 rabbits	1% in propylene glycol	No effects on iris or cornea, conjunctival irritation in 3/6 (average Draize scores after 1, 2, 3 days: 2, 0.33, 0 (maximum 110)), cleared by day 3 Not irritating	RIFM (1979l)

n.f.i.: no further information.

[a] Calculated for every animal as the mean following grading at 24, 48 and 72 h after instillation of the test material.

[b] In the study an additional grade of "0.5" for cornea opacity was defined with the following description: "any change from normal, including slight dulling of corneal luster". As this grade does not exist in the OECD TG 405 and grade 1 is defined as "scattered or diffuse areas of opacity (other than slight dulling of normal luster)" the grade "0.5" is treated as grade "0".

5.6.2.2. Repeated application. Undiluted 2-heptylidenecyclopentan-1-one caused necrosis after open application on 2 consecutive days (RIFM, 1980r). Ten percent 2-hexylidene cyclopentanone was slightly irritating during the irritation phase of an Open Epicutaneous Test (OET), whereas higher concentrations like 30 and 100% did not induce irritation (RIFM, 1985a). During the induction phase of a maximization pre-test, the methyl ester, methyl jasmonate, at a concentration of 10% in guinea pigs treated 3 times per week for 3 weeks, did not induce irritation (RIFM, 1980g). Details are provided in Table 6-2b.

5.7. Mucous membrane irritation

5.7.1. Sensory irritation

5.7.1.1. Human data. Six volunteers were exposed for 7 min to various concentrations of cyclopentanone to determine threshold concentrations for nose and throat irritation. Throat irritation occurred at concentrations of 150 ppm and higher, nose irritation at 390 ppm and higher. At 80 ppm no sensory irritation was reported by the subjects (RIFM, 1965).

5.7.1.2. Animal data. Mice were exposed for one minute to various concentrations of isojasmone and the respiratory rate depression as a measure of upper respiratory tract irritation was recorded. The ED_{25} (respiratory rate depression 25% compared to baseline) was 0.63 mg/l (90 ppm). An ED_{50} (similar to the RD_{50} of the Alarie-test) could not be achieved with the concentrations employed (Troy, 1977).

5.7.2. Eye irritation

5.7.2.1. Human data. Six volunteers were exposed 7 min to cyclopentanone to determine threshold concentrations for eye irritation. Eye irritation occurred at 390 ppm. At 150 ppm, no eye irritation was reported by the subjects (RIFM, 1965).

5.7.2.2. Animal data. An overview of eye irritation studies in rabbits can be found in Table 7. The overall assessment of eye irritation potential was done according to the Globally Harmonized System of Classification and Labeling of Chemicals (United Nations, 2007) when the presentation of experimental data allowed the calculation of irritation scores. In the text, only studies with known vehicle or studies with undiluted substances are described. In several of the studies with diluted materials, the vehicle alcohol SDA 39C itself caused irritation, therefore, the irritating potential of the material tested cannot be evaluated with certainty. When Tween 80 was used as solvent, the effects were mostly more serious as compared to the undiluted test substance (e.g. 2-heptylidenecyclopentan-1-one (RIFM, 1980w,v) or 2-hexylcyclopentanone (RIFM, 1982o)), therefore, these studies were not used for the evaluation of eye irritation.

Undiluted 2-heptylcyclopentanone (RIFM, 1980s), 2-heptylidenecyclopentan-1-one (RIFM, 1980v), isojasmone (Troy, 1977), 2-(*p*-menth-1-ene-10-yl) cyclopentanone (RIFM, 1989f), 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one (RIFM, 1981j), 2,2,5-trimethyl-5-pentylcyclopentanone (RIFM, 1979h), and the methyl esters methyl dihydrojasmonate (tested according to OECD TG 405, RIFM, 1971g, 1986e,f, 2000f) and methyl jasmonate (RIFM, 1980bb) were not irritating to rabbit eyes.

Table 8–1a
Skin sensitization studies in humans

Material	Method	Concentration	Subjects	Reactions	References
Cyclopentanone	Maximization study	10% in petrolatum (6900 μg/cm^2)	25 (7 males, 18 females)	0/25	RIFM (1976c)
Dihydroisojasmone	Maximization study	4% in petrolatum (2760 μg/cm^2)	29	0/29	RIFM (1976d)
2-Heptylcyclopentanone	HRIPT	1.25% in ethanol (969 μg/cm^2)	40[a] (12 males, 28 females)	0/40[b]	RIFM (1964a)
	Maximization study	10% in petrolatum (6900 μg/cm^2)	25 males	0/25	RIFM (1973b)
Hexenylcyclopentanone	Maximization study	10% in petrolatum (6900 μg/cm^2)	25 (10 males, 15 females)	0/25	RIFM (1976c)
2-Hexylcyclopentanone	Maximization study	10% in petrolatum (6900 μg/cm^2)	27 males	0/27	RIFM (1980h)
2-Hexylidene cyclopentanone	HRIPT	1% in alcohol SDA 39C (139 μg/cm^2) (occlusive) 2ndchallenge: 0.2% (28 μg/cm^2) (occlusive) 3rd challenge: 1% (139 μg/cm^2) (semi-occlusive and uncovered)	51 5 2ndchallenge: 1/5 4	5/51 3rd challenge: 4/4 (semi-occlusiive at 24 h); 0/4 (uncovered) sensitizing	RIFM (1982d)
	HRIPT	0.6% in DEP/ethanol (3:1) (300 μg/cm^2)	102	0/102	RIFM (2005a)
	Maximization study	5% in petrolatum (3450 μg/cm^2)	25 males	3/25, 1 additional strong delayed reaction at SLS treated site (re-challenge negative) Mildly sensitizing	RIFM (1979m)
	Maximization study	5% in petrolatum (3450 μg/cm^2)	23	8/23 Moderately sensitizing (up to grade 4+)	RIFM (1981c)
Isojasmone	HRIPT	0.5% in ethanol (388 μg/cm^2)	38 (6 males, 32 females)	0/38 (4 were absent at second scoring of challenge)	RIFM (1964b)
	Maximization study	8% in petrolatum (5520 μg/cm^2)	25 (16 males, 9 females)	0/25	RIFM (1974b)
cis-Jasmone	HRIPT	1% in alcohol SDA 39C (775 μg/cm^2)	38 (12 males, 26 females)	0/38	RIFM (1972j)
	HRIPT	2% in DMP[c]	54	0/54	RIFM (1972b)
	Maximization study	8% in petrolatum (5520 μg/cm^2)	25	0/25	RIFM (1977c)
	Maximization study	8% in petrolatum (5520 μg/cm^2)	21	0/21	RIFM (1977c)
2-(*p*-Menth-1-ene-10-yl) cylopentanone	HRIPT	5% in DMP (2500 μg/cm^2)	53	0/53	RIFM (1996)
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one	HRIPT	1% in alcohol SDA 39C (775 μg/cm^2)	38 (12 males, 26 females)	0/38	RIFM (1972c)
	Maximization study	4% in petrolatum (2760 μg/cm^2)	25 males	0/25	RIFM (1972d)
3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one	HRIPT	10% in white petrolatum	50 (9 males, 41 females)	1/50, no rechallenge	RIFM (1981d)
	HRIPT	1% in DEP/ethanol (3:1) (1181 μg/cm^2)	100	0/100	RIFM (2010a)
2-Pentylcyclopentan-1-one	HRIPT	10% in petrolatum	50 (15 males, 35 females)	0/50	RIFM (1978e)
2,2,5-Trimethyl-5-pentylcyclopentanone	HRIPT	10% in petrolatum (5540 μg/cm^2)	50	0/50	RIFM (1978f)
Methyl ester					
Methyl dihydrojasmonate	HRIPT	20% in DEP (10,000 μg/cm^2)	100	0/100	RIFM (2003d)
	HRIPT	20% in DEP/ethanol (3:1) (10,000 μg/cm^2)	111	0/111	RIFM (2005b)
	HRIPT	10% in alcohol SD39C (7752 μg/cm^2)	23 (5 males, 18 females)	0/23	RIFM (1971b)
	HRIPT	2.42% in alcohol SD39C (1876 μg/cm^2)	23 females	0/23	RIFM (1971c)
	Maximization study	20% in petrolatum (13,800 μg/cm^2)	25 females	0/25	RIFM (1976c)

(*continued on next page*)

Table 8–1a (*continued*)

Material	Method	Concentration	Subjects	Reactions	References
Methyl jasmonate	HRIPT	10%, vehicle not reported	50 (9 males, 41 females)	0/50	RIFM (1980i)
	HRIPT	1% in alcohol SD39C (1000 μg/cm^2)	43 (9 males, 34 females)	0/43	RIFM (1978g)
Methyl hexyl oxo cyclopentanone carboxylate	Maximization study	2% in petrolatum (1380 μg/cm^2)	25 males	0/25	RIFM (1972e)

DEP: diethyl phthalate.
DMP: dimethyl phthalate.
HRIPT: human repeated insult patch test.
Note: a density of 1 g/cm^3 was assumed for dose calculations.
[a] Number of persons who finished challenge.
[b] Number with significant positive reactions/persons tested.
[c] Dosing volume and/or patch size and/or unit area not reported; dose/unit area could not be calculated.

Table 8–1b
Diagnostic patch tests.

Material	Method	Concentration	Subjects	Results	References
2-Pentylcyclopentan-1-one	Patch test	5% in petrolatum	178 male and female patients with contact dermatitis due to fragrance materials	0/178	Larsen et al. (2001)
Methyl ester					
Methyl dihydrojasmonate	Patch test	1, 5% in petrolatum	100 dermatological patients	0/100	Frosch et al. (1995)
	Patch test	5% in petrolatum	1606 contact dermatitis patients	9/1606 (0.6%)	Frosch et al. (2002)
	Patch test	5% in petrolatum	318 eczema patients (*part of* Frosch et al. (2002))	0/318	Paulsen and Andersen (2005)

Cyclopentanone caused moderate or marked erythema, chemosis and discharge and effects on iris and cornea. The effects on conjunctiva and cornea were declining with time but still present on day 14 (RIFM, 1982a; Guillot et al., 1982b). The substance is irritating.

Undiluted 2-hexylcyclopentanone has been tested for eye irritation in two studies, using only two rabbits (RIFM, 1982o) or only one rabbit (RIFM, 1982p). In the study with two rabbits mild conjunctival irritation and slight corneal opacity were observed. The rabbit used in the second study showed mild conjunctival irritation and moderate corneal opacity. Based on the last study 2-hexylcyclopentanone should be regarded as an eye irritant although only one animal was tested.

Undiluted 2-pentylcyclopentan-1-one elicited conjunctival irritation with redness, chemosis and discharge. The effects subsided within 7 days. A solution of 20% 2-pentylcyclopentan-1-one in corn oil caused slight conjunctival irritation with redness, which cleared within 48 h (RIFM, 1979g). Undiluted 2-pentylcyclopentan-1-one is considered an eye irritant and a 20% dilution in corn oil is not eye irritating.

A solution of 1% 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one in alcohol SDA 39C caused conjunctival irritation with erythema, chemosis and discharge. The effects cleared within 4 days. In control rabbits, conjunctival irritation was similar but lasted three days longer (RIFM, 1972i). Therefore it seems to be plausible that 1% 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one is not an eye irritant.

1% *cis*-jasmone in alcohol SDA 39C produced very slight conjunctival irritation which cleared within 2 days. Therefore a 1% dilution in alcohol SDA 39C is not an irritant.

5.8. Skin sensitization

5.8.1. Human studies

Sixteen of the cyclopentanones and cyclopentenones under review have been evaluated for their potential to induce sensitization in humans (see Tables 8–1a and 8–1b).

5.8.1.1. Induction of human sensitization. No evidence of a sensitizing effect in maximization tests with volunteers or in Human Repeat-Insult Patch Tests (HRIPTs) was observed with 14 materials at the respective concentrations as follows:

Ten percent cyclopentanone (RIFM, 1976c), 10% or 1.25% 2-heptylcyclopentanone (RIFM, 1964a, 1973b), 10% 2-hexenylcyclopentanone (RIFM, 1976c), 10% 2-hexylcyclopentanone (RIFM, 1980h), 10% 2-pentylcyclopentan-1-one (RIFM, 1978e), 10% 2,2,5-trimethyl-5-pentylcyclopentanone (RIFM, 1978f), 8% and 0.5% isojasmone (RIFM, 1964b, 1974b), 8%, 1% or 2% *cis*-jasmone (RIFM, 1972b,j, 1977c), 4% dihydroisojasmone (RIFM, 1976d), 5% 2-(*p*-menth-1-ene-10-yl) cyclopentanone (RIFM, 1996), 4% or 1% 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one (RIFM, 1972d,f), 0.6% 2-hexylidene cyclopentanone (RIFM, 2005a) as well as the methyl esters in the following concentrations: 20% methyl dihydrojasmonate (RIFM, 1976c, 2003d, 2005b), 10% methyl dihydrojasmonate (RIFM, 1971b), 2.42% methyl dihydrojasmonate (RIFM, 1971c), 10% methyl jasmonate (RIFM, 1980i), 1% methyl jasmonate (RIFM, 1978g) and 2% methyl hexyl oxo cyclopentanone carboxylate (RIFM, 1972e).

In a HRIPT with 1% 2-hexylidene cyclopentanone after occlusive application, 5/51 volunteers were possibly sensitized. These 5 volunteers were rechallenged with 0.2% under an occlusive patch. One of the five volunteers had a positive sensitization reaction. The semi-occlusive application of the same concentration on the same individual was negative. The remaining 4 volunteers were rechallenged with a 1% solution both under a semi-occlusive patch and with an open application. The open application was negative at 6 and 24 h, while the semi-occlusive application was negative at 6 h and positive (4/4) at 24 h (RIFM, 1982d). 3/25 and 8/23 volunteers showed positive reactions in two maximization tests with 5% 2-hexylidene cyclopentanone (RIFM, 1979m, 1981c). Due to its sensitization potential, the use of 2-hexylidene cyclopentanone is restricted in fragrance materials by an IFRA Standard (IFRA, 2008). Concentration limits for 2-hexylidene cyclopentanone in the 11 categories of fragrance products range from 0.2% to 0.01%. The No Effect Sensitization Induction Level (NESIL) is 300 μg/cm^2.

Table 8–2a
Skin sensitization studies in animals.

Material	Method	Concentration	Species	Results	References
Dihydroisojasmone	OET	Induction: n.f.i. challenge: 4% vehicle: n.f.i.	Guinea pig (⩾6/group)	Not sensitizing	Klecak (1985)
2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone	Modified Buehler test induction: occluded patch, 0.4 ml, 24 h for first application, 6 h for applications 2–9, three times weekly challenge: 24 h, occluded patch	undiluted	Guinea pig (control: 5, test group: 10 males)	Not sensitizing	RIFM (1991b)
2-Heptylcyclopentanone	Maximization test	Induction: 1% in DOBS/saline (intradermal), 10% in ethanol (percutaneous) challenge: 1% in ethanol	Guinea pig (10/group)	barely perceptible erythema (24 h), scattered, mild erythema (48 h)	RIFM (1980k)
				Not sensitizing	
	OET	Induction: n.f.i. challenge: 10% vehicle: n.f.i.	Guinea pig (⩾6/group)	Not sensitizing	Klecak (1985)
2-Hexylcyclopentanone	Maximization test	Induction: 2% in DOBS/saline (intradermal), 100% (percutaneous) 3 challenges: 25% 4th challenge: 5% vehicle: acetone/PEG	Guinea pig (control: 4/group, test group: 10)	sensitizing	RIFM (1982q)
	Maximization test	Induction: 2% in DOBS/saline (intradermal), 100% (percutaneous) 1st challenge: 25% 2nd + 3rd challenge: 15% vehicle: acetone/PEG	Guinea pig (control: 4/group, test group: 10)	Not sensitizing	RIFM (1982g)
	Maximization test	Induction: 2% in DOBS/saline (intradermal), 100% (percutaneous) 1st challenge: 25% 2nd challenge: 15% 3rd challenge: 5% vehicle: acetone/PEG	Guinea pig (control: 4/group, test group: 10)	Not sensitizing	RIFM (1983b)
	Maximization test	Induction: 2% in DOBS/saline (intradermal), 100% (percutaneous) 1st challenge: 25% 2nd challenge: 15% 3rd challenge: 5% vehicle: acetone/PEG	Guinea pig (control: 4/group, test group: 10)	Not sensitizing, as positive reactions could not be reproduced	RIFM (1983c)
	Maximization test	Induction: 2% in DOBS/saline (intradermal), 100% (percutaneous) 1st challenge: 25% 2nd challenge: 15% 3rd challenge: 5% vehicle: acetone/PEG	Guinea pig (control: 4/group, test group: 10)	Not sensitizing	RIFM (1983d)
	Maximization test	Induction: 2% in DOBS/saline (intradermal), 100% (percutaneous) 1st challenge: 25% 2nd challenge: 15% 3rd challenge: 5% vehicle: acetone/PEG	Guinea pig (control: 4/group, test group: 10)	Not sensitizing, as positive reactions could not be reproduced	RIFM (1983e)
2-Hexylidene cyclopentanone	Maximization test	Induction: 0.8% in 0.01% DOBS/saline (intradermal), 5% in ethanol (percutaneous) challenge: 0.1, 0.5% in ethanol	Guinea pig (control: 4, test groups: 10)	sensitizing	RIFM (1980n)
	Maximization test	Induction: 0.8% in 0.01% DOBS/saline (intradermal), 5% in ethanol (percutaneous) challenge: 0.5, 1% in ethanol	Guinea pig (control: 4, test groups: 10)	sensitizing	RIFM (1981e)
	Maximization test	Induction: 0.75% in 0.01% DOBS/saline (intradermal) 5% in acetone/PEG (percutaneous) challenge: 2.5% in acetone/PEG 3 re-challenges (weekly intervals): decreasing concentrations (0.0025–0.25%)	Guinea pig (control: 4, test groups: 10)	sensitizing at 0.025%, 0.25% and 2.5%	RIFM (1982j)
	Maximization test	Induction: 0.75% in 0.01% DOBS/saline (intradermal), 5% in acetone/PEG (percutaneous) challenge: 0.0025–2.5% in acetone/PEG	Guinea pig (control: 4, test groups: 20)	sensitizing at 2.5% and 0.25%	RIFM (1982i)
	Maximization test	Induction: 0.75% in 0.01% DOBS/saline (intradermal), 5% in acetone/PEG (percutaneous) challenge: 0.0025–0.25% in acetone/PEG	Guinea pig (control: 4, test groups: 10)	sensitizing at 0.25%	RIFM (1982i)
	Maximization test	Induction: 0.15% in 0.01% DOBS/saline (intradermal), 1% in acetone/PEG (percutaneous) challenge: 0.025–2.5% in acetone/PEG	Guinea pig (control: 4, test groups: 10)	sensitizing at 2.5%	RIFM (1982i)
	Maximization test	Induction: 0.075% in 0.01% DOBS/saline (intradermal), 0.5% in acetone/PEG (percutaneous) challenge: 0.025–2.5% in acetone/PEG	Guinea pig (control: 4, test groups: 10)	sensitizing at 2.5%	RIFM (1982i)

(*continued on next page*)

Table 8–2a (*continued*)

Material	Method	Concentration	Species	Results	References
	Maximization test	Induction: 0.0375% in 0.01% DOBS/saline (intradermal), 0.25% in acetone/PEG (percutaneous) challenge: 0.025–2.5% in acetone/PEG	Guinea pig (control: 4, test groups: 10)	sensitizing after 2nd challenge at 2.5%	RIFM (1982i)
	Maximization test	Induction: 0.0075% in 0.05% SLS (intradermal), 0.05% in 0.2% SLS (percutaneous) challenge: 0.025–2.5% in acetone/PEG	Guinea pig (control: 4, test groups: 10)	sensitizing	RIFM (1982r)
	Maximization test	Induction: 0.00375% in 0.05% SLS (intradermal), 0.25% in 0.2% SLS (percutaneous) challenge: 0.025–2.5% in acetone/PEG	Guinea pig (control: 4, test groups: 10)	sensitizing	RIFM (1983f)
	Maximization test	Induction: 0.00375% in 0.05% SLS (intradermal), 0.025% in 0.2% SLS (percutaneous) challenge: 0.025–2.5% in acetone/PEG	Guinea pig (control: 4, test groups: 10)	Not sensitizing	RIFM (1982s)
	modified Buehler test induction: occluded patch, 0.3 ml, 6 h once a week for three weeks; challenge: 2 weeks after last induction, 6 h, 0.3 ml, occluded patch	induction: 1% in 80% ethanol challenge: 0.5, 1.5, 5% in DEP controls: 1.5, 5% in DEP	guinea pig (control: 5/sex, test group: 10/sex)	Mean severity of skin scores (24, 48 h): 5%: 0.4, 0.4, control: 0.2, 0 (2/10) 1.5%: 0.4, 0.3, control: 0.1, 0.1 0.5%: 0.2 sensitizing	RIFM (1986b)
	modified Buehler test induction: occluded patch, 0.3 ml, 6 h once a week for three weeks; challenge: 2 weeks after last induction, 6 h, 0.3 ml, occluded patch	induction: 2.5% in 80% ethanol; challenge: 2.5% in acetone	guinea pig (control: 9, test group: 20)	Mean severity of skin scores (24, 48 h): 0.7, 0.5, control 0, 0.1 (3/10) sensitizing	RIFM (1985b)
	Modified Buehler test induction: occluded patch, 0.1 ml, 24 h, 10 applications on alternate days during three weeks; challenge: 2 weeks after last induction, 24 h occluded patch	10% in PEG	Guinea pig ($n = 11$)	Not sensitizing (n.f.i.)	RIFM (1971d)
	Modified Draize test (only 1 intradermal injection, each 2.5 times the intradermal concentration giving slight but perceptible irritation but no edema; 14 days later challenge, if no reactions at first challenge, induction and challenge were repeated), scoring 24 h after application	induction: 4 x 0.1 ml, 0.25% challenge: 0.1%, (intradermal), 5% (percutaneous, open), vehicle: n.f.i.	Guinea pig (control: 4, test group: 10)	sensitizing after second treatment	Sharp (1978)
	Modified Draize test as above, additionally: after repeated induction and challenge a confirmatory challenge was done 7 days later	Induction: 4 x 0.1 ml, 0.2% in 0.01% DOBS/saline, challenge: 0.08% in 0.01% DOBS/saline (intradermal), 4% in absolute alcohol (percutaneous, open)	guinea pig (control: 4, test group: 10)	Not sensitizing	RIFM (1977g)
	OET	Induction: 3, 10, 30, 100% 1st and 2nd challenge: 30% vehicle: ethanol	Guinea pig (3/sex/group)	Not sensitizing 100%: due to severe discoloration at the application areas, erythema could not be observed exactly	RIFM (1985a)
	FCAT	Induction: 5% in FCA (intradermal) challenge: "non-irritating concentration" in ethanol, n.f.i. (percutaneous)	Guinea pig (control: 10, test group:10)	sensitizing	RIFM (1985a)
Isojasmone	Maximization test	Induction: 5% in propylene glycol (intradermal), 25% in petrolatum (percutaneous) challenge: 5, 10% in petrolatum	Guinea pig (control: 5, test group: 10)	10%: positive reactions in 10/10 5%: positive reactions in 6/10 mildly senstizing	RIFM (1982k)
	OET	Induction: n.f.i. challenge: 8% vehicle: n.f.i.	Guinea pig ($\geqslant$6/group)	Not sensitizing	Klecak (1985)
cis-Jasmone	Maximization test	Induction: 10% challenge: 10% vehicle: n.f.i.	Guinea pig (n.f.i.)	Not sensitizing	Ishihara et al. (1986)
	Maximization test	Induction: 3% in FCA (intradermal), 25% (percutaneous) in petrolatum challenge: 3% in petrolatum	Guinea pig (control: 6–8, test group: 6)	Not sensitizing	RIFM (1978k)
	Modified Buehler test induction: occluded patch, 0.1 ml, 24 h, 10 applications on alternate days during three weeks; challenge: 2 weeks after last induction, 24 h occluded patch	10% in PEG for both induction and challenge	Guinea pig ($n = 11$)	Not sensitizing (n.f.i.)	RIFM (1971d)

Table 8–2a (*continued*)

Material	Method	Concentration	Species	Results	References
	Draize test	Induction: 0.05 ml 0.1% in saline (intradermal) challenge: 0.5 ml 0.1% in saline	Guinea pig (control: 6–8, test group: 6)	Not sensitizing	RIFM (1978k)
	OET	100%, 30%, 10%, 3% in acetone	Guinea pig (control: 6–8, test group: 4)	Not sensitizing	RIFM (1978k)
	OET	Induction: 8% challenge: 8% vehicle: n.f.i.	Guinea pig (⩾6/group)	Not sensitizing	Klecak (1985)
	FCAT	Induction: 50% in FCA (intradermal) challenge: "non-irritating concentration" (percutaneous)	Guinea pig (control: 6–8, test group: 6)	Not sensitizing	RIFM (1978k)
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	Maximization test	Induction: 10% in FCA (intradermal), 100% (percutaneous) challenge: 100%	Guinea pig (control: 20, test groups: 20)	Not sensitizing	RIFM (1989f)
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one *Methyl ester*	OET	Induction: n.f.i. challenge: 4% vehicle: n.f.i.	Guinea pig (⩾6/group)	Not sensitizing	Klecak (1985)
Methyl dihydrojasmonate	Maximization test	Induction: 5% in 0.01% DOBS/saline (intradermal), 100% (percutaneous) challenge: 40% in ethanol (5 challenges)	Guinea pig (control: 4, test group: 10)	sensitizing after 3rd challenge	RIFM (1981h)
	Maximization test	Induction: 4% in 0.01% DOBS/saline (intradermal), 100% (percutaneous) challenge: 40% in ethanol	Guinea pig (control: 4, test group: 10)	sensitizing	RIFM (1981i)
	Maximization test	Induction: 2.5% in 0.01% DOBS/saline (intradermal), 100% (percutaneous) challenge: 40% in ethanol	Guinea pig (control: 4, test group: 10)	sensitizing	RIFM (1979f)
	Maximization test	Induction: 2.5% in 0.01% DOBS/saline (intradermal), 100% (percutaneous) challenge: 40% in ethanol (4 challenges)	Guinea pig (control: 4, test group: 10)	sensitizing after 4^{th} challenge	RIFM (1980p)
	Maximization test	Induction: 2.5% in 0.01% DOBS/saline (intradermal), 100% (percutaneous) challenge: 40% in ethanol	Guinea pig (control: 4, test group: 10)	Not sensitizing	RIFM (1981i)
	Maximization test	Induction: 1% in DOBS/saline (intradermal), 100% (percutaneous) challenge: 40% in acetone/PEG	Guinea pig (control: 4, test group: 10)	Not sensitizing	RIFM (1982l)
	Maximization test	Induction: 1% in DOBS/saline (intradermal), 100% (percutaneous) challenge: 40% in acetone/PEG (2 challenges), 100%	guinea pig (control: 4, test group: 10)	Not sensitizing	RIFM (1982m)
	Maximization test	Induction: 1% in DOBS/saline (intradermal), 100% (percutaneous) challenge: 40% in acetone/PEG	Guinea pig (control: 4, test group: 10)	Not sensitizing	RIFM (1982n)
	Maximization test	Induction: 1% in 0.01% DOBS/saline (intradermal), 100% (percutaneous) challenge: 100%	Guinea pig (control: 4, test group: 10)	Not sensitizing	RIFM (1986c)
	Modified Buehler test induction: occluded patch, 0.1 ml, 24 h, 10 applications on alternate days during three weeks; challenge: 2 weeks after last induction, 24 h occluded patch	10% in PEG	Guinea pig (n = 11)	Not sensitizing (n.f.i.)	RIFM (1971d)
	Maximization test	10% in alcohol SDA 39C	Guinea pig (n = 10)	Not sensitizing	RIFM (1980g)

DEP: Diethyl phthalate.
DOBS: Dodecylbenzene sulfonate.
FCAT: intradermal test with Freund's Complete Adjuvant (FCA).
n.f.i.: no further information.
OET: Open epicutaneous test.
PEG: Polyethylene glycol.
SLS: sodium lauryl sulfate.

For one material, a concentration without sensitizing effect was not determined: In a HRIPT, 10% 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one produced positive reactions in 1 of 50 volunteers. A rechallenge was not performed and lower concentrations were

Table 8–2b
Local lymph node assays (LLNA).

Material	Method	Concentration	Species(No./group)	Results	References
2-Heptylidenecyclopentan-1-one	LLNA	2.5% 5.0% 10.0% 25.0% 50.0% In 1:3 ethanol:DEP		SI (2.5%) = 1.7 SI (5.0%) = 1.5 SI (10.0%) = 2.7 SI (25.0%) = 3.4 SI (50.0%) = 7.5 EC_3 = 16.4% (4100 μg/cm^2)	RIFM (2010b)
2-Hexylidene cyclopentanone	LLNA	0.1, 0.5, 1, 2.5, and 5% in 1:3 ethanol:DEP	CBA/CA mice (5 female)	SI (2.5%)=3.1 EC_3 = 2.4% (14.4 ug/cm^2) considered sensitizing, however SI (5%) was not in sensitizing range	RIFM (2008b)
Methyl ester					
Methyl dihydrojasmonate	LLNA, 0.025 ml, open, dorsal surface of the ear, 3 consecutive days	0, 1, 5, 10, 20, 40% in acetone/olive oil (4:1)	CBA/J female Mouse (controls: 8, test groups: 5)	SI (1–40%) < 3 EC_3 > 40% (>10,000 μg/cm^2) Not sensitizing	RIFM (2004c)

SI: Stimulation index.
LLNA: Local lymph node assay.
EC_3: Concentration of test material required to provoke a 3-fold increase in lymphocyte proliferation.

Table 9
Phototoxicity.

Material	Method	Concentration	Species	Results	References
2-Heptylcyclopentanone	Phototoxicity study single open application of 0.1 ml, 20 min later irradiation with UV light (300–400 nm, 12 J/cm^2) for 2 h 23 min, examination 3, 6, 24, 48 and 72 h after end of irradiation	10% in ethanol	Rat (10/group)	Not phototoxic	RIFM (1982e)
2-Hexylcyclopentanone	Phototoxicity study single open application of 0.1 ml, 20 min later irradiation with UV light (300–400 nm, 12 J/cm^2) for 2 h 29 min, examination 3, 6, 24, 48 and 72 h after end of irradiation	30% in ethanol	Rat (10/group)	Not phototoxic	RIFM (1982h)
2-Hexylidene cyclopentanone	Phototoxicity study single open application of 0.1 ml spread across slipped skin, 20 min later irradiation with UV light (300–400 nm, 7.4 J/cm^2) for 2 h 12 min, examination 3, 6, 24, 48 and 72 h after end of irradiation	10% in ethanol	Rat (10/group)	Not phototoxic	RIFM (1980o)
cis-Jasmone	Neutral Red Test 96 well plates (100 μl/well) were pre-incubated in the dark for 1 h, then one plate of cells received a radiation dose of 5 J/cm^{2}UVA while the other plate was kept in the dark for 50 min, cells were washed and incubated overnight and then both plates were treated with neutral red dye, uptake of the dye by the cells was measured after 3 h	7.8, 15.6, 31.3, 62.5, 125, 250, 500 and 1000 μg/ml dissolved in acetone	Balb/c 3T3 cells clone 31	photoinhibition factor (PIF) of 1 Not phototoxic	RIFM (2002)
2,2,5-Trimethyl-5-pentylcyclopentanone	Phototoxicity study single open application of 0.025 ml/cm^2, 30 min later irradiation with UV light (320–400 nm, 20 J/cm^2), duration not stated, examination 4, 24 and 48 h after application	3% in ethanol with 2% DMSO	Guinea pigs (10/group)	Not phototoxic	RIFM (1984a)
Methyl ester					
Methyl dihydrojasmonate	Phototoxicity study single open application of 0.1 ml, 20 min later excess test substance removed, irradiation with UV light (300–400 nm, 9.9 J/cm^2, at distance of 33 cm) for 3 h, examination 3, 6, 24, 48 and 72 h after treatment	100%	Rat (10/group)	Inconclusive	RIFM (1979n)
	Phototoxicity study single open application of 0.1 ml, 20 min later excess test substance removed, irradiation with UV light (300–400 nm, 9.94 J/cm^2, at a distance of 33 cm) for 3 h, examination 3,6,24,48 and 72 h after treatment	30% in ethanol	Rat (10/group)	Not phototoxic	RIFM (1979o)

DMSO: Dimethyl sulfoxide.

Table 10-1
Photosensitization in humans.

Material	Method	Concentration	Species	Results	References
3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one	Photosensitization study as part of HRIPT test (Draize Repeated Insult Patch Test) with 9 applications, irradiation with UVA (365 nm, 1680 mW/cm^2) for 15 min, irradiation applied at application 1, 4, 7, 9 and at challenge, challenge 24 h after last application	10% in white petrolatum	20 volunteers (4 males, 16 females)	Not photosensitizing	RIFM (1981d)
2-Pentylcyclopentan-1-one	Photosensitization study as part of a HRIPT (Draize-Shelanski Repeated Insult Patch Test modified) with 8 24-h applications starting at application day 4 of the HRIPT, irradiation with UV Hanovia lamp (20 inches from light source, wavelength and energy not stated) for 30 s 24 h after beginning of application, irradiation applied after application days 4, 5, 7, 8, 10 and after challenge, challenge 24 h after last application	10% in petrolatum	25 female volunteers	Not photosensitizing	RIFM (1978l)
	Photosensitization study as part of HRIPT with 0.5 ml, volunteers exposed to light (45 s at a distance of 20 inches) following the evaluation of the sensitization patch	10% in petrolatum	25 volunteers	Not photosensitizing	RIFM (1978e)
Methyl ester					
Methyl jasmonate	Photosensitization study as part of HRIPT test (Draize Repeated Insult Patch Test) with 9 applications, irradiation with UVA light (365 nm, 1680 mW/cm^2) for 15 min, irradiation applied at application days 1, 4, 7, 9 of the HRIPT and at challenge, challenge 24 h after last application	10%, vehicle not stated	20 volunteers (2 males, 18 females)	Not photosensitizing	RIFM (1980i)

HRIPT: Human repeated insult patch test.

Table 10-2
Photosensitization in animals.

Material	Method	Concentration	Species	Results	Reference
2,2,5-Trimethyl-5-pentylcyclopentanone	Photosensitization study Induction: intradermal FCA injection and topical administration of 0.1 ml, 30 min later irradiation with UVA light (320–400 nm, 10 J/cm^2) for 1 h 32 min, induction repeated 4 times within 2 weeks without FCA injection, control: only FCA during induction challenge on day 35: 0,025 ml ± UVA light irradiation, observations 24 and 48 h after challenge	Induction: 10% in ethanol challenge: 3% in ethanol	Guinea pigs (10/group)	Not photosensitizing	RIFM (1984b)

FCA: Freund's complete adjuvant.

not tested (RIFM, 1981d). To follow up on this study, an HRIPT on 100 subjects with 1% 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one in a vehicle of three parts diethyl phthalate to one part ethanol (3 DEP: 1 EtOH) was performed (RIFM, 2010a). No sensitization reactions were observed and the study therefore supports a QRA category 4 level of 0.5% based on a NESIL of 1100 μg/cm^2. An IFRA Standard restricting the use of this material as a fragrance ingredient was issued in June, 2011.

5.8.1.2. Diagnostic patch tests. When patch-tested with 5% 2-pentylcyclopentan-1-one in petrolatum, no positive reactions were found in patients with suspected contact dermatitis due to fragrance materials (Larsen et al., 2001).

In a patch test with methyl dihydrojasmonate, 1% and 5% in petrolatum were negative in 100 patients (Frosch et al., 1995), whereas in another patch test 5% in petrolatum elicited positive reactions in 9 of 1606 (0.6%) patients (Frosch et al., 2002). A patch test with 5% methyl dihydrojasmonate in 318 eczema patients elicited no positive reactions (Paulsen and Andersen, 2005).

5.8.2. Animal studies

5.8.2.1. Sensitization. Eleven of the cyclopentanones and cyclopentenones under review were tested in various animal tests for their contact sensitization potential. Results are shown in Table 8–2a. Results of the guinea pig maximization tests were reevaluated using the criteria defined in Kligman and Basketter (1995): Positive reactions were not counted if their strength diminished over time, and a substance was regarded as sensitizing, if at least 30% of test animals showed positive reactions (United Nations, 2007).

4% Dihydroisojasmone and 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one were negative in OETs (Klecak, 1985). In a modified Buehler test, undiluted 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone was also negative for sensitization (RIFM, 1991b). 2-Heptylcyclopentanone was negative in a guinea pig maximization test with a challenge concentration of 1% (RIFM,

Table 11
Summary of UV spectra data.

Material	UV spectra range of absorption (nm)
Cyclopentanone	Peaked at 280–300, return to baseline by 330
2-Cyclopentylcyclopentanone	N/A
Cyclotene propionate	N/A
Didhydroisojasmone	Peaked at 220–240, return to baseline by 260
2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone	N/A
3-Ethyl-2-hydroxy-2-cyclopenten-1-one	N/A
2-Heptylcyclopentanone	Peaked at 290–300, return to baseline by 330
2-Heptylidenecyclopentan-1-one	N/A
Hexenylcyclopentanone	N/A
2-Hexylcyclopentanone	N/A
2-Hexylidene cyclopentanone	Peaked at 240–260, return to baseline by 280
2-Hydroxy-3,4-dimethyl-2-cyclopenten-1-one	N/A
Isojasmone	Peaked at 220–240, return to baseline by 280
cis-Jasmone	N/A
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	Peaked at 200–220, return to baseline by 240
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one	Peaked at 230–250, return to baseline by 270
3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one	N/A
3-Methyl-2-pentylcyclopentan-1-one	N/A
3-Methyl-2-(pentyloxy)- 2-cyclopenten-1-one	Peaked at 240–260, return to baseline by 290
2-Pentylcyclopentan-1-one	Peaked at 225–325, return to baseline by 330
2,2,5-Trimethyl-5-pentylcyclopentanone	N/A
Methyl dihydrojasmonate	Peaked at 285–295, return to baseline by 330
Methyl hexyl oxo cyclopentanone carboxylate	Peaked at 280–300, return to baseline by 330
Methyl jasmonate	N/A
Methyl 3-oxo-2-(pent-2-enyl) cyclopentaneacetate	N/A

N/A: UV absorption spectra were not available for these materials.

1980k) and in an OET with a challenge concentration of 10% (Klecak, 1985).

In six different guinea pig maximization tests, an intradermal induction concentration of 2% 2-hexylcyclopentanone followed by a topical induction application of 100% 2-hexylcyclopentanone and challenge doses of 5–25% resulted in sensitization responses ranging from none to weak. Mostly, positive reactions at initial challenge could not be reproduced (RIFM, 1982g,q, 1983b,c,d,e). Judging from the structure of the substance, a sensitization potential is not plausible. 2-Hexylcyclopentanone is probably not a sensitizer or is a weak sensitizer in this test system.

In eleven guinea pig maximization tests, intradermal induction concentrations of 0.00375–0.8% 2-hexylidene cyclopentanone followed by a topical induction application of 0.025–5% and up to 4 challenge doses of 0.0025–2.5% resulted in responses ranging from none to strong. It was not considered a sensitizer in a study using an intradermal injection of 0.00375% followed by a topical induction application of 0.025% and challenge doses from 0.025% to 2.5%. Strong sensitization reactions were noted in studies with an intradermal induction with 0.75%, followed by a topical induction application of 5% and challenge doses of 0.0025–2.5% (RIFM, 1982j,i). A weak response was seen in most of the other studies (RIFM, 1980n, 1981e, 1982s,r,i, 1983f). 2-Hexylidene cyclopentanone was identified as skin sensitizer in a variety of other assays including the modified Buehler test (RIFM, 1985b, 1986b), modified Draize test (Sharp, 1978), closed epicutaneous test (RIFM, 1985c), and intradermal test with Freund's Complete Adjuvant (FCA) (RIFM, 1985a). No responses were, however, observed with induction concentrations up to 100% and a challenge concentration of 30% in the OET (RIFM, 1985a).

Isojasmone was negative using a challenge concentration of 10% in a guinea pig maximization test (RIFM, 1982k). No reactions were observed in the OET using 8% as challenge concentration (Klecak, 1985).

cis-Jasmone was negative in a guinea pig maximization tests with 10% as induction and challenge concentration (Ishihara et al., 1986), and with 3% as induction and challenge (RIFM, 1978k). No reactions were observed in a modified Buehler test using 10% as challenge concentration (RIFM, 1971d) and in OETs with 8% (Klecak, 1985) or 3%, 10%, 30% or 100% (RIFM, 1978k). It was not sensitizing in a Draize test with 0.1% induction and challenge (RIFM, 1978k) or in a Freund's Complete Adjuvant Test (FCAT) with 50% induction and a challenge of "non-irritating concentration" (RIFM, 1978k).

2-(*p*-Menth-1-ene-10-yl) cyclopentanone was not sensitizing in a guinea pig maximization test with intradermal induction of 10% followed by 100% topical induction and a challenge of 100% (RIFM, 1989f).

Methyl dihydrojasmonate was negative in the modified Buehler test with 10% (RIFM, 1971d). In guinea pig maximization tests, intradermal induction concentrations of 1–5% followed by a topical induction application of undiluted methyl dihydrojasmonate and up to 5 challenge doses of 5–100% resulted in responses ranging from none to strong (RIFM, 1979f, 1980p, 1981g,h,i, 1982l,m,n, 1986c).

Methyl jasmonate was negative in a guinea pig maximization test with 10% (RIFM, 1980g).

5.8.2.2. Local lymph node assays. After repeated application in a local lymph node assay (LLNA), 40% methyl dihydrojasmonate did not produce irritation at the dorsal surface of the ear of mice and the increase of ear thickness was less than 10%, indicating no irritation potential as well (RIFM, 2004c).

An LLNA with 0.1%, 0.5%, 1%, 2.5% and 5% 2-hexylidene cyclopentanone in 1:3 EtOH:DEP was performed on groups of 5 female CBA/CA mice. The concentration of test material required to provoke a threefold increase in lymphocyte proliferation was determined to be 2.4%. At the 2.5% dose level, the stimulation index was found to be greater than 3, indicating skin sensitizing activity. However, the authors noted that at the highest dose level (5%), the stimulation index was 2.5, a value which is not in the skin sensitization range (RIFM, 2008b).

In an LLNA with 2.5%, 5%, 10%, 25% and 50% 2-heptylidenecyclopentan-1-one, stimulation indices of 1.7, 1.5, 2.7, 3.4 and 7.5, respectively, were obtained. The concentration of test material required to provoke a threefold increase in lymphocyte proliferation (EC_3) value was 16.4% (4100 μg/cm^2) (RIFM, 2010b). Based on these results, an IFRA Standard for 2-heptylidenecyclopentan-1-one has been issued. The Standard sets concentration limits for

the 11 categories of fragrance products between 0.01% and 2.5%, and is based on a NESIL of 1000 μg/cm^2 (IFRA, 2011).

5.9. Phototoxicity and photosensitization

Limited data were available with regard to the phototoxicity and photosensitization of cyclopentanones and cyclopentenones (see Tables 9, 10-1, 10-2). UV spectra have been obtained for 12 materials (methyl dihydrojasmonate, cyclopentanone, 2,5,5-trimethyl-5-pentylcyclopentanone, 2-cyclopenten-1-one, 3-methyl-2-(pentyloxy), 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one, 2-hexylidene cyclopentanone, 2-pentylcyclopentan-1-one, isojasmone, 2-(*p*-menth-1-ene-10-yl) cyclopentanone, 2-heptylcyclopentanone, methyl hexyl oxo cyclopentanone carboxylate, and dihydroisojasmone). Most have peak UV absorbance well below the UVB range of 290–320 nm and return to baseline by 290 nm. In general, the materials that do absorb light in the UVB range, have only minor absorbance (see Table 11).

5.9.1. Phototoxicity

From human and animal studies, reliable data were available on the phototoxicity of 2-heptylcyclopentanone, 2-hexylcyclopentanone, 2-hexylidene cyclopentanone, *cis*-jasmone, 2,2,5-trimethyl-5-pentylcyclopentanone and the methyl ester methyl dihydrojasmonate.

No phototoxic reactions were observed in guinea pigs exposed to 3% 2,2,5-trimethyl-5-pentylcyclopentanone, 10% 2-heptylcyclopentanone, 10% 2-hexylidene cyclopentanone, 30% 2-hexylcyclopentanone followed by irradiation with UVA light (RIFM, 1980o, 1982h,e, 1984a). Concentrations of 30% methyl dihydrojasmonate in ethanol were not phototoxic (RIFM, 1979o). Undiluted methyl dihydrojasmonate resulted in edema 6 h after treatment in rats. The level of edema was significantly greater than control groups; however, the differences were not statistically significant 24 h and 48 h after treatment. There were no other significant differences among treatment groups. The differences in the levels of reaction were minimal and not considered conclusive evidence of phototoxicity (RIFM, 1979n).

cis-Jasmone, at concentrations ranging from 7.8–1000 μg/ml, was not considered phototoxic when the neutral red dye test was performed on Balb/c 3T3 clone 31 cells after a radiation dose of 5 J/cm^2 UVA for 50 min (RIFM, 2002).

5.9.2. Photosensitization

3-Methyl-2-(pentyloxy)-2-cyclopenten-1-one, 2-pentylcyclopentan-1-one, 2,2,5-trimethyl-5-pentylcyclopentanone and the methyl ester methyl jasmonate were tested for photosensitization.

5.9.2.1. Human studies. No photosensitization was seen in volunteers treated with 10% 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one in white petrolatum (RIFM, 1981d), 10% 2-pentylcyclopentan-1-one in petrolatum (RIFM, 1978l,e), and 10% methyl jasmonate (vehicle not stated) (RIFM, 1980i).

5.9.2.2. Animal studies. 2,2,5-Trimethyl-5-pentylcyclopentanone was tested for its photosensitization in a reliable test with guinea pigs (RIFM, 1984b). No photosensitization was seen in the animals once injected with FCA followed by topical administration of 10% 2,2,5-trimethyl-5-pentylcyclopentanone, irradiation with UVA light and challenge with 3% 2,2,5-trimethyl-5-pentylcyclopentanone.

Based on the UV spectra and review of phototoxicity/photosensitization data, cyclopentanones and cyclopentenones with the exception of methyl dihydrojasmonate would not be expected to elicit phototoxicity or photosensitization under the current conditions of use as a fragrance ingredient.

6. Conclusion

Only cyclopentanone and 2-hexylidene cyclopentanone have been examined in metabolic studies.

The main pathways are:

- reduction of the keto group to the alcohol,
- conjugation of the alcohol with sulfate or glucuronic acid,
- addition of glutathione to compounds with an α,β-conjugated double bond,
- excretion of the conjugates in the urine.

In addition, side-chain oxidation and reduction of the double bond are expected. As to the methyl esters under review, it is plausible that the ester bond is hydrolyzed by carboxylesterases to methanol and the corresponding acid. Methanol is subsequently oxidized to formaldehyde and formic acid in the organism, the acid may be conjugated and excreted. Studies on the metabolism of the four esters under review are not available.

The cyclopentanones and cyclopentenones have not been evaluated at exposure levels other than those reported in this group summary. Use of these fragrance ingredients beyond the higher maximum dermal levels or higher systemic exposure levels requires reevaluation by the panel. Safety concerns regarding the cyclopentanones and cyclopentenones are not indicated under the reported levels of exposure for their use in fine fragrances and consumer products. Since all the short term and repeated dose studies revealed a low toxicity, this conclusion applies both to the cyclopentanone and cyclopentenone group of fragrance ingredients and their metabolites.

The panel is of the opinion that there are no safety concerns regarding cyclopentanones and cyclopentenones under the present declared levels of use and exposure for the following reasons:

- The cyclopentanones and cyclopentenones evaluated have a low order of acute toxicity. Most rabbit dermal, and mouse and rat oral LD_{50} values exceed 2000 mg/kg body weight with the majority of values being greater than 5000 mg/kg body weight.
- Four materials were tested for repeated dose toxicity. Methyl dihydrojasmonate is of low systemic toxicity upon 90-day repeated oral application with a NOAEL of 100 mg/kg body weight per day in rats, the highest dose tested. In a 13-week study with 2-hexylidene cyclopentanone, the only tested dose of 3 mg/kg body weight/day did not induce any toxicity. In a 28 day dermal toxicity test in rats, 2-(*p*-menth-1-ene-10-yl) cyclopentanone, had a NOEL of 1000 mg/kg body weight per day, the highest dose tested. In a repeat dose inhalation study in rats, cyclopentanone (6 h/day, 5d/week, 15 weeks) at the highest dose tested (300 p.p.m.) resulted in no reactions and no appreciable organ toxicity.
- Nine materials were tested for mutagenicity in bacteria and proved negative: cyclopentanone, dihydroisojasmone, 2-heptylcyclopentanone, 2-hexylidene cyclopentanone, *cis*-jasmone, 2-(*p*-menth-1-ene-10-yl) cyclopentanone, 2-pentylcyclopentan-1-one and the methyl esters methyl dihydrojasmonate and methyl hexyl oxo cyclopentanone carboxylate. 2-Ethyl-2-hydroxy-2-cyclopenten-1-one and *cis*-jasmone were negative in sister chromatid exchange assays. Methyl dihydrojasmonate was also inactive in mouse lymphoma tests and a chromosome aberration test. It could be expected that materials with a reactive conjugated double bond might be genotoxic, but the alpha,beta-unsaturated ketones dihydroisojasmone, 2-hexylidene cyclopentanone and *cis*-jasmone were not mutagenic in bacteria. It is expected therefore, that the other alpha,beta-unsaturated compounds of this group are not genotoxic.

Table 12
Calculated margin of safety.

Material	Dermal systemic exposure (mg/kg/d)	No Effect Level (mg/kg body weight/d)	Method	Result = no effect level/ systemic exposure (assumes 100% dermal absorption)	References[c]
Cyclopentanone	0.0005[a]	50	Developmental toxicity, gavage, gestational day 6–15	100,000	Rusch et al. (1988)
2-Cyclopentylcyclopentanone	0.0005[a]	50[b]	n/a	100,000	n/a
Cyclotene propionate	0.0005[a]	50[b]	n/a	100,000	n/a
Didhydroisojasmone	0.0041	50[b]	n/a	12,195	n/a
2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone	0.0005[a]	50[b]	n/a	100,000	n/a
3-Ethyl-2-hydroxy-2-cyclopenten-1-one	0.0005[a]	50[b]	n/a	100,000	n/a
2-Heptylcyclopentanone	0.0209	50[b]	n/a	2,392	n/a
2-Heptylidenecyclopentan-1-one	0.0005[a]	50[b]	n/a	100,000	n/a
Hexenylcyclopentanone	0.0005[a]	50[b]	n/a	100,000	n/a
2-Hexylcyclopentanone	0.0008	50[b]	n/a	62,500	n/a
2-Hexylidene cyclopentanone	0.0003	50[b]	n/a	166,667	n/a
2-Hydroxy-3,4-dimethyl-2-cyclopenten-1-one	0.0005	50[b]	n/a	100,000	n/a
Isojasmone	0.0003	50[b]	n/a	166,667	n/a
cis-Jasmone	0.0094	50[b]	n/a	5,319	n/a
2-(*p*-Menth-1-ene-10-yl) cyclopentanone	0.0199	1000	Repeat dose toxicity, dermal, 28 day	50,251	RIFM (1989c)
3-Methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one	0.0028	50[b]	n/a	17,857	n/a
3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one	0.0069	50[b]	n/a	7,246	n/a
3-Methyl-2-pentylcyclopentan-1-one	0.0005[a]	50[b]	n/a	100,000	n/a
3-Methyl-2-(pentyloxy)- 2-cyclopenten-1-one	0.0025	50[b]	n/a	20,000	n/a
2-Pentylcyclopentan-1-one	0.0008	50[b]	n/a	62,500	n/a
2,2,5-Trimethyl-5-pentylcyclopentanone	0.0059	50[b]	n/a	8,475	n/a
Methyl dihydrojasmonate	0.7122	80	Developmental toxicity, gavage, gestational day 7–20	112	RIFM (2007)
Methyl hexyl oxo cyclopentanone carboxylate	0.0596	50[b]	n/a	839	n/a
Methyl jasmonate	0.0015	50[b]	n/a	33,333	n/a
Methyl 3-oxo-2-(pent-2-enyl) cyclopentaneacetate	0.0063	50[b]	n/a	7,937	n/a

[a] A default value of 0.02% was used to calculate dermal systemic exposure.
[b] When not available for a particular material, the lowest no effect level for the group is used instead.
[c] Reference cited is for the study where the no effect level was determined; n/a indicates that a no effect level was not available, hence there is no study to cite.

- Most of the cyclopentanones and cyclopentenones have been well studied for their potential skin irritation in humans. Minimal, if any, evidence of skin irritation in humans is associated with current levels of use. Highest concentrations in consumer products were reported for methyl dihydrojasmonate (13%), which is non-irritating up to concentrations of 20% in humans. Concentrations for other materials are below 1% (Table 1). The no adverse effect concentrations (NOAECs) are higher than the highest concentrations of the materials applied to skin.
- Eleven cyclopentanones and cyclopentenones and two methyl esters were tested undiluted for eye irritation. 2-Heptylcyclopentanone, 2-heptylidenecyclopentan-1-one, 2-hexylidene cyclopentanone, isojasmone, *cis*-jasmone, 2-(*p*-menth-1-ene-10-yl) cyclopentanone, 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one, 2,2,5-trimethyl-5-pentylcyclopentanone and the methylesters methyl dihydrojasmonate and methyl jasmonate were not irritating to the eye. Undiluted cyclopentanone, 2-hexylcyclopentanone and 2-pentylcyclopentan-1-one are eye irritants. Twenty percent 2-pentylcyclopentan-1-one in corn oil and 1% *cis*-jasmone in alcohol SDA 39C are not considered eye irritating. The irritation potential of 1% 3-methyl-2-(*n*-pentanyl)-2-cyclopenten-1-one cannot be assessed with certainty, because the vehicle used is itself a mild eye irritant in the same test. Nevertheless, from these studies it can be deduced, that this substance is at most a mild eye irritant in the concentration tested.
- Sixteen substances were tested with respect to sensitization in humans. Concentrations of 1% 2-hexylidene cyclopentanone and 10% 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one are sensitizing in humans. 2-Hexylidene cyclopentanone is a weak sensitizer. Its use in fragrance materials is restricted by an IFRA Standard. In the 11 fragrance product categories the concentration limits for 2-hexylidene cyclopentanone ranged from 0.01% to 0.2%. Additionally, based on the results of a recent LLNA, an IFRA Standard for 2-hepylidenecyclopentan-1-one has been issued. The Standard sets concentration limits for the 11 categories of fragrance products between 0.01% and 2.5%. 0.6% 2-hexylidene cyclopentanone did not induce skin sensitization and the maximum concentration applied to skin is 0.01%, well below sensitizing concentrations. For 3-methyl-2-(pentyloxy)-2-cyclopenten-1-one, a new HRIPT supports a QRA category 4 level of 0.5%. An IFRA Standard has recently been issued restricting its use as a fragrance ingredient. Fourteen materials are non-sensitizing in HRIPT or maximization tests; the concentrations tested are generally higher than the maximum concentrations applied to skin. Undiluted 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone was not tested in humans, but was negative in the modified Buehler test. No sensitization tests are available on 2-cyclopentylcyclopentanone and methyl 3-oxo-2-(pent-2-enyl) cyclopentaneacetate. These materials are not chemically reactive. 2-Cyclopentylcyclopentanone is an alkylated cyclopentanone and will have a similar biochemical pathway as methyl dihydrojasmonate. The molecular structure and physical chemical properties are very similar to 2-pentylcyclopentan-1-one. Both molecules are cyclopentanones with a saturated five carbon group attached at the 2 position. The molecular weight differs by only two mass units with similar octanol water partition coefficients. 2-Pentylcyclopentan-1-one is not a dermal sensitizer in humans when tested at 10% and no contact allergy was observed in patients with fragrance

contact dermatitis. Methyl-3-oxo-2-(pent-2-enyl) cyclopentaneacetate is nearly identical to methyl jasmonate, which shows no dermal sensitization potential in humans up to 10% and in guinea pigs. The non-conjugated double bond is expected to have an insignificant effect on the overall biochemical outcome of this material when compared with methyl dihydrojasmonate. In addition to this, the use of each of these materials is only < 1 metric tons/year worldwide. Overall, the risk of sensitization to the cyclopentanones and cyclopentenones covered in this review seems to be small under current levels of use.

- No phototoxic and photosensitization reactions were seen with 9 cyclopentanones and cyclopentenones in humans or animals. A 30% solution of methyl dihydrojasmonate in ethanol was not phototoxic in rats. Undiluted methyl dihydrojasmonate resulted in edema 6 h after treatment in rats. The level of edema was significantly greater than control groups; however, the differences were not statistically significant 24 h and 48 h after treatment. There were no other significant differences among treatment groups. The differences in the levels of reaction were minimal and not considered conclusive evidence of phototoxicity. As methyl dihydrojasmonate is used frequently and there are no reports on phototoxic effects, the phototoxic potential in humans is considered low.
- To calculate margin of safety for the group of materials, the lowest NOEL of 100 mg/kg body weight (for a 13 week dietary repeat dose toxicity study on methyl dihydrojasmonate) is used as a representative worst-case scenario for the group (assuming 100% oral absorption). The dermal systemic exposure for this material is 0.7122 mg/kg body weight/day (this also happens to represent the highest exposure level for the group); the margin of safety is calculated to be 112. If a margin of safety of 100 were used, the maximum allowable exposure would be 1 mg/kg body weight/day. This is well above the reported dermal systemic exposures for all materials in the group.
- Table 12 shows calculated margin of safety for each of the materials in the group. For materials for which there was not a NOEL, the lowest no effect level for the group was used. Calculated margins of safety for all the materials in the group ranged from 112 to 166,667.

Conflict of Interest

This research was supported by the Research Institute for Fragrance Materials, an independent research institute that is funded by the manufacturers of fragrances and consumer products containing fragrances. The authors are all members of the Expert Panel of Research Institute for Fragrance Materials, an independent group of experts who evaluate the safety of the fragrance materials.

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