Food and Chemical Toxicology 62 (2013) S1–S44

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

A toxicological and dermatological assessment of alkyl cyclic ketones when used as fragrance ingredients ☆

The RIFM Expert Panel

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ARTICLE INFO

Keywords:
Group summary
Alkyl cyclic ketone
Toxicology
Dermatology
Assessment

ABSTRACT

The alkyl cyclic ketone (ACK) fragrance ingredients are a diverse group of structures with similar metabolic and toxicity profiles. ACK fragrance materials demonstrate low acute toxicity. Upon repeat dose testing, some adverse effects in biochemical and hematological parameters, and slightly increased liver and kidney weights were reported, primarily at high doses, resulting from adaptive effects. Developmental effects occurred only in the presence of maternal toxicity. Assays in bacteria and mammalian cell systems and the mouse micronucleus assay did not demonstrate genotoxicity. ACK fragrance ingredients are considered non-irritating to the skin of humans; results showed few reactions, most of which were equivocal or involved doses greater than those in consumer products. Mild to moderate eye irritation in animal tests was observed with most compounds; however, full recovery was usually observed. Human sensitization studies indicate that ACK fragrance ingredients have a low sensitization potential. Diagnostic patch-tests indicated low sensitizing potential in humans; except for fragrance materials which caused reactions at 1% or 5%. Phototoxicity and photosensitization were not demonstrated in humans, and, with the possible exception of acetyl cedrene, would not be expected. It is concluded that ACK materials do not present a safety concern at current levels of use as fragrance ingredients.

Contents

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http://dx.doi.org/10.1016/j.fct.2013.09.033

1. Introduction

In 2013, complete literature searches were conducted for the alkyl cyclic ketone (ACK) fragrance materials. This document provides safety assessment and critical evaluation of the pertinent data for the ACK fragrance materials currently used in commerce. This scientific evaluation focuses on dermal exposure, which is considered to be the primary route for fragrance materials. Toxicity, metabolism, and biological fate data from other exposures have been considered where relevant.

The evaluation of the ACK compounds in this safety assessment is supported by more detailed Fragrance Material Reviews (FMRs) published concurrently for each of the ACK fragrance ingredients. Appendix A lists materials in group summary without a corresponding FMR either because the material is structurally related, but not used as a fragrance ingredient or because it is a captive material (a material manufactured exclusively by one company). This 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 articles from 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 data are identified in tabular form in the group summary. Details that are provided in the tables are not always discussed in the text of the group summary. The separate FMRs, which cover individual fragrance materials, contain more comprehensive descriptions of all published and unpublished reports including complete bibliographies (Scognamiglio et al., in press-a, in press-b, in press-c, in press-d, in press-e, in press-f, in press-g, in press-h, in press-i, in press-j, in press-k, in press-l, in press-m, in press-n, in press-o, in press-p, in press-q, in press-r, in press-s).

2. Chemical identity, regulatory status, and exposure

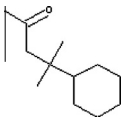
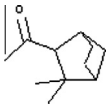
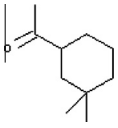
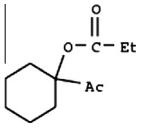
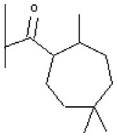
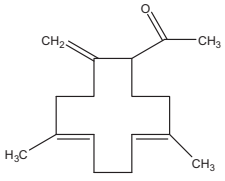
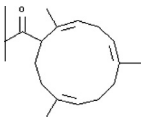
The ACK fragrance materials discussed in this report may be blended with each other and/or other chemical classes of fragrance ingredients and used in a variety of products that may include decorative cosmetics, fine fragrances, personal care products such as shampoos, soaps, and other toiletries, and household products such as cleaners and detergents. This safety assessment summarizes the animal and human toxicology data for oral, dermal, and inhalation exposures for the ACK compounds that are currently used as fragrance ingredients. The ACK data were integrated to determine the potential for human health effects and risks associated with the use of the ACK fragrance ingredients. This ACK group summary focuses primarily on available metabolism, toxicokinetic, and toxicity data for the dermal route of exposure; however, other routes of potential consumer exposure to fragrance ingredients, such as inhalation, were also evaluated.

This ACK safety assessment provides a comprehensive review of all the available information selected from a large bibliography of sponsored ACK studies and reports, which are maintained by the Research Institute of Fragrance Materials (RIFM) in a proprietary database. The ACK toxicology data reviewed herein include published and unpublished reports that were deemed to be appropriate and relevant for the objectives of this report. Data inclusivity was based on the following criteria: the purpose, clarity, and transparency of the protocols; the quality of the data; and the use of route(s) of potential human exposure. Group summaries of related ACK compounds, the ionone and damascene fragrance ingredients (Belsito et al., 2007) and the compound-specific FMRs have already been published and, when appropriate, these data may be cited.

Table 1 provides a list of the ACK fragrance ingredients and structurally related materials. This ACK group summary includes 23 synthetic fragrance materials that can be organized into two categories based on the following structural elements:

- Saturated alkyl cyclic ketones (4) in which either the alkyl or cyclic portion of the molecule does not contain any double bonds.
- Unsaturated alkyl cyclic ketones (19) in which either the alkyl or cyclic portion of the molecule has at least one double bond. This category is further subdivided based on structural similarities:
  - Unsaturated macrocyclic ring (2)
  - Unsaturated bicyclic ring (4)
  - Unsaturated 6-member ring not conjugated (6)
  - α, β-Unsaturated cyclic fused 3 or more members (1)
  - α, β-Unsaturated 5 or 6 member ring (4)
  - α, β-Unsaturated ketones with unsaturated ring (2)

Table 1
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]
Alkyl cyclic ketones					
Saturated alkyl cyclic ketones					
Cyclohexyl methyl pentanone $C_{12}H_{22}O$ CAS#: 4927-39-3 Log K_{ow}(calculated): 3.89 Molecular weight: 182.31 Vapor pressure: 0.107 mm Hg @ 25 °C Water solubility: 25.66 mg/l @ 25 °C	4-Cyclohexyl-4-methyl-2-pentanone; 4-Cyclohexyl-4-methylpentan-2-one; 1-(2-Methyl-4-oxopentyl)-2-cyclohexane; 2-Pentanone, 4-cyclohexyl-4-methyl-; Vetival		0.1–1	0.0068	0.03
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one $C_{11}H_{18}O$ CAS#: 42370-07-0 Log K_{ow}(calculated): 2.80 Molecular weight: 166.64 Vapor pressure: 0.303 mm Hg @ 25 °C Water solubility: 262.5 mg/l @ 25 °C	1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethanone; Ethanone, 1-(3,3-dimethylbicyclo[2.2.1]hept-2-yl)-; Camek DH		0.1–1	0.0005[e]	0.02[e]
1-(3,3-Dimethylcyclohexyl)ethan-1-one $C_{10}H_{18}O$ CAS#: 25304-14-7 Log K_{ow}(calculated): 2.91 Molecular weight: 154.53 Vapor pressure: 0.586 mm Hg @ 25 °C Water solubility: 239.8 mg/l @ 25 °C	1-(3,3-Dimethylcyclohexyl)ethanone; Ethanone, 1-(3,3-dimethylcyclohexyl)-; 1-Acetyl-3,3-dimethylcyclohexane; Dimac (Herbac)		1–10	0.0086	0.05
1-[1-(1-Oxopropoxy)cyclohexyl]-ethanone[f] $C_{11}H_{18}O_3$ CAS#: 82721-48-0 Log K_{ow}(calculated): N/A Molecular weight: 198.26 Vapor pressure: N/A Water solubility: N/A	1-Acetyl cyclohexyl propionate		0	0	0
1-(2,5,5-Trimethylcycloheptyl)ethan-1-one $C_{12}H_{22}O$ CAS#: 23361-88-8 Log K_{ow}(calculated): 3.81 Molecular weight: 182.07 Vapor pressure: 0.109 mm Hg @ 25 °C Water solubility: 29.66 mg/l @ 25 °C	Ethanone, 1-(2,5,5-trimethylcycloheptyl)-; 1-(2,5,5-Trimethylcycloheptyl)ethanone; Trimethyl Acetyl Cycloheptane		<0.01	0.0005[e]	0.02[e]
Unsaturated alkyl cyclic ketones					
Unsaturated macrocyclic ring					
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene $C_{17}H_{26}O$ CAS#: 144020-22-4 Log K_{ow}(calculated): 3.64 Molecular weight: 246.39 Vapor pressure: 0.00045 mm Hg @ 25 °C Water solubility: 4.8 mg/l @ 25 °C	Trimofix O		10–100	0.0358	0.81
Methyl 2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone $C_{17}H_{26}O$ CAS#: 28371-99-5 Log K_{ow}(calculated): 5.98 Molecular weight: 246.94 Vapor pressure: 0.000166 mm Hg @ 25 °C Water solubility: 0.1943 mg/l @ 25 °C	Ethanone, 1-(2,6,10-trimethyl-2,5,9-cyclododecatrien-1-yl)-; 1-(2,6,10-Trimethylcyclododeca-2,5,9-trien-1-yl)ethanone; Cyclisone		10–100	0.1	0.65

(*continued on next page*)

Table 1 (*continued*)

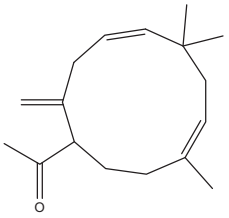
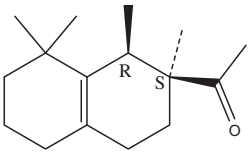
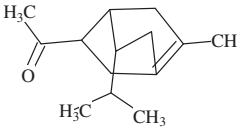
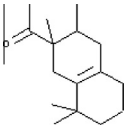
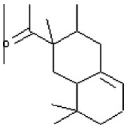
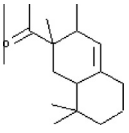
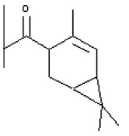
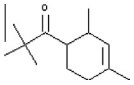
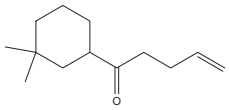
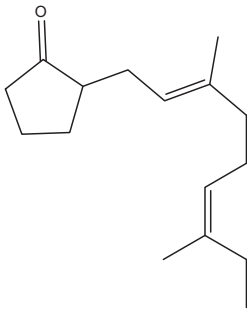
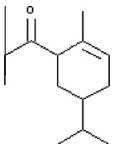
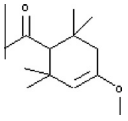
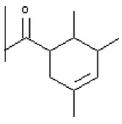
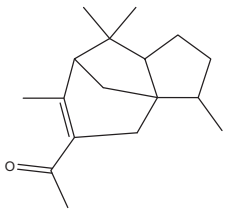
Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure (mg/kg/day)[b]	Maximum skin level (%)[c,d]
Alkyl cyclic ketones					
1-(6,6,9-Trimethyl-2-methylene-4,8-cycloundecadien-1-yl)-ethanone[f] $C_{17}H_{26}O$ CAS#: 55987-49-0 Log K_{ow}(calculated): 5.89 Molecular weight: 246.40 Vapor pressure: 0.000337 mm Hg @ 25 °C Water solubility: 0.2314 mg/l @ 25 °C	1-(6,6,9-Trimethyl-2-methylenecycloundeca-4,8-dien-1-yl)ethanone; 1-(6,6,9-trimethyl-2-methylenecycloundeca- 4,8-dien-1-yl)ethan-1-one		0	0	0
Unsaturated bicyclic ring					
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-,rel- $C_{16}H_{26}O$ CAS#: 185429-83-8 Log K_{ow}(calculated): N/A Molecular weight: 234.38 Vapor pressure: N/A Water solubility: N/A	Georgywood		Captive[i] – Givaudan		
1-[5(Or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one $C_{14}H_{22}O$ CAS#: 68259-33-6 Log K_{ow}(calculated): 4.20 Molecular weight: 206.29 Vapor pressure: 0.00929 mm Hg @ 25 °C Water solubility: 10.44 mg/l @ 25 °C	Ethanone, 1-[5(or 6)-methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]- ; Felvinone		0.1–1	0.0025	0.12
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone[g] $C_{16}H_{26}O$ CAS#: 54464-57-2 Log K_{ow}(measured): 5.6–5.7[h] Molecular weight: 234.38 Vapor pressure: 0.0011 mm Hg @ 25 °C Water solubility: 1.077 mg/l @ 25 °C	Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-; 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one; 1-(2,3,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethanone; OTNE; Amberonne; Boisvelone; Isocyclemone E; Iso E super		>1000	0.4604	8.17
1-(1,2,3,4,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one $C_{16}H_{26}O$ CAS#: 68155-67-9 Log K_{ow}(calculated): 4.71 Molecular weight: 234.83 Vapor pressure: 0.00151 mm Hg @ 25 °C Water solubility: 2.725 mg/l @ 25 °C	Ethanone, 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-; 1-(2,3,8,8-Tetramethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)ethanone		>1000	0.0005[e]	0.02[e]
1-(1,2,3,5,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one $C_{16}H_{26}O$ CAS#: 68155-66-8 Log K_{ow}(calculated): 4.71 Molecular weight: 234.83 Vapor pressure: 0.00151 mm Hg @ 25 °C Water solubility: 2.725 mg/l @ 25 °C	Ethanone, 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-; 1-(2,3,8,8-Tetramethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)ethanone		>1000	0.0005[e]	0.02[e]
Unsaturated 6-member ring not conjugated					
Acetylcarene $C_{12}H_{18}O$ CAS#: 3608-11-5 Log K_{ow}(calculated): 3.47 Molecular weight: 178.28 Vapor pressure: 0.0886 mm Hg @ 25 °C Water solubility: 61.11 mg/l @ 25 °C	Car-2-en-4-yl methyl ketone; Ethanone, 1-(4,7,7-trimethylbicyclo[4.1.0]hept-4-en-3-yl)-; 1-(4,7,7-Trimethylbicyclo[4.1.0]hept-4-en-3-yl)ethanone; Carenko		<0.01	0.0010	0.002

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure (mg/kg/day)[b]	Maximum skin level (%)[c,d]
Alkyl cyclic ketones					
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one $C_{13}H_{22}O$ CAS#: 69929-17-5 Log K_{ow}(calculated): 4.15 Molecular weight: 194.18 Vapor pressure: 0.0466 mm Hg @ 25 °C Water solubility: 13.45 mg/l @ 25 °C	1-Propanone, 1-(2,4-dimethyl-3-cyclohexen-1-yl)-2,2-dimethyl-		0.01–0.1	0.0005[e]	0.02[e]
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one $C_{13}H_{22}O$ CAS#: 56973-87-6 Log K_{ow}(calculated): 4.24 Molecular weight: 194.32 Vapor pressure: 0.031 mm Hg @ 25 °C Water solubility: 11.13 mg/l @ 25 °C	4-Penten-1-one, 1-(3,3-dimethylcyclohexyl)-; Galbaniff		1–10	0.0003	0.002
2-(3,7-Dimethyl-2,6-nonadien-1-yl)-cyclopentanone $C_{16}H_{26}O$ CAS#: 1206769-45-0 Log K_{ow}(calculated): N/A Molecular weight: 234.38 Vapor pressure: N/A Water solubility: N/A	Miranone		0.01–0.1	0.0005[e]	0.02[e]
1-(*para*-Menthen-6-yl)-1-propanone $C_{13}H_{22}O$ CAS#: 31375-17-4 Log K_{ow}(calculated): 4.18 Molecular weight: 194.32 Vapor pressure: 0.0381 Hg @ 25 °C Water solubility: 12.49 mg/l @ 25 °C	1-(5-Isopropyl-2-methylcyclohex-2-en-1-yl)propan-1-one; Menthenyl ketone; 1-(*p*-Menth-1-en-6-yl)propan-1-one; 1-Propanone, 1-[2-methyl-5-(1-methylethyl)-2-cyclohexen-1-yl]-; Nerone		0.1–1	0.0019	0.03
1-(4-Methoxy-2,2,6,6-tetramethyl-3-cyclohexen-1-yl)ethan-1-one[f] $C_{13}H_{22}O_2$ CAS#: 16556-48-2 Log K_{ow}(calculated): 2.85 Molecular weight: 210.17 Vapor pressure: 0.0149 mm Hg @ 25 °C Water solubility: 141.8 mg/l @ 25 °C	Ethanone, 1-(4-methoxy-2,2,6,6-tetramethyl-3-cyclohexen-1-yl)-; 1-(4-Methoxy-2,2,6,6-tetramethylcyclohex-3-en-1-yl)ethanone; 4-Acetyl-1-methoxy-3,3,5,5-tetramethyl-1-cyclohexene		0	0	0
1-(3,5,6-Trimethyl-3-cyclohexen-1-yl)ethan-1-one $C_{11}H_{18}O$ CAS#: 68480-14-8 Log K_{ow}(calculated): 3.20 Molecular weight: 166.64 Vapor pressure: 0.176 mm Hg @ 25 °C Water solubility: 118 mg/l @ 25 °C	Ethanone, 1-(3,5,6-trimethyl-3-cyclohexen-1-yl)-; 1-(3,5,6-Trimethylcyclohex-3-en-1-yl)ethanone; Methyl Cyclo Citrone		0.01–0.1	0.0005[e]	0.02[e]
α,β-unsaturated cyclic fused 3 or more members					
Acetyl cedrene $C_{17}H_{26}O$ CAS#: 32388-55-9 Log K_{ow}(calculated): 5.02 Molecular weight: 246.39 Vapor pressure: 0.000573 mm Hg @ 25 °C Water solubility: 1.278 mg/l @ 25 °C	1-Cedr-8-en-9-ylethanone; Ethanone, 1-(2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H- 3a,7-methanoazulen-5-yl)-,[3R-(3α,3a*β*,7*β*, 8aα)]-; [3R-(3α,3a*β*,7*β*,8aα)]-1-(2,3,4,7,8,8a-Hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)ethan-1-one; Cedar ketone; Cedarwood oil, acetylated Coeur; Cedryl methyl ketone; Lixetone; Methyl cedryl ketone; Methyl Cedrylone; Vertofix		>1000	0.1368	3.90

(*continued on next page*)

Table 1 (*continued*)

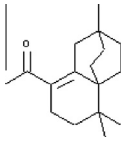
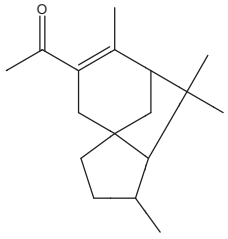
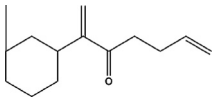
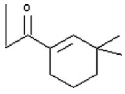
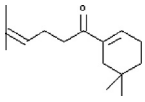
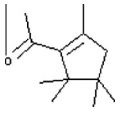
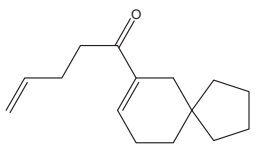
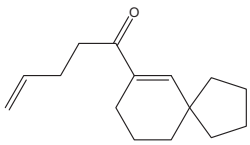
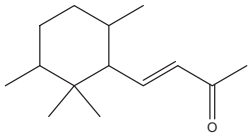
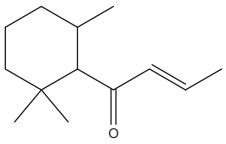
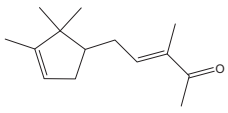
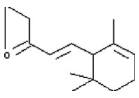
Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure (mg/kg/day)[b]	Maximum skin level (%)[c,d]
Alkyl cyclic ketones					
5-Acetyl-2,2,8-trimethyltricyclo(6.2.2.01,6) dodec-5-ene[f] $C_{17}H_{26}O$ CAS#: 32388-56-0 Log K_{ow}(calculated): 5.13 Molecular weight: 246.94 Vapor pressure: 0.000425 mm Hg @ 25 °C Water solubility: 1.031 mg/l @ 25 °C	Ethanone, 1-(1,3,4,4a,5,6,7-hexahydro-2,5,5-trimethyl-2H-2,4a-ethanonaphthalen-8-yl)-; 1-(1,3,4,4a,5,6,7-Hexahydro-2,5,5-trimethyl-2H-2,4a-ethanonaphthalen-8-yl)ethan-1-one; 1-(2,5,5-Trimethyl-1,3,4,5,6,7-hexahydro-2H-2,4a-ethanonaphthalen-8-yl)ethanone		0	0	0
1-(2,3,4,7,8,8a-Hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)ethan-1-one[f] $C_{17}H_{26}O$ CAS#: 68039-35-0 Log K_{ow}(calculated): 5.02 Molecular weight: 246.39 Vapor pressure: 0.000573 mm Hg @ 25 °C Water solubility: 1.278 mg/l @ 25 °C	1-Cedr-8-en-9-ylethanone; Ethanone, 1-(2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)-; 9-Acetyl-2,6,6,8-tetramethyltricyclo(5.3.1.01,5)undec-8-ene		0	0	0
α,β-Unsaturated 5 or 6 member ring					
2-Cyclohexyl-1,6-heptadien-3-one $C_{13}H_{20}O$ CAS#: 313973-37-4 Log K_{ow}(calculated): 4.9 Molecular weight: 192.3 Vapor pressure: N/A Water solubility:N/A	1,6-Heptadien-3-one, 2-cyclohexyl-; Cyclohexyl heptadienone; Pharaone		0.01–0.1	0.0005[e]	0.02[e]
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[f] $C_{10}H_{16}O$ CAS#: 22463-19-0 Log K_{ow}(calculated): 3.11 Molecular weight: 152.24 Vapor pressure: 0.426 mm Hg @ 25 °C Water solubility: 164.1 mg/l @ 25 °C	3,3-Dimethyl-1-cyclohexen-1-yl methyl ketone; Ethanone, 1-(3,3-dimethyl-1-cyclohexen-1-yl)-; 1-Acetyl-3,3-dimethyl-1-cyclohexene; Artemone		0	0	0
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one[g] $C_{13}H_{20}O$ CAS#: 56973-85-4 Log K_{ow}(calculated): 4.45 Molecular weight: 192.02 Vapor pressure: 0.0187 mm Hg @ 25 °C Water solubility: 7.642 mg/l @ 25 °C	1-(5,5-Dimethylcyclohex-1-en-1-yl)pent-4-en-1-one; 4-Penten-1-one, 1-(5,5-dimethyl-1-cyclohexen-1-yl)-; α-Dynascone; Galbanone; Galbascone		10–100	0.0014	0.09
1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one[g] $C_{12}H_{20}O$ CAS#: 13144-88-2 Log K_{ow}(calculated): 4.04 Molecular weight: 180.91 Vapor pressure: 0.118 mm Hg @ 25 °C Water solubility: 19.61 mg/l @ 25 °C	Ethanone, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)-; 1-(2,4,4,5,5-Pentamethylcyclopent-1-en-1-yl)ethanone; 2-Acetyl-1,3,3,4,4-pentamethyl-1-cyclopentene; Alpinone		0.01–0.1	0.0005[e]	0.02[e]
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one $C_{15}H_{22}O$ CAS#: 224031-70-3 Log K_{ow}(calculated): N/A Molecular weight: 218.34 Vapor pressure: N/A Water solubility: N/A	Spirogalbanone Pure		1–10	0.0005[e]	0.02[e]

Table 1 (*continued*)

Alkyl cyclic ketones					
Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure (mg/kg/day)[b]	Maximum skin level (%)[c,d]
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[f] $C_{15}H_{22}O$ CAS#: 224031-71-4 Log K_{ow}(calculated): N/A Molecular weight: 218.34 Vapor pressure: N/A Water solubility: N/A	N/A		0	0	0
4-(2,2,3,6-Tetramethylcyclohexyl)-3-buten-2-one $C_{14}H_{24}O$ CAS#: 54992-90-4 Log K_{ow}(calculated): 4.37 Molecular weight: 208.34 Vapor pressure: N/A Water solubility: 4.14 mg/l @ 20 °C	Myrrhone		Captive[i] – Firmenich Inc.		
1-(2,2,6-Trimethylcyclohexyl)-2-buten-1-one[f] $C_{13}H_{22}O$ CAS#: 39900-18-0 Log K_{ow}(calculated): 4.38 Molecular weight: 194.32 Vapor pressure: 0.0307 mm Hg @ 25 °C Water solubility: 8.514 mg/l @ 25 °C	2-Buten-1-one, 1-(2,2,6-trimethylcyclohexyl)-		0	0	0
α,β-unsaturated ketone with unsaturated ring					
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one $C_{14}H_{22}O$ CAS#: 65113-95-3 Log K_{ow}(calculated): 4.84 Molecular weight: 206.29 Vapor pressure: 0.0102 mm Hg @ 25 °C Water solubility: 2.98 mg/l @ 25 °C	3-Methyl-5-(2,2,3-trimethylcyclopent- 3-en-1-yl)pent-3-en-2-one; 3-Penten-2-one, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-		<0.01	0.0005[e]	0.02[e]
1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one[g] $C_{14}H_{22}O$ CAS#: 7779-30-8 Log K_{ow}(calculated): 4.78 Molecular weight: 206.29 Vapor pressure: 0.00651 mm Hg @ 25 °C Water solubility: 3.328 mg/l @ 25 °C	1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-; 1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en-3-one		>1000	0.0348	0.73

[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 FMRs 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.
[d] 2008 Use level survey (IFRA, 2008).
[e] A default value of 0.02% was used to calculate dermal systemic exposure.
[f] These materials belong to the Alkyl Cyclic Ketones group; they are not being reviewed because there is no reported use of these materials as fragrance ingredients.
[g] These materials have an IFRA Standard restricting their use as fragrance ingredients based on the critical effect of sensitization.
[h] RIFM, 1996a.
[i] Captive = a material that is manufactured exclusively by a RIFM member company.

Table 1 includes the following types of data for each of the ACK fragrance ingredients and related congeners: Chemical Abstract Service registry number (CAS RN), synonyms (alternative nomenclature), molecular formula, molecular weight, physiochemical properties that are relevant for absorption and biological activity (i.e., Log K_{ow}, vapor pressure, water solubility); annual worldwide production as determined by International Fragrance Association (IFRA, 2008), and dermal systemic exposure estimates. Table 1 includes eight structurally related compounds currently not used as fragrance ingredients. These are: 1-[(1-(1-oxopropoxy)cyclohexyl]ethanone; 1-(6,6,9-trimethyl-2-methylene-4,8-cycloundecadien-1-yl)-ethanone; 1-(4-methoxy-2,2,6,6-tetramethyl-3-cyclohexen-1-yl)ethan-1-one; 5-acetyl-2,2,8-trimethyltricyclo(6.2.2.01,6)d odec-5-ene; 1-(2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5- yl)ethan-1-one; 1-(3,3-dimethylcyclohex-1-en-1-yl)ethanone; 1-spiro[4.5]dec-6-en-7-yl-4-penten-1-one; and 1-(2,2,6-trimethylcyclohexyl)-2-buten-1-one.

Tables 2–9 summarize the ACK toxicology data in the RIFM database. These data were derived from both the publically available peer reviewed literature and studies sponsored by RIFM or its member companies. Available toxicology data for the structurally related compounds that have no reported use as fragrance ingredients are included in Tables 2–9. These materials are: 1-

(6,6,9-trimethyl-2-methylene-4,8-cycloundecadien-1yl)ethanone and 1-(3,3-dimethylcyclohex-1-en-1-yl)ethanone. The data on these non-fragrance materials will not be reviewed in the text of this safety report.

2.1. Rationale for grouping alkyl cyclic ketones

The common structural element for the two categories of ACK fragrance ingredients is a ketone carbonyl group, C=O, which is also referred to as an "oxo" or "keto" functionality. The generic ACK formula can be represented as $(R_1)(R_2)$ C=O. ACK fragrance ingredients can be described as being composed of an alkyl, R_1, and various substituted and bicyclic saturated or unsaturated cyclic hydrocarbons, R_2, in which one of the rings may include up to 12 carbons. Alternatively, R_2 may be a carbon bridge of C2—C4 carbon chain length between the ketone and cyclic hydrocarbon.

The structural details of the 23 fragrances in the two ACK categories are depicted in Table 1. The alkyl group may be a linear or branched carbon chain that in two cases contains another double bond that is not in conjugation with the ketone group. The majority of the R_1 alkyl groups are simple saturated linear methyl and ethyl groups; R_1 may also be a C4 saturated branched alkyl group, i.e., R_1—$C(CH_3)_3$ (1) or an unsaturated C4 alkyl group with a terminal isolated double bond, i.e., R_1—$(CH_2)_2CH$=CH_2 (2). The R_2 groups are structurally diverse and may be composed of either a saturated or unsaturated monocyclic, spiro, bicyclic, or complex bridged bicyclic hydrocarbon. The R_2 cyclic hydrocarbon ring may also contain additional alkyl substituent(s), such as one or more methyl or isopropyl groups. The ketone carbonyl group may also be in conjugation with a double bond in the cyclic hydrocarbon portion of the molecule.

The ACK fragrance materials are postulated to be metabolized by common pathways that will be discussed in detail in Section 3, Metabolism. With the exception of the previously published ionone fragrances (Belsito et al., 2007), there are currently no mammalian metabolism studies available for the ACK fragrance materials listed in Table 1. Biotransformation has been postulated for the two categories of ACK fragrance materials based on published metabolism studies for compounds with similar chemical functionality. The predominant primary metabolic pathway for all of the saturated and unsaturated ACK fragrance ingredients is reduction of the ketone by alcohol dehydrogenases and NADH/NADPH dependent cytosolic carbonyl reductases to generate a secondary alcohol metabolite which may either be converted back to the parent ketone (and excreted unchanged) or conjugated with glucuronic acid and excreted (Hoffmann and Maser, 2007; JECFA, 1999; Ahmed et al., 1979).

The molecular weights of the 23 ACK fragrance ingredients listed in Table 1 range from a high of 246.94 g/mol for the unsaturated alkyl cyclic ketone, methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl to a low of 154.53 g/mol for the saturated alkyl cyclic ketone 1-(3,3-dimethylcyclohexyl)ethan-1-one. The ACK fragrance ingredients demonstrate low to moderate lipophilicity and should not bioaccumluate in fatty tissues. Increasing carbon chain length or cyclic hydrocarbon ring size increases lipophilicity with the calculated Log K_{ow} ranging from 2.80 for 1-(3,3-dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one (a saturated C11 ACK) to 5.98 for methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone (an unsaturated C17 ACK). Water solubility, which is generally inversely proportional to Log K_{ow}, ranged from 262.5 mg/L at 25 °C for 1-(3,3-dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one (a saturated C11 ACK) to 0.1943 mg/L at 25 °C for methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone (an unsaturated C17 ACK). The ACK fragrance materials demonstrate generally low volatility, with vapor pressure less than 1 mm Hg at 25 °C, ranging from 0.000166 mm Hg at 25 °C for methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone (an unsaturated C17 ACK) to 0.586 at 25 °C for 1-(3,3-dimethylcyclohexyl)ethan-1-one (a saturated C10 ACK).

2.2. Occurrence and use

The ACK compounds listed in Table 1 are used solely as fragrance ingredients. The annual worldwide production of the individual ACK fragrance materials varies from less than 0.01 to greater than 1000 metric tons.

Table 2.1
Acute toxicity studies – dermal.

Material	Species (number/dose)	LD_{50}	Reference
Saturated alkyl cyclic ketones			
Cyclohexyl methyl pentanone	Rabbit (5/sex)	>2000 mg/kg	RIFM (1993a)
Unsaturated alkyl cyclic ketones			
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	Rat (5/sex)	>2000 mg/kg	RIFM (2007a)
Acetyl carene	Rabbit (5)	>5000 mg/kg	RIFM (1974a)
Acetyl cedrene	Rabbit (10)	>2000 mg/kg	RIFM (1972a)
Acetyl cedrene	Rabbit (6)	>5 mL/kg (>5025 mg/kg)[c]	RIFM (1979a)
2-Cyclohexyl-1,6-heptadien-3-one	Rat (5/sex) OECD 402	>2000 mg/kg	RIFM (2004a)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	Rat (10) OECD 402	>2000 mg/kg	RIFM (1991a)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Rabbit (2/sex)	>3038 mg/kg	RIFM (1977a)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Rabbit (3/sex)	>2000 mg/kg	RIFM (1979b)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Rat (5/sex) OECD 402	>2000 mg/kg	RIFM (1996b)
2-(3,7-Dimethyl-2,6-nonadien-1-yl)cyclopentanone	Rabbit (5/sex)	> 5000 mg/kg	RIFM (2010a)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	Rat (5/sex) OECD 402	>2000 mg/kg	RIFM (1996c)
1-(*para*-Menthen-6-yl)-1-propanone	Rabbit (2/sex)	>10 mL/kg (>9140 mg/kg)[c]	RIFM (1971a)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Rabbit (2/sex)	9 mL/kg (9000 mg/kg)	RIFM (1980a)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Rat (5/sex)	>2000 mg/kg	RIFM (1993b)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2- naphthalenyl)ethanone	Rat (8/sex)	>5000 mg/kg	RIFM (1980b)
4-(2,2,3,6-Tetramethylcyclohexyl)-3-buten-2-one)[b]	Rat (5/sex) OECD 402	>2000 mg/kg	RIFM (1991b)
1-(6,6,9-Trimethyl-2-methylene-4,8-cycloundecadien-1-yl)ethanone[a]	Rabbit (6)	>2000 mg/kg	RIFM (1979c)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Rat (5/sex) OECD 402	>2000 mg/kg	RIFM (2005a)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Rat (5/sex) OECD 402	>2000 mg/kg	RIFM (2005a)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.
[c] Units have been altered from original reported units for the sake of comparison.

Table 2.2
Acute toxicity studies – oral.

Material	Species (number/dose)	LD_{50}	Reference
Saturated alkyl cyclic ketones			
Cyclohexyl methyl pentanone	Rat (3/sex)	>10 mL/kg (>9100 mg/kg)[c]	RIFM (1977b)
Cyclohexyl methyl pentanone	Rat (5/sex)	>2000 mg/kg	RIFM (1991c)
Unsaturated alkyl cyclic ketones			
Acetyl carene	Rat (10)	3000 mg/kg	RIFM (1974a)
Acetyl cedrene	Rat (8/sex)	4.5 mL/kg (4522 mg/kg)[c]	RIFM (1979d)
Acetyl cedrene	Rat (10 M)	5.2 mL/kg (5226 mg/kg)[c]	RIFM (1972a)
Acetyl cedrene	Mouse (2–6)	> 2 mL/kg (>2010 mg/kg)[c]and <5 mL/kg (<5025 mg/kg)[c]	RIFM (1979e)
Acetyl cedrene	Mouse (2–6)	>5 and <10 mL/kg (>5025 and <10,050 mg/kg)[c]	RIFM (1979f)
Acetyl cedrene	Mouse (2–6)	~5 mL/kg (~5025 mg/kg)[c]	RIFM (1979g)
Acetyl cedrene	Mouse (2–6)	~5 mL/kg (~5025 mg/kg)[c]	RIFM (1979h)
Acetyl cedrene	Mouse (2–6)	~5 mL/kg (~5025 mg/kg)[c]	RIFM (1979i)
Acetyl cedrene	Mouse (2–6)	~5 mL/kg (~5025 mg/kg)[c]	RIFM (1976a)
2-Cyclohexyl-1,6-heptadien-3-one	Rat (6) OECD 423	>2000 mg/kg	RIFM (2001c)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	Rat (10) OECD 401	>2000 mg/kg	RIFM (1991d)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	Rat (5/sex)	>2000 mg/kg	RIFM (1994a)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	Rat (5/sex)	4600 mg/kg	RIFM (1987a)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	Mouse (10 M)	>4000 mg/kg and <8000 mg/kg	RIFM (1985a)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Rat (2/sex)	7563 ± 767.7 mg/kg	RIFM (1977a)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Rat (5/sex)	>5000 mg/kg	RIFM (1979b)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Rat (5/sex) OECD 401	>2000 mg/kg	RIFM (1999a)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Rat (5/sex)	5,055 mg/kg	RIFM (1983a)
2-(3,7-Dimethyl-2,6-nonadien-1-yl)cyclopentanone	Rat (3 F) OECD 425	>5000 mg/kg	RIFM (2010b)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro- 1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	Rat (5/sex) OECD 420	>2000 mg/kg	RIFM (1996d)
1-(*para*-Menthen-6-yl)-1-propanone	Rat (10)	3.8 mL/kg (3470 mg/kg)[c]	RIFM (1958)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Rat (5/sex)	15.5 mL/kg (14,833 mg/kg)[c]	RIFM (1979j)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Rat (5/sex) OECD 401	>5 mL/kg (4925 mg/kg)[c]	RIFM (1986a)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	Rat (5)	> 5000 mg/kg	RIFM (1983b)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2- naphthalenyl)ethanone	Rat (10/sex)	>5000 mg/kg	RIFM (1980c)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	Rat (no further information)	>5 mL/kg (5000 mg/kg)[c]	RIFM (1979k)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Rat (6) OECD 423	> 2000 mg/kg	RIFM (2000a)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Rat (3/sex) OECD 423	>2000 mg/kg	RIFM (2000a)
4-(2,2,3,6-Tetramethylcyclohexyl)-3-buten-2-one)[b]	Rat (5/sex) OECD L251	>2000 mg/kg	RIFM (1992a)
1-(6,6,9-Trimethyl-2-methylene-4,8-cycloundecadien-1-yl)ethanone[a]	Rat (9)	>10,000 mg/kg	RIFM (1978a)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.
[c] Units have been altered from original reported units for the sake of comparison.

2.3. Estimated consumer exposure

All of the ACK exposure data in Table 1 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).

Potential consumer exposure to fragrance materials occurs through the dermal and inhalation routes of exposure. When

Table 3.1
Repeat-dose toxicity studies (dermal route).

Material	Route and duration	Dose	Species (number/dose)	Results	Reference
Saturated alkyl cyclic ketones					
None					
Unsaturated alkyl cyclic ketones					
Acetyl cedrene	2-Week dermal study	0 (water), 300, 600, 1000 mg/kg/day	Rat (5/sex)	Dermal LOAEL 300 mg/kg/day based on skin irritation at all doses; Systemic NOAEL <300 mg/kg/day based on hyaline droplet formation indicative of kidney nephropathy in males and increased mean relative liver weights in females receiving 600 or 1000 mg/kg/day	RIFM (2000b)
Acetyl cedrene	13-Week dermal study with 4-week recovery period (OECD 411, 410)	0 (water), 50, 150, 300 mg/kg/day)	Rat (15/sex)	Dermal NOAEL 50 mg/kg/day based on skin irritation, mild chronic inflammation and hyperkeratosis at all doses (resolved after recovery); Systemic NOEL 150 mg/kg/day based on kidney nephropathy in males at 300 mg/kg/day indicative of alpha-2-micro-globulin toxicity specific to male rat; higher activated partial thromboplastin time for males treated with 300 mg/kg/day (resolved after recovery)	Letizia et al. (2005), RIFM (2002a)

conservative estimates for evaporation, rinsing, and other forms of product removal are taken into account (Cadby et al., 2002), worst-case scenario calculations indicate that application to skin following use of cosmetics represents the major route of exposure to fragrance ingredients. 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 for the ACK fragrance ingredients ranges from less than 0.01 metric tons per year for 1-(2,5,5-trimethylcycloheptyl)ethan-1-one; acetylcarene; and 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one to greater than 1000 metric tons per year for 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone; 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one; 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one; acetyl cedrene; and 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one (IFRA, 2008). The reported volume for each ACK fragrance ingredient represents the annual volume used in formulated mixtures of fragrances in all the finished consumer product categories. The volume of use is determined by IFRA approximately every 4 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.

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 in cosmetic products is calculated based on the concentrations in the 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 these data from the formulations. This upper 97.5 percentile concentration is then used to estimate the concentrations of fragrances for all ten 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 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 a conservative estimate of daily consumer exposure. It is unlikely that a consumer will consistently, on a daily basis, use a number of the different consumer products that are all perfumed with the upper 97.5 percentile level of the fragrance ingredient from fine fragrance type products (Cadby et al., 2002; Ford et al., 2000). The total consumer exposures to the ACK fragrance ingredients ranges from 0.0003 mg/kg body weight/day for 1-(3,3-dimethylcyclohex-1-en-1-yl) to 0.4604 mg/kg body weight/day for 1-(1,2,3,4,5,6,7,8-octohydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone in the high-end user of cosmetic products containing these materials (see Table 1) (IFRA, 2008).

The third method provides maximum skin levels. For consideration of potential adverse skin effects, e.g. sensitization, phototoxicity, etc., the exposure is calculated as the percent concentration of the fragrance ingredient in the top 10 concentration 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 ACK compounds that form part of the formulae of fine fragrances vary widely and have been reported to range from 0.002% for acetylcarene and 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one to 8.17% 1-(1,2,3,4,5,6,7,8-octohydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone. The maximum skin exposures for the ACK compounds in fine fragrance products are listed in Table 1.

The recently revised IFRA (2009), IFRA (2008), IFRA (2011) and IFRA, 2007, respectively Standards on 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one; 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone; 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one; and 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one are based on the dermal sensitization quantitative risk assessment (QRA) approach for fragrance ingredients (Api et al., 2008). The details of the Standards can be found in this fragrance review (see Section 6.7). Exposure data were not available for all the ACK fragrance materials. These materials include 1-(3,3-dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one; 1-(2,5,5-trimethylcycloheptyl)ethan-1-one; 1–3,5,6-trimethyl-3-cyclohexen-1-yl)ethan-1-one; 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8, 8-tetramethyl-2-naphthyl)ethan-1-one; 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8, 8-tetramethyl-2-naphthyl)ethan-1-one; 1-(2,4-dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one; 1-(3,5,6-trimethyl-3-cyclohexen-1-yl)ethan-1-one; 2-cyclohexyl-1,6-heptadien-3-one; 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one; 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one and 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one. A default value of 0.02% was then used to

Table 3.2
Repeat-dose toxicity studies (oral route).

Material	Route and duration	Dose	Species (number/dose)	Results	Reference
Saturated alkyl cyclic ketones					
None					
Unsaturated alkyl cyclic ketones					
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	4-Week gavage study with 2-week recovery (OECD 407)	0 (Corn oil), 15, 150, or 1000 mg/kg/day	Rat (5/sex, control and high dose had another 5/sex for recovery period)	NOAEL 150 mg/kg/day based on differences in hematology, blood biochemistry, and urinary parameters as well as increased liver and kidney weights at 1000 mg/kg/day. Effects were reversible at 150 mg/kg/day and decreased at 1000 mg/kg/day after recovery, thus a mild level of systemic toxicity persisted at the 1000 mg/kg/day dose	RIFM (2007b)
2-Cyclohexyl-1,6-heptadien-3-one	4-Week gavage study with 2-week recovery (OECD 407)	0 (PEG 300), 50, 200, 800 mg/kg/day	Rat (5/sex, control and high dose group had another 5/sex for recovery period	NOEL 50 mg/kg bodyweight/day. At this dose level there were no deaths, no clinical signs of toxicological relevance, no differences from controls in the functional observational battery, no differences in hematology, clinical biochemistry, urinalysis, organ weights and no microscopic or macroscopic findings NOAEL 200 mg/kg/day based on clinical signs of toxicity at the highest level which included: ruffled fur, hunched posture, salivation, emaciation, toe-walking and/or dyspnea, test material related reductions in the mean fore- and hind limb grip strength values, test material related differences in the mean daily food consumption observed chiefly in males, treatment related liver weight increases and thymus weight reductions after four weeks of treatment	RIFM (2004b)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	4-Week gavage study (OECD 407)	0 (Corn oil), 15, 150, or 250 mg/kg/day	Rat (5/sex)	NOAEL 250 mg/kg/day highest dose tested. LOEL 15 mg/kg/day based on liver size and weight adaptive effects and kidney effects not relevant to humans	RIFM (1996e)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	4-Week gavage study with 2-week recovery (OECD 407)	0 (Rapeseed oil), 60, 220, 1000 mg/kg bw/day	Rat (6/sex, additional 6/sex for control and high dose groups for recovery period)	NOEL 60 mg/kg/day At 220 mg/kg/day there was an increase in triglycerides in the females of 45%, there were minimal to slight degeneration and slight to moderate hyaline droplets in the proximal tubular epithelium of the kidneys in the males At 1000 mg/kg/day there were increased bilirubin (males 10%, females 50%), increased cholesterol (males 37%, females 71%), increased triglycerides (females 139%), decreased cholinesterase (females 34%), an increase in the absolute and relative liver weights in the males and females in week 4, in 4 males the kidneys had gray-white and/or yellow foci and/or clay-colored discolorations, minimal centrilobular hepatocellular hypertrophy was noted in 4/6 males, all males had degeneration and an increase in the severity of hyaline droplets in the proximal tubular epithelium of the kidneys	RIFM (1997a)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	4-Week gavage	0 (Corn oil), 15, 150, or 1000 mg/kg/day	Rat (5/sex)	NOAEL 15 mg/kg/day based on increased salivation, decreased body weight gain in males during 4th week, decreased plasma triglyceride levels in females, hematology and plasma changes in females, increased relative liver weight in females, increased kidney weight in males at 150 mg/kg/day	RIFM (1994b)

(*continued on next page*)

Table 3.2 (*continued*)

Material	Route and duration	Dose	Species (number/dose)	Results	Reference
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	7-Day gavage dose range-finding study	0, 600, 750, or 1000 mg/kg/day formulated as 10%, 15%, or 20% solution in corn oil	Rat (3/sex)	Slightly higher liver weights at 1000 mg/kg/day, no other effects observed. 1000 mg/kg/day chosen as high dose for 28 day study.	RIFM (1995a)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	4-Week gavage study with 2-week recovery (OECD 407)	0 (Corn oil), 15, 150, or 1000 mg/kg/day	Rat (5/sex, control and high dose had another 5/sex for recovery period)	NOAEL 1000 mg/kg/day highest dose tested, centrilobular hepatocyte enlargement observed in high dose animals but returned to normal after recovery, minor biochemical changes still seen and considered to be related to metabolism of substance. NOEL 15 mg/kg/day based on non-dose dependent body weight decrease in males and kidney toxicity characteristic of alpha microglobulin nephropathy syndrome specific to male rats at 150 mg/kg/day and higher, findings were still present after recovery in high dose males but reduced.	RIFM (1997b)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	4-Week gavage study (OECD 407)	0 (Corn oil), 50, 200, or 1000 mg/kg/day	Rat (5/sex)	NOAEL 50 mg/kg/day At this dose, increased amounts of hyaline droplets were noted in the males related to test article exposure but due to the male rat predisposition for hyaline droplet formation, it was not considered toxicologically relevant At 200 mg/kg, signs of toxicity included: piloerection, salivation, sedation, hunched posture, prostration, significant reduction of reflexes, emaciation, elevation in cholesterol, triglyceride, alanine aminotransferase, gamma glutamyltransferase and phospholipids, changes in electrolytes, calcium levels were elevated in the males and potassium levels were elevated in the females	RIFM (2005b)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	4-Week gavage study (OECD 407)	0 (Corn oil), 50, 200, or 1000 mg/kg/day	Rat (5/sex)	NOAEL 50 mg/kg/day At this dose, increased amounts of hyaline droplets were noted in the males related to test article exposure but due to the male rat predisposition for hyaline droplet formation, it was not considered toxicologically relevant At 200 mg/kg, signs of toxicity included: piloerection, salivation, sedation, hunched posture, prostration, significant reduction of reflexes, emaciation, elevation in cholesterol, triglyceride, alanine aminotransferase, gamma glutamyltransferase and phospholipids, changes in electrolytes, calcium levels were elevated in the males and potassium levels were elevated in the females	RIFM (2005b)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.

calculate the maximum daily exposure on the skin that corresponds to 0.0005 mg/kg body weight for high end users of these products.

In assessing safety, the calculated dermal systemic exposure in cosmetic products can then be compared to the indices of systemic toxicity such as no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL), which 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).

3. Metabolism

Structurally complex molecules with multiple functionalities, such as the ACK fragrance ingredients, rarely undergo a single primary metabolism pathway. Thus, several pathways may compete to detoxify the compound for conjugation and excretion.

Metabolism studies for the ACK fragrance ingredients listed in Table 1 are currently not available, and published studies were

Table 4.1
Mutagenicity and genotoxicity – *in vitro* bacterial studies.

Material	Test system	Bacterial strain	Concentration	Results	Reference
Saturated alkyl cyclic ketones					
Cyclohexyl methyl pentanone	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ±S9	Up to 100 μg/plate	Negative	RIFM (1979l)
1-(3,3-Dimethylcyclohexyl)ethan-1-one	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 ±S9	Up to 313–625 μg/plate	Negative	RIFM (2006a)
1-(3,3-Dimethylcyclohexyl)ethan-1-one	Reverse mutation	*Escherichia coli* WP2 uvrA ±S9	Up to 625 μg/plate	Negative	RIFM (2006a)
Unsaturated alkyl cyclic ketones					
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 ±S9	Up to 5000 μg/plate	Negative	RIFM (2007d)
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	Reverse mutation	*Escherichia coli* WP2 uvrA ±S9	Up to 5000 μg/plate	Negative	RIFM (2007d)
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	Reverse mutation OECD 471	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 ±S9	Up to 5000 μg/plate	Negative	RIFM (2007c)
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	Reverse mutation OECD 471	*Escherichia coli* WP2 uvrA ±S9	Up to 5000 μg/plate	Negative	RIFM (2007c)
Acetyl cedrene	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ±S9	Up to 5000 μg/plate	Negative	RIFM (1982a)
2-Cyclohexyl-1,6-heptadien-3-one	Reverse mutation OECD 471	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 ±S9	up to 5000 μg/plate in EtOH	Negative	RIFM (2001d)
2-Cyclohexyl-1,6-heptadien-3-one	Reverse mutation	*Escherichia coli* WP2 uvrA ±S9	Up to 5000 μg/plate in DMSO	Negative	RIFM (2007e)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ±S9	Up to 500 μg/plate	Negative	RIFM (1991e)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	Reverse mutation	*Salmonella typhimurium* TA97, TA98, TA100, TA102 TA1535, TA1538 ±S9	Up to 200–2000 μg/plate	Negative	RIFM (1994)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Reverse Mutation OECD 471	*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 ±S9	Up to 5000 μg/plate	Negative	RIFM (2005c)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Reverse Mutation OECD 471	*Escherichia coli* WP2uvrA-±S9	Up to 5000 μg/plate	Negative	RIFM (2005c)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Reverse mutation OECD compliant (guideline number not stated)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ±S9	Up to 5000 μg/plate	Negative	RIFM (1990)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Reverse mutation OECD, n.f.i.	*Escherichia coli* WP2 uvrA ±S9	Up to 5000 μg/plate	Negative	RIFM (1990)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-,rel-[b]	Reverse mutation OECD 471	*Salmonella typhimurium* TA97, TA98, TA100, TA102 and TA1535 ±S9	Up to 2500 μg/plate	Negative	RIFM (1996f)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ±S9	0.007–0.2 μL in 0.1 mL acetone/plate	Negative	RIFM (1979m)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ±S9	Up to 100,000 μg/plate	Negative	RIFM (1986b)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 ±S9	Up to 5000 μg/plate	Negative	RIFM (1993c)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Reverse mutation OECD 471	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 ±S9	Up to 5000 μg/plate	Negative	RIFM (2007f)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Reverse mutation OECD 471	*Escherichia coli* WP2 uvrA ±S9	Up to 5000 μg/plate	Positive	RIFM (2007f)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ±S9	Up to 150 μl/plate	Negative	RIFM (1984a)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Reverse mutation Test designed to follow OECD guidelines	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ±S9	Up to 5000 μg/plate	Negative	RIFM (1997c)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Reverse mutation Test designed to follow OECD guidelines	Escherichia coli WP2 uvrA ±S9	Up to 5000 μg/plate	Negative	RIFM (1997c)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Reverse Mutation OECD 471	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537 ±S9	Up to 5000 μg/plate	Negative	RIFM (2000c)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Reverse Mutation OECD 471	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537 ±S9	Up to 5000 μg/plate	Negative	RIFM (2000c)

(*continued on next page*)

Table 4.1 (*continued*)

Material	Test system	Bacterial strain	Concentration	Results	Reference
4-(2,2,3,6-Tetramethylcyclohexyl)-3-buten-2-one[b]	Reverse mutation OECD 471	*Salmonella typhimurium* strains TA1535, TA1537, TA98, TA102, and TA100 ±S9	Up to 5000 μg/plate	Negative	RIFM (2005d)
4-(2,2,3,6-Tetramethylcyclohexyl)-3-buten-2-one[b]	Reverse mutation	*Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100	40 μg/plate in the absence of S9 and 200 μg/plate in the presence of S9	Negative	RIFM (1991f)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.

Table 4.2
Mutagenicity and genotoxicity – *in vitro*mammalian cell studies.

Material	Test System	Cell Line	Concentration	Results	Reference
Saturated alkyl cyclic ketones					
None					
Unsaturated alkyl cyclic ketones					
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	Forward mutation assay OECD 476	Mouse lymphoma cells L5178Y ± TK ±S9	up to 2469.4 μg/mL	Negative	RIFM (2007g)
Acetyl cedrene	Chromosome aberration	Chinese Hamster ovary cells ±S9	up to 50 μg/mL	Negative	RIFM (2003a)
2-Cyclohexyl-1,6-heptadien-3-one	Chromosome aberration OECD 473	Chinese hamster V79 cells	up to 40 μg/mL without S9; up to 31.3 μg/mL with S9	Negative without S9; positive at highest concentration with S9	RIFM (2004c)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Chromosome aberration	Cultured human lymphocytes	7.8–62.5 μg/ml (-S9); 7.8–125 μg/ml (+S9)	Negative	RIFM (1996g)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	Chromosome aberration OECD 473	Chinese hamster V79 cells	Up to 40 μg/ml	Negative	RIFM (1997d)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Chromosome aberration	Cultured human lymphocytes	7.8–75 μg/ml (-S9); 25–100 μg/ml (+S9)	Negative	RIFM (1993d)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Chromosome aberration	Cultured human lymphocytes	7.5–50 μg/ml (-S9); 15.6–125 μg/ml (+S9)	Negative	RIFM (1997e)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Chromosome aberration OECD 473	Chinese hamster V79 cells	up to 50 μg/mL	Negative	RIFM (2005e)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Chromosome aberration OECD 473	Chinese hamster V79 cells	up to 50 μg/mL	Negative	RIFM (2005e)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.

Table 4.3
Mutagenicity and genotoxicity – *in vivo* studies.

Material	Test system	Mouse strain	Dose	Results	Reference
Saturated alkyl cyclic ketones					
None					
Unsaturated alkyl cyclic ketones					
2-Cyclohexyl-1,6-heptadien-3-one	Micronucleus test bone marrow erythrocytes OECD 474	NMRI mice (6/sex)	500, 1000, 2000 mg/kg body weight	Negative	RIFM (2005f)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Micronucleus test bone marrow erythrocytes OECD 474	CD-1 mice (15/sex)	5000 mg/kg body weight	Negative	RIFM (1990)

used as the basis to postulate primary and secondary ACK metabolic routes, which may include one or more of the following biotransformation pathways:

Primary Metabolism:

- Reduction of the ketone group to a secondary alcohol
- Hydroxylation/oxygenation of the cyclohexene ring
- Oxidation of the angular methyl groups
- Reduction of the double bond in the exocyclic alkenyl side chain or cyclic portion of the molecule to form dihydro derivatives
- Epoxidation of isolated (non-conjugated) double bonds of exocyclic alkyl side chains and subsequent reaction with epoxide hydrolases or glutathione transferase.

Secondary Metabolism:

- Conjugation of the hydroxylated metabolites with glucuronic acid
- Conjugation of epoxide metabolites with glutathione.

Carbonyl reduction of the ketone (oxo) functionality by carbonyl reducing (reductase) enzymes has been well-characterized

Table 5
Developmental studies – oral.

Material	Method	Dose	Species (number/dose)	Results	Reference
Saturated alkyl cyclic ketones					
None					
Unsaturated alkyl cyclic ketones					
Acetyl cedrene	Dose range-finding developmental study – gavage GD7-17	0 (Corn oil), 50, 100, 250, 500, 1000 or 2000 mg/kg/day	Rat (8F)	Maternal LOAEL 50 mg/kg/day based on reduced maternal body weight; Developmental NOAEL 250 mg/kg/day based on reduced fetal weight at 500 mg/kg/day and higher	RIFM (2002b)
Acetyl cedrene	Developmental study – gavage GD7-17	0 (Corn oil), 25, 50, or 100 mg/kg/day	Rat (25F)	Maternal NOAEL 50 mg/kg/day based on reduced body weight gain and food consumption at 100 mg/kg/day and above; Developmental NOAEL was 100 mg/kg/day (highest dost tested)	RIFM (2004d), RIFM (2004e), Lapczynski et al. (2006)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Dose range-finding developmental study – gavage GD7-17	0 (Water), 240, 480, 960, or 1920 mg/kg/day	Rat (8F)	Maternal and developmental NOAEL not determined. Decreased body weight gains and feed consumption in 960 and 1920 mg/kg/day dosage groups for the entire dose period and maternal mortality at 1920 mg/kg/day. No c-section or litter parameters were affected by dosages as high as 1920 mg/kg/day	RIFM (2002c)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Developmental study – gavage GD7-17	0 (Water), 96, 240, or 480 mg/kg/day	Rat (25F)	Maternal and developmental NOAEL 240 mg/kg/day based on continued decreased body weight gains after treatment for the 480 mg/kg/day dams and decreased fetal body weights at 480 mg/kg/day	Politano et al. (2009), RIFM (2002d), Letizia et al. (2004)

and should be the major and predominant primary route for ACK metabolism unless the ketone is sterically hindered (Belsito et al., 2007; Hoffmann and Maser, 2007; JECFA, 1999; Ahmed et al., 1979). The biotransformation of the ketone is mediated by alcohol dehydrogenase and by NADH/NADPH-dependent cytosolic carbonyl reductases. The secondary alcohol metabolite may be either converted back to the parent ketone (and excreted unchanged) or conjugated with glucuronic acid and excreted. On a case-by-case basis, differences in the alkyl and cyclic hydrocarbon group functionality and steric hindrance may affect the rate of metabolism of the specific ACK fragrance material by either inhibiting or decreasing the activity of carbonyl reductases or other enzymes involved in primary or secondary metabolism.

Primary secondary alcohol (hydroxyl) metabolites are less lipophilic than the parent ketones and are generally not retained. Secondary metabolism, conjugated with glucuronic acid, occurs readily and is followed by elimination of the glucuronide in the urine. Carbonyl reducing enzymes are found mainly in the liver and kidney, but are also reported to be present in the brain, lung, spleen and adrenal glands. The difference in tissue and intracellular distribution substantiate the possibility that several enzymes could be involved in the reduction of the ACK fragrance materials. These ACK reducing enzymes may include a short-chain dehydrogenase/reductase (SDR), such as NADPH secondary alcohol oxidoreductases; pluripotent hydroxysteroid dehydrogenases (HSD); and/or a pyridine nucleotide-dependent oxidoreductase that may also catalyze carbonyl reduction of nonsteroidal ketone, which mediate the inter-conversion of the alkyl cyclic alcohol metabolite back to the parent ACK. An example of ACK carbonyl reductase metabolism is illustrated below in Fig. 1.

It is also possible that the double bonds of ACK fragrance ingredients may undergo other biotransformations that may precede or occur in tandem with carbonyl reductases. The available literature for unsaturated compounds with one or more non-conjugated or conjugated double bonds in alkyl or cyclic hydrocarbon groups generally supports metabolism that results in a possible complex mixture of oxidative metabolites that are primary alkyl, secondary alkyl, and ring hydroxyl metabolites (Waring, 1971; Leibman and Ortiz, 1973; Chiappe et al., 1998; Sakamaki et al., 2004). Depending on the structural properties of the particular ACK in which steric hindrance may shield the double bond or ketone, these types of oxidative biotransformation would either precede or occur in tandem with carbonyl reduction. Examples of relevant ACK carbonyl reductase/allylic oxidation metabolism have been demonstrated and were previously published for the ACK related fragrance material, β-ionone (Belsito et al., 2007) and pulegone (Madyastha and Thulasiram, 1999).

In vivo reduction of the double bond in α,β-unsaturated ketones by hepatic cytosolic reductase may be an initial primary route of metabolism to generate the saturated ketone, which may then be acted upon by carbonyl reductase to generate the secondary alcohol metabolite. An example of conjugate double bond reduction as a primary metabolic step is reported for a benzilidene keto coumarin derivative (Lindstrom and Whitaker, 1984). The proposed metabolism for α,β-unsaturated ACK (double bond reduction and carboxyl reduction metabolism) is depicted in Fig. 2. This example illustrates a proposed pathway for the two (structurally less complex) examples in which the α,β-unsaturation of the ACK ketone is not contained within the cyclic hydrocarbon (3-methyl-5-(2,2,3-trimethyl-3–3-cyclopenten-1-yl)pent3-en-2-one and 1-(2,2,6-trimethyl-2-cyclohenen-1-yl)pent-1-en-3-one).

Isolated non-conjugated double bonds such as in the terminal double bond of 1-(3,3,-dimethylcyclohexyl)pent-4-en-1-one and 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one or in the double bond in the alkyl chain between the ketone and the ring structure of 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one or 3-methyl-5-(2,2,3-trimethyl-3–3-cyclopenten-1-yl)pent3-en-2-one may undergo initial primary cytochrome P450 oxidation to form an epoxide. The epoxide should have a transient existence and be rapidly detoxified by epoxide hydrolase. There is also the possibility that the epoxy intermediate could bind to epidermal proteins. The resultant diol may be conjugated and excreted by various mechanisms (Nelson and Gordon, 1983; Chiappe et al., 1998). However, if carbonyl reduction occurs prior to epoxidation, then the ACK alcohol may be excreted as the glucuronide with the double bond intact. An example of a proposed ACK epoxidation is illustrated in Fig. 3 for (1-(3,3,-dimethylcyclohexyl)pent-4-en-1-one and 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one).

Table 6.1
Skin irritation studies in humans.

Material	Method	Concentration	Results	Reference
Saturated alkyl cyclic ketones				
Cyclohexyl methyl pentanone	HRIPT induction [c]	12% in DEP:EtOH (1:3)	11/106	RIFM (1988a)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	HRIPT induction[c]	5% in EtOH	0/43	RIFM (1973a)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	HRIPT induction[c]	5% in EtOH	0/43	RIFM (1973b)
1-(3,3-Dimethylcyclohexyl)ethan-1-one	HRIPT induction[c]	5% in EtOH	0/37	RIFM (1966a)
1-(3,3-Dimethylcyclohexyl)ethan-1-one	HRIPT induction[c]	2.5% in EtOH	0/44	RIFM (1972b)
1-(2,5,5-Trimethylcycloheptyl)ethan-1-one	HRIPT induction[c]	2.5% in EtOH	0/40	RIFM (1973c)
Unsaturated alkyl cyclic ketones				
Acetyl carene	HRIPT induction[c]	5% in EtOH	0/41	RIFM (1971b)
Acetyl carene	Maximization pretest [d]	10% in petrolatum	0/5	RIFM (1972c)
Acetyl cedrene	Modified Primary dermal irritation[e]	30% in DEP:EtOH (3:1)	0/23	RIFM (2004f)
Acetyl cedrene	Modified Primary dermal irritation[e]	30% in DEP:EtOH (1:3)	0/23	RIFM (2004f)
Acetyl cedrene	HRIPT induction[c]	30% in DEP:EtOH (3:1)	3/101	RIFM (2004g)
Acetyl cedrene	HRIPT induction[c]	5% in EtOH	2/39	RIFM (1964)
Acetyl cedrene	Maximization pretest[d]	30% in petrolatum	0/25	Frosch et al. (1995)
2-Cyclohexyl-1,6-heptadien-3-one	HRIPT induction[c]	2% (vehicle not stated)	0/47	RIFM (2003b)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	HRIPT induction[c]	2% in DMP	0/53	RIFM (1996h)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT induction[c] FDA 21CFR parts 50,56,312	5% in DEP	0/100	RIFM (1999b)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT induction[c]	5% in EtOH:DEP (3:1)	0/105	RIFM (2001e)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT induction[c] (photosensitization control during induction)	1% in petrolatum	0/50	RIFM (1979n)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT induction[c]	1% (unspecified volatile vehicle)	0/53	RIFM (2002e)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT induction[c]	1% in DEP	0/102	RIFM (2003c)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT induction[c]	0.1% in petrolatum	0/51	RIFM (1977c)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	HRIPT induction[c]	1% in EtOH	0/48	RIFM (1983c)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]- ,rel-[b]	HRIPT induction[c]	15% (vehicle not stated)	0/57	RIFM (1998)
1-(*para*-Menthen-6-yl)-1-propanone	Schwartz patch induction[f]	100% (as supplied)	0/50	RIFM (1960a)
1-(*para*-Menthen-6-yl)-1-propanone	HRIPT induction[c]	2% in DMP	0/50	RIFM (1960b)
1-(*para*-Menthen-6-yl)-1-propanone	Maximization pretest[d]	4% in petrolatum	0/10	RIFM (1971c)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	HRIPT induction[c]	2% in unspecified vehicle	0/50	RIFM (1984c)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Modified Primary dermal irritation[e]	20%, 40%, 60%, or 75% in DEP:EtOH (3:1)	1/23 (at 20%) 0/23 (at $\geqslant$40%)	RIFM (2004h)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Modified primary dermal irritation[e]	20%, 40%, 60%, or 75% in DEP: EtOH (1:3)	0/23	RIFM (2004h)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT induction[c]	40% in DEP:EtOH (3:1)	4/100 mild	RIFM (2004i)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT induction[c]	22.5% in DEP:ETOH (1:3)	0/53	RIFM (1999c)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT induction[c]	12.5% in EtOH	2/51 mild	RIFM (1979o)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT induction[c]	2.5% in EtOH	0/36	RIFM (1973d)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT induction[c]	2.5% in EtOH	0/44	RIFM (1977d)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT induction[c]	2.5% in EtOH	0/45	RIFM (1978b)
1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one	HRIPT induction[c]	2% in unspecified vehicle	0/52	RIFM (1979ii)

Table 6.1 (*continued*)

Material	Method	Concentration	Results	Reference
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Primary irritation	100%	0/29	Jirova et al. (2010)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	HRIPT induction[c]	0.1% in unspecified vehicle	0/97	RIFM (2006b)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	HRIPT induction[c]	0.1% in unspecified vehicle	0/97	RIFM (2006b)
1-(3,5,6-Trimethyl-3-cyclohexen-1-yl)ethan-1-one	HRIPT induction[c]	0.5% in EtOH	1/42	RIFM (1965a)
1-(2,2,6-Trimethylcyclohexyl)-2-buten-1-one[a]	48 h closed patch test (readings at 2 and 24 h)	2, 5% in petrolatum	2%: 1/45 at 2 and 24 h 5%: 5/45 at 2 h; 2/45 at 24 h	RIFM (2002g)
1-(6,6,9-Trimethyl-2-methylene-4,8-cycloundecadien-1-yl)ethanone[a]	HRIPT induction[c]	5% in petrolatum	0/50	RIFM (1975a)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.
[c] Human repeat insult patch test (HRIPT) generally consists of 9 induction patches and one challenge patch. Irritation reported in this table is during the induction phase only. Patch applications are 24 h in duration unless noted.
[d] Maximization pretests for irritation are 48 h in duration.
[e] Modified primary dermal irritation test consists of 24-h patch that is repeated after 48 h.
[f] Schwartz patch tests consist of one 48-h patch followed by challenge 1 week later. Irritation reported in this table is during the induction phase only.

The ACK fragrance materials in which the α,β-unsaturation is within the hydrocarbon ring are more structurally complex and potentially sterically hindered, but could nonetheless undergo the same process of double bond and ketone reduction, though likely at a much slower rate.

4. Toxicokinetics

Pharmacokinetic data in humans were not available. However, there are *in vitro* skin penetration data describing acetyl cedrene and some *in vitro* skin penetration and *in vivo* data on animals for 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE). Overall there is a data gap in understanding the fate of these structurally diverse compounds in the body.

4.1. Dermal Route of Exposure

Radiolabeled dermal exposure studies for the purpose of studying the kinetics of the ACK materials were not available. *In vitro* skin penetration with OTNE and acetyl cedrene was conducted according to FDA guidelines with human epidermal membranes from breast or abdominal skin, by measuring the permeation rate of tritiated water (RIFM, 2001a). OTNE and acetyl cedrene permeation were measured over 48 h, after which the epidermal membranes were tape stripped 10 times and radiolabel content was determined. After 48 h of exposure to 1% w/v of the compound in ethanol, 15.3% of the OTNE and 11.3% of the acetyl cedrene applied dose had permeated into the receptor phase. Overall recovery for these fragrances was 53.3% and 68.1% of the applied dose, respectively, indicating that a portion of the applied dose had evaporated. The percutaneous absorption levels of these fragrances were significant and linear without significant plateau (RIFM, 2001a).

4.2. Oral route of exposure

Radiolabeled OTNE in corn oil was administered by gavage to two groups of 18 pregnant rats at low or high dose levels of 2 or 20 mg/kg/day from gestational day (GD) 14 up to postnatal day 7 (RIFM, 2001b). Milk and blood samples from three animals at each dose level were taken at 4, 8, and 24 h on days 3 and 7 after parturition. Following the last daily oral low dose of C^{14}-OTNE, plasma radioactivity decreased 63% and 80% between the 4 and 24 h sampling time on days 3 and 7 respectively. After the last high dose, plasma radioactivity decreased approximately 57% on either day, and was approximately 10 times the radioactivity measured in the low dose animals. Radioactivity was detected in the milk, demonstrating movement into this body compartment; however, the parent compound OTNE was not detected in the milk, indicating that OTNE was completely metabolized. Total radioactivity concentrations in the high dose milk samples were 10–19 times greater than those of the low-dosed animals. After the last daily dose, radioactivity concentrations in milk had declined by greater than 79% at 24 h post dose for both the low and high level doses for both days. Whole-body autoradiographs of pregnant rats sacrificed at 4 and 24 h after the last of five daily oral doses of C^{14}-OTNE indicated that radioactivity levels in the fetus and placenta were barely detectable. In whole-body autoradiography of treated dams, qualitative radioactivity levels were highest in the small intestine contents and preputial gland; lower levels were detected in the stomach, liver, large intestine contents, thyroid, and bladder, and the lowest levels were detected in all other examined tissues.

5. Toxicological studies

Available studies on acute toxicity, repeat-dose exposures, mutagenicity/genotoxicity, developmental toxicity, skin irritation, mucous membrane irritation, skin sensitization or phototoxicity/photosensitization with the ACK fragrance materials are listed in Tables 2–9. Of the 23 fragrances, there were no toxicity data for four of the unsaturated ACK materials: 1-(2,4-dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one; 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one; 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-napthyl)ethan-1-one; and1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-napthyl)ethan-1- one.

5.1. Acute toxicity

Acute dermal toxicity studies with rabbits and rats were identified for one of the saturated ACK materials and eleven of the unsaturated ACK materials. All of the compounds have low acute toxicity by the dermal route (Table 2.1).

Acute oral toxicity studies (by gavage) have been performed with one saturated ACK material and fourteen unsaturated ACK fragrance materials. All of these compounds have low acute toxicity by the oral route as well (Table 2.2).

No acute inhalation data were identified.

Table 6.2a
Skin irritation studies in animals – single application.

Material	Method	Concentration	Species (number/dose)	Results	Reference
Saturated alkyl cyclic ketones					
Cyclohexyl methyl pentanone	LD_{50}	100%	Rabbit (5/sex)	10/10 Erythema, clear by day 14	RIFM (1993a)
Cyclohexyl methyl pentanone	24-h Patch	100%	Rabbit (6 intact 6 abraded)	12/12 Moderate irritation	RIFM (1980d)
Cyclohexyl methyl pentanone	4-h Semi-occlusive patch OECD 404	10% in Petrolatum	Rabbit (3)	0/3	RIFM (1991g)
Cyclohexyl methyl pentanone	Maximization pretest (intradermal injection)	5% (10% in white petrolatum diluted with water and FCA)	Guinea pig (1/sex)	0/2	RIFM (1991h)
Cyclohexyl methyl pentanone	Maximization pretest (topical)	5%, 7.5%, 10% in Petrolatum	Guinea pig (1/sex)	5%: 0/2 7.5%: 1/2 Slight erythema 10%: 2/2 slight erythema	RIFM (1991h)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	24-h Occlusive patch	5% in EtOH	Rabbit (3)	0/3	RIFM (1973e)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	24-h Occlusive patch	5% in EtOH	Rabbit (3)	0/3	RIFM (1973f)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	24-h Occlusive patch	2.5% in EtOH	Rabbit (3)	1/3 Mild irritation, clear by day 2	RIFM (1967a)
1-(3,3-Dimethylcyclohexyl)ethan-1-one	24-h Occlusive patch	2.5% in EtOH	Rabbit (3)	3/3 Mild irritation	RIFM (1967b)
1-[1-(1-Oxopropoxy) cyclohexyl]-ethanone[a]	Determination of highest non-irritating concentration for associated sensitization test (24 h occlusive patch)	2.5%, 5%, 10% In alcohol SDA 39C	Guinea pig (2 M, 2 F)	0/4 At all doses	RIFM (1980n)
1-(2,5,5-Trimethylcycloheptyl)ethan-1-one	24-h Occlusive patch	2.5% in EtOH	Rabbit (3)	0/3	RIFM (1973g)
Unsaturated alkyl cyclic ketones					
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	LD_{50}	100%	Rat (5/sex)	0/10	RIFM (2007a)
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	4-h Semi-occlusive patch OECD 404	100% (95.7% purity)	Rabbit (3)	3/3 Mild irritation	RIFM (2007h)
Acetyl carene	LD_{50}	100%	Rabbit (10)	10/10 Slight to moderate erythema	RIFM (1974a)
Acetyl cedrene	LD_{50}	100%	Rabbit (10)	10/10 Slight to moderate erythema and 8/10 slight to moderate edema	RIFM (1972a)
Acetyl cedrene	LD_{50}	100%	Rabbit (6)	6/6 Slight to mild erythema, clear by day 8	RIFM (1979a)
Acetyl cedrene	4-h Semi-occlusive patch	100%	Rabbit (8)	8/8 Erythema	RIFM (1979p)
Acetyl cedrene	2-h Occluded patch	0%, 10%, 25%, or 50% in DEP:EtOH (3:1)	Guinea pig (5)	0/5 (Similar to controls)	RIFM (2005g)
Acetyl cedrene	Maximization pretest (intradermal injection)	0.1%, 0.25%, 0.5%, 0.75%, or 1% in 0.1% dobs saline	Guinea pig (5 M)	All doses: 5/5 slight erythema and edema (all doses 1%: 4/5 white center on test site	RIFM (1979q)
Acetyl cedrene	Maximization pretest (topical)	5%, 10%, or 20% in EtOH	Guinea pig (5F)	20%: 5/5 Mild irritation 10%: 3/5 slight irritation 5%: no irritation (0/5)	RIFM (1979q)
Acetyl cedrene	Maximization pretest (intradermal injection)	0.05%, 0.1%, 0.25%, 0.5%, or 1% in 0.1% dobs saline	Guinea pig (4 M)	$\geqslant$0.25%: 4/4 mild erythema	RIFM (1975b)
Acetyl cedrene	Maximization pretest (topical)	20%, 40%, 60%, or 100% in EtOH	Guinea pig (4 M)	20%, 40%, 60%: Very slight to slight irritation (4/4) 100%: moderate irritation (4/4)	RIFM (1975b)
Acetyl cedrene	Maximization pretest (intradermal injection)	0.1%, 0.25%, 0.5%, or 1% in dobs/saline	Guinea pig (5 M)	All doses: 5/5 slight erythema and edema	RIFM (1979r)
Acetyl cedrene	Maximization pretest (topical)	2.5%, 5% or 10% in EtOH	Guinea pig (5F)	2.5–5%: 1/5 Barely perceptible erythema 10%: 2/5 mild erythema	RIFM (1979r)
Acetyl cedrene	Maximization pretest (topical)	5%, 10%, 20%, 40% or 60% in EtOH	Guinea pig (4F)	5%: 0/4 (5%), 10–20%: 1/4 barely perceptible erythema 40–60%: 4/4 mild erythema	RIFM (1976b)
Acetyl cedrene	Maximization pretest (intradermal injection)	0.025%, 0.05%, 0.1%, 0.25%, 0.5% in dobs/saline	Guinea pig (2/sex)	0.5–0.25%: 4/4 mild erythema ± white center $\leqslant$ 0.1%: 4/4 slight (faint) erythema	RIFM (1975c)

Table 6.2a (*continued*)

Material	Method	Concentration	Species (number/dose)	Results	Reference
Acetyl cedrene	Maximization pretest (topical)	5%, 10%, 20%, 40%, 60%, or 100% in EtOH	Guinea pig (4F)	5–10%: 0/4 No irritation 20%: 4/4 slight erythema ⩾ 40%:4/4 erythema ± edema	RIFM (1975c)
Acetyl cedrene	Maximization pretest (intradermal injection)	0.1%, 0.25%, 0.5% or 1% in 0.01% dobs saline	Guinea pig (5 M)	All doses: 5/5 slight (pale) erythema and edema	RIFM (1979r)
Acetyl cedrene	Maximization pretest (topical)	2.5, 5, or 10% in EtOH	Guinea pig (4 M)	5% And 10%: 3/4 slight erythema 2.5%: 1/4 slight erythema	RIFM (1979s)
Acetyl cedrene	Phototoxicity pretest	10%, 30%, or 100% in EtOH	Rat (5)	10%: 5/5 Very slight erythema and edema 30%: 5/5 slight erythema and edema 100%: 5/5 mild erythema and edema not clear by day 4	RIFM (1982b)
2-Cyclohexyl-1,6-heptadien-3-one	Primary irritation OECD 404	100%	Rabbit (3)	3/3	RIFM (2001f)
2-Cyclohexyl-1,6-heptadien-3-one	Maximization pretest (intradermal) OECD 406	50%, 75%, 100% in PEG 300	Guinea pig (1)	1/1 Discrete, patchy erythema at ⩾50%	RIFM (2001g)
2-Cyclohexyl-1,6-heptadien-3-one	Maximization pretest (topical) OECD 406	3%, 5%, 10%, 15%, 25%, 50%, 75%, 100% in PEG 300	Guinea pig (4)	4/4 moderate erythema at ⩾5%	RIFM (2001g)
2-Cyclohexyl-1,6-heptadien-3-one	Photosensitization control CFTA guidelines	3%, 5%, 10%, 15% in PEG 300	Guinea pig (4)	3/4 Irritation reactions at 10%, 15%	RIFM (2002f)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	LD_{50} OECD 402	100%	Rat (10)	0/10	RIFM (1991a)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	Primary skin irritation OECD 404	1%, 5%, 10%, 25%, 100% in EtOH: DEP (1:1)	Rabbit (4)	25%, 100%: slight to moderate erythema and edema <25%: no reactions	RIFM (1991i)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	Maximization pretest (intradermal) OECD 406	5% in FCA	Guinea Pig (20)	0/20	RIFM (1991j)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	Maximization pretest (topical) OECD 406	100%	Guinea Pig (20)	Mild to moderate erythema in 18/20 after 1 h; mild to moderate erythema in 12/20 after 24 h	RIFM (1991j)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	4-h Semi-occlusive patch	100% (92.1% purity)	Rabbit (3)	3/3 Well-defined irritation, not clear by day 14	RIFM (1994d)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	4-h Semi-occlusive patch	100%	Rabbit (6)	4/6 Slight irritation, clear by day 7	RIFM (1987b)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	48-h Closed patch (MIC) and 24-h occlusive patch (HNIC) OECD 406	25%, 50%, 75%, or 100% In mineral oil	Guinea pig (2/sex for all doses, plus an additional 2 F for 75% and 100%)	25% and 50%: 0/4 75%: 1/6 100%: 6/6	RIFM (2003d)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	LD_{50}	1% In diethylene glycol monoethyl ether	Rabbit (2/sex)	4/4 Moderate to severe irritation, not clear by day 14	RIFM (1977a)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	24-h Occlusive patch	50% in DEP	Rabbit (6)	2/6 Slight irritation (not irritating)	RIFM (1979t)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	6-h Semi-occlusive patch OECD 406	25%, 50%, 75%, 100% in EtOH	Guinea pig (4)	0/4	RIFM (1999d)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	4-h Semi-occlusive patch OECD 404	100% (93.2% purity)	Rabbit (3)	1/3 Slight irritation, clear by day 2 (not irritating)	RIFM (1999e)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Maximization pretest (intradermal injection) OECD 406	1%, 3%, 5% in PEG 400	Guinea pig (1M)	1/1 Mild irritation	RIFM (1999f)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Maximization pretest (topical) OECD 406	24%, 50%, 75%, 100% In polyethylene glycol 400	Guinea pig (2M)	0/2 (Similar to control)	RIFM (1999f)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Maximization pretest (intradermal injection) OECD 406	1%, 3%, 5% In mineral oil or FCA	Guinea pig (2)	2/2 Very faint to faint erythema	RIFM (2003d)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	LD_{50} OECD 402	100% (92.1% Purity)	Rat (5/sex)	10/10 Slight erythema ± slight edema, clear by day 7	RIFM (1996b)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	4-h Occlusive patch OECD, n.f.i.	100%	Rabbit (3/sex)	6/6 Slight erythema and edema, clear by day 7	RIFM (1983d)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Maximization pretest (intradermal injection) OECD 406	Intradermal: 0.1%, 0.25%, 0.5%, 1.0%, 2.5%, 5.0%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, or 80% in Alembicol D: FCA (1:1) or 100%	Guinea pig (2)	0.1–40%: 2/2 Slight to moderate irritation similar to control ⩾50%: 2/2 moderate irritation and necrosis	RIFM (1996i)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Maximization pretest (topical) OECD 406	Topical: 30%, 50%, 70%, or 100% in Alembicol D	Guinea pig (4)	0/4	RIFM (1996i)
2-(3,7-Dimethyl-2,6-nonadien-1-yl)cyclopentanone	LD_{50}	100%	Rabbit (5/sex)	0/5	RIFM (2010a)
2-(3,7-Dimethyl-2,6-nonadien-1-yl)cyclopentanone	Primary irritation EPA OPPTS 870.2400	N/A	Rabbit (3)	0/3	RIFM (2010c)

(*continued on next page*)

Table 6.2a (*continued*)

Material	Method	Concentration	Species (number/dose)	Results	Reference
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	Primary irritation OECD 404	100%	Rabbit (3)	1/3 Very slight erythema at 48 h, 72 h and 7 days Considered non-irritating	RIFM (1996j)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	Maximization pretest (intradermal injection)	Intradermal: 1%, 3%, 5% in mineral oil	Guinea pig (2)	Very slight erythema and edema at all dose	RIFM (1996k)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	Maximization pretest (topical)	Topical: 25%, 50%, 75%, 100% in mineral oil	Guinea pig (4)	0/4	RIFM (1996k)
1-(*para*-Menthen-6-yl)-1-propanone	LD_{50}	100%	Rabbit (4)	4/4 Well defined erythema, clear by day 10	RIFM (1971a)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl) bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	LD_{50}	100%	Rabbit (6 intact 6 abraded)	12/12 Severe irritation	RIFM (1980a)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	LD_{50}	100%	Rat (5/sex)	0/10	RIFM (1993b)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	4-h Semi-occlusive patch	100%	Rabbit (3)	3/3 Moderate irritation, not clear by day 14	RIFM (1988b)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Maximization pretest (intradermal injection)	5%, 10%, or 25% In propylene glycol	Guinea pig (3)	3/3 Erythema, abscesses and edema	RIFM (1987c)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Maximization pretest (topical)	10%, 25%, 100% In petrolatum	Guinea pig (3)	$\geqslant$25%: 3/3 erythema	RIFM (1987c)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Maximization pretest (intradermal)	0.1%, 0.25%, 0.5%, 1% or 2% in 0.01% DOBS/saline	Guinea pig (4 M)	0/4	RIFM (1988c)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Maximization pretest (topical)	10%, 25%, 50%, or 100% In acetone:PEG 400	Guinea pig (4M)	0/4	RIFM (1988c)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	OET pre-test	1%, 3%, 10%, 30%, 100% in EtOH, acetone, water, petrolatum, PEG or other suitable vehicle	Guinea Pig (6)	30%: lowest irritating concentration 10%: maximum non-irritating concentration	RIFM (1983e)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	OET induction	3%, 10%, 30%, 100% In EtOH, acetone, water, petrolatum, PEG or other suitable vehicle (0.1 mL)	Guinea Pig (6)	3%: No irritation 10%: slight irritation 30% and 100%: moderate to strong irritation	RIFM (1983e)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	LD_{50}	100%	Rabbit (10/sex)	0/20	RIFM (1980b)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	24-h Occlusive patch	2.5% in EtOH	Rabbit (3)	0/3	RIFM (1973h)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	24-h Occlusive patch	2.5% in EtOH	Rabbit (3)	0/3	RIFM (1977e)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	24-h Occlusive patch	2.5% in EtOH	Rabbit (3)	0/3	RIFM (1978c)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	4-h Occlusive patch pilot study	0.62%, 1.25%, 2.5%, 5%, 10%, or 20% in EtOH	Guinea pig (4)	0.62%, 1.25%: Very slight to slight erythema in 2/4 2.5%, 10% and 20%: moderate erythema and edema 5%: 0/4	RIFM (1973i)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	4-h OET CFTA guidelines	10% in EtOH	Guinea pig (10)	0/10	RIFM (1982c)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	LD_{50} OECD 402	100%	Rat (10)	10/10	RIFM (2005a)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Primary irritation OECD 404	100%	Rabbit (3)	3/3 defined erythema	RIFM (2000d)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	OET induction OECD 406	1%, 5%, 10% in EtOH	Guinea pig (6)	6/6 Slight to moderate erythema at 10%	RIFM (2000e)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Maximization pretest (intradermal injection) OECD 406	50%, 75%, 100% in PEG 300	Guinea pig (1)	1/1 All doses	RIFM (2000f)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Maximization pretest (topical) OECD 406	50%, 75%, 100% in PEG 300	Guinea pig (2)	0/2	RIFM (2000f)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Photosensitization pretest CFTA guidelines	0.5%, 1%, 2.5%, 4% in PEG 300	Guinea pig (4)	0/4	RIFM (2001h)

Table 6.2a (*continued*)

Material	Method	Concentration	Species (number/dose)	Results	Reference
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Photosensitization control CFTA guidelines	1%, 10%, 100% in PEG 300	Guinea pig (20)	0/20	RIFM (2001h)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	LD_{50} OECD 402	100%	Rat (10)	10/10	RIFM (2005a)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	LD_{50} OECD 402	100%	Rat (10)	10/10	RIFM (2005a)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Primary irritation OECD 404	100%	Rabbit (3)	3/3 Defined erythema	RIFM (2000d)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	OET induction OECD 406	1%, 5%, 10% in EtOH	Guinea pig (6)	6/6 Slight to moderate erythema at 10%	RIFM (2000e)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Maximization pretest (intradermal injection) OECD 406	50%, 75%, 100% in PEG 300	Guinea pig (1)	1/1 All doses	RIFM (2000f)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Maximization pretest (topical) OECD 406	50%, 75%, 100% in PEG 300	Guinea pig (2)	0/2	RIFM (2000f)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Photosensitization pretest CFTA guidelines	0.5%, 1%, 2.5%, 4% in PEG 300	Guinea pig (4)	0/4	RIFM (2001h)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Photosensitization control CFTA guidelines	1%, 10%, 100% in PEG 300	Guinea pig (20)	020	RIFM (2001h)
4-(2,2,3,6-Tetramethylcyclohexyl)-3-buten-2-one[b]	Primary irritation	100%	Rabbit (4)	Moderate irritant in 3/4, reversible within 14 days	RIFM (1992b)
1-(6,6,9-Trimethyl-2-methylene-4,8-cycloundecadien-1-yl)ethanone[a]	LD_{50}	100%	Rabbit (6)	6/6 Mild erythema and edema, clear by day 2	RIFM (1979c)

OET – Open Epicutaneous Test.
LD50 – 24 h occlusive patch.
n.f.i. – no further information provided.
[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.

5.2. Repeat-dose toxicity

The evaluation of repeat-dose systemic toxicity is based on a dermal study with one material and oral studies with five materials. The longest of these is the 90-day dermal study with acetyl cedrene; all of the oral studies were up to 28 days in duration. No carcinogenic bioassay data was identified for the ACK materials, thus longer-term data after exposure are lacking. Also, no inhalation studies with the ACK fragrance materials were available for review.

5.2.1. Dermal Studies

After a 14-day dermal toxicity study with rats of Sprague–Dawley origin (5 per sex) in which the NOAEL of acetyl cedrene was considered to be less than 300 mg/kg body weight/day based on increased mean relative liver weights in females receiving 600 or 1000 mg/kg/day and hyaline droplet formation indicative of kidney nephropathy in males receiving 300 mg/kg/day (RIFM, 2000b), a 13-week dermal repeat dose study with acetyl cedrene was examined with rats (15 per sex) with 0 (water), 50, 150, or 300 mg/kg body weight/day followed by a 4-week recovery period (RIFM, 2002a). A statistically significant slightly higher activated partial thromboplastin time for males treated with 300 mg/kg/day was observed, which resolved after recovery. At terminal sacrifice, relative kidney weight increases were noted in males given 150 and 300 mg/kg/day, and increased incidence and severity of hyaline droplet formation in the renal tubular epithelial cells were also observed in males receiving 300 mg/kg/day (and at 600 and 1000 mg/kg/day in the 14-day study), but not the females, which is indicative of $\alpha 2\mu$-globulin nephropathy specific only to the male rat, and thus is not considered to be a relevant adverse finding. In addition to skin irritation during the study, at terminal sacrifice, mild chronic inflammation and hyperkeratosis were noted in the skin from all dose groups and both sexes. The Expert Panel concluded that the NOEL for dermal effects was less than 50 mg/kg body weight/ day; while the NOEL for systemic toxicity was 150 mg/kg body weight/day. After recovery, all changes for all dose groups had completely resolved, thus the NOAEL for effects after recovery was 50 mg/kg/day, the lowest dose tested, see Table 3.1.

No dermal studies on the saturated ACK materials were identified.

5.2.2. Oral studies

No oral studies on the saturated ACK fragrance materials were identified.

Unsaturated alkyl cyclic ketones

Male and female CD rats of Sprague–Dawley origin (5 per sex) were administered acetic acid, anhydride with reaction products of 1,5,10-trimethyl-1,5,9-cyclododecatriene in an OECD 407 guideline study for 28 days. Administration was by gavage at doses of 0 (corn oil), 15, 150, or 1000 mg/kg body weight/day (RIFM, 2007b). The control and high dose groups had another 10 animals (5 per sex) that underwent a 2-week recovery period. At the high dose, there were a number of differences from controls in hematology, blood biochemistry, and urinary parameters, as well as increased liver and kidney weights that were generally reversible. Treatment-related findings were also evident at 150 mg/kg/day, but to a lesser degree. The NOAEL was classified as 150 mg/kg/day based on the full recovery of these animals and systemic toxicity that was observed at the high dose level (1000 mg/kg/day), that decreased only partially during recovery. At the high dose, centrilobular and generalized hepatocyte hypertrophy was identified, consistent with the proliferation of the smooth endoplasmic reticulum with increased activity of drug-metabolizing enzymes, indicative of an adaptive response. A concomitant incidence of thyroid follicular cell hypertrophy appeared to be related to this response.

Male and female CD rats of Sprague–Dawley origin (5 per sex) were administered 2-cyclohexyl-1,6-heptadien-3-one in an OECD 407 guideline study for 28 days. Rats were dosed (gavage) at 0

Table 6.2b
Skin irritation studies in animals – repeated application.

Material	Method	Concentration	Species (number/dose)	Results	Reference
Saturated alkyl cyclic ketones					
Cyclohexyl methyl pentanone	Buehler induction (6 h closed patch)	25% in EtOH (reduced to 10% on day 14)	Guinea pig (10M)	25%: 9/10 Severe erythema 10%: reduced to 3/10 slight erythema	RIFM (1981a)
Cyclohexyl methyl pentanone	Maximization induction (intradermal injection)	5% In propylene glycol ± FCA	Guinea pig (10M)	0/10 (Similar to control)	RIFM (1980e)
Cyclohexyl methyl pentanone	Maximization induction (topical)	25% In petrolatum	Guinea pig (10M)	0/10	RIFM (1980e)
1-[1-(1-Oxopropoxy) cyclohexyl]-ethanone[a]	Delayed contact hypersensitivity induction (6 h closed patch)	10% In alcohol SDA 39C	Guinea pig (15)	0/15	RIFM (1980n)
Unsaturated alkyl cyclic ketones					
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Buehler induction OECD 406	100%	Guinea pigs (20)	3/20 Faint erythema	RIFM (1999d)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	OET induction OECD 406	0.5%, 5%, or 10% in EtOH	Guinea pigs (6F)	0/6	RIFM (2000g)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	OET induction OECD 406	0.5%, 5%, Or 10% in dipropylene glycol	Guinea pigs (6F)	0.5%: 3/6 Very slight erythema 5%: 4/6 slight erythema 10%: 5/6 slight to well defined erythema	RIFM (2000h)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Maximization induction (intradermal injection) OECD 406	5% In polyethylene glycol 400 or FCA:saline (1:1)	Guinea pigs (10M)	10/10 Mild to moderate irritation	RIFM (1999f)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Maximization induction (topical) OECD 406	100%	Guinea pigs (10M)	10/10 Mild to moderate irritation	RIFM (1999f)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Maximization induction (topical) OECD 406	100%	Guinea pigs (10M)	10/10 Weak irritation, similar to control	RIFM (2000g)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Maximization induction (topical) OECD 406	100%	Guinea pigs (10)	10/10 Moderate to severe erythema	RIFM (2003d)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Maximization induction (intradermal injection) OECD 406	40% In Alembicol D ± FCA (1:1)	Guinea pig (10)	10/10 Slight irritation (without FCA); 10/10 irritation and necrosis (with FCA), similar to controls	RIFM (1996i)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Maximization induction (topical) OECD 406	100% (95% Purity)	Guinea pig (10)	0/10	RIFM (1996i)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Maximization induction (intradermal injection)	10% in PG ± FCA	Guinea pig (10/sex)	20/20 (Moderate erythema and abscesses, similar to control)	RIFM (1987c)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Maximization induction (topical)	25% In petrolatum	Guinea pig (10/sex)	17/20 Slight erythema	RIFM (1987c)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Maximization induction (intradermal injection)	50% in PG ± FCA	Guinea pig (10M)	10/10 (Abscesses following injections similar to control)	RIFM (1979u)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Maximization induction (topical)	100%	Guinea pig (10M)	0/10	RIFM (1979u)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Guinea pig sensitization[c]	2.5% In EtOH	Guinea pig (10)	10/10 Irritation (pink to bright pink with thickened to markedly thickened skin)	RIFM (1973i)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	OET induction	3%, 10%, 30%, 100% in EtOH	Guinea pigs (6)	3%: 0/6 No irritation 10–100%: increasing irritation with dose (slight to strong)	RIFM (1980f)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] Open Epicutaneous Test (OET) – open application daily for 3 weeks or 5 times weekly for 4 weeks challenge on days 21 and 35. Irritation reported in this table is during the induction phase only. Patch applications are 24 h in duration unless noted.
[c] Guinea pig sensitization by the Maguire method (year): occlusive application on day 1, 2, 4, and 7; on day 4 dermal application.
[d] Buehler guinea pig sensitization - 6 h occlusive application 1/week for 3 weeks.
[e] Maximization induction: intradermal injections of test substance ± FCA given X times followed by topical application one week later.

(PEG 300), 50, 200, or 800 mg/kg body weight/day (RIFM, 2004b). The control and high dose groups had another 10 animals (5 per sex) that underwent a 2-week recovery period. The NOEL of the test material was 50 mg/kg bodyweight/day. No deaths occurred at this dose level. No clinical signs of toxicological relevance were observed in rats at this dose level, nor were there any differences from controls in the functional observational battery performed at week 4. There were no differences in hematology, clinical biochemistry, urinalysis, organ weights and no microscopic or macroscopic findings at this dose level. A NOAEL of 200 mg/kg/day was based on clinical signs of toxicity at the highest dose level. Some of these toxic signs were ruffled fur, hunched posture, salivation, emaciation, dyspnea, reductions in the mean grip strength values, differences in the mean daily food consumption (observed chiefly in males) and treatment related liver weight increases and thymus weight reductions after four weeks of treatment. Differences in hematology parameters, microscopic findings and organ weights were observed generally only at 200 mg/kg/day and 800 mg/kg/day and most were considered treatment related and adaptive, and were not considered toxic effects of the test material.

Table 7
Mucous membrane studies – eye irritation.

Material	Concentration (%) and Volume	Species (number/dose)	Results	Reference
Saturated alkyl cyclic ketones				
Cyclohexyl methyl pentanone	100% (95.7% Purity) (0.1 mL)	Rabbit (3)	2/6 Slight irritation, clear by day 3	RIFM (1980d)
Cyclohexyl methyl pentanone	10% In petrolatum (0.1 mL) OECD 405	Rabbit (3)	1/3 Slight conjunctival erythema, clear by day 2 (non-irritant)	RIFM (1991k)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	5% in EtOH (0.1 mL)	Rabbit (3)	3/3 Mild conjunctival irritation, clear by day 7	RIFM (1973j)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	5% in EtOH (0.1 mL)	Rabbit (3)	3/3 Mild conjunctival irritation with corneal involvement, not clear by day 7	RIFM (1973k)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	5% in EtOH (0.1 mL)	Rabbit (3)	3/3 Severe conjunctival irritation with corneal involvement, not clear by day 10	RIFM (1975d)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	2.5% in EtOH (0.1 mL)	Rabbit (3)	3/3 Conjunctival irritation with corneal involvement, clear by day 10	RIFM (1975e)
1-(3,3-Dimethylcyclohexyl)ethan-1-one	5% in EtOH (0.1 mL)	Rabbit (3)	3/3 Mild conjunctival irritation, not clear by day 7	RIFM (1966b)
1-[1-(1-oxopropoxy) cyclohexyl]-ethanone[a]	100% (0.1 mL)	Rabbit (6)	0/6 Irritation; no observed effects; one death unrelated to dosing; considered practically non-irritating	RIFM (1980m)
1-(2,5,5-Trimethylcycloheptyl)ethan-1-one	2.5% in EtOH (0.1 mL)	Rabbit (3)	3/3 Mild conjunctival irritation, clear by day 7	RIFM (1973l)
Unsaturated alkyl cyclic ketones				
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	100% (95.7% purity) (0.1 mL) OECD 405	Rabbit (3)	3/3 Minimal conjunctival irritation, clear by day 3	RIFM (2007i)
Acetyl cedrene	100% (0.1 mL)	Rabbit (3)	2/3 Slight corneal opacity and conjunctivitis; clear by day 2	RIFM (1979v)
Acetyl cedrene	100% (0.1 mL)	Rabbit (3)	2/3 Corneal opacity, conjunctivitis and edema	RIFM (1979w)
Acetyl cedrene	100% (0.1 mL)	Rabbit (3)	2/3 Corneal conjunctivitis, clear by day 3	RIFM (1977g)
Acetyl cedrene	100% (0.1 mL)	Rabbit (3)	2/3 Slight corneal opacity and 1/3 slight conjunctivitis, clear by day 4	RIFM (1979x)
Acetyl cedrene	100% (0.1 mL)	Rabbit (3)	0/3	RIFM (1980g)
Acetyl cedrene	100% (0.1 mL)	Rabbit (3)	3/3 Slight corneal opacity and conjunctivitis; clear by day 5	RIFM (1979y)
Acetyl cedrene	50% in Tween 80 (0.1 mL)	Rabbit (3)	3/3 Moderate to severe corneal opacity, moderate conjunctivitis, iritis, and peripheral pannus, not clear by day 9	RIFM (1979z)
Acetyl cedrene	50% in Tween 80 (0.1 mL)	Rabbit (3)	3/3 Severe irritation	RIFM (1979aa)
Acetyl cedrene	50% in unspecified vehicle (0.1 mL)	Rabbit (3)	3/3 Corneal conjunctivitis and swelling, clear by day 8	RIFM (1978d)
Acetyl cedrene	50% in Tween 80 (0.1 mL)	Rabbit (3)	3/3 Moderate irritation	RIFM (1979bb)
Acetyl cedrene	10% in Tween 80 (0.1 mL)	Rabbit (3)	0/3	RIFM (1979cc)
Acetyl cedrene	10% in Tween 80 (0.1 mL)	Rabbit (3)	2/3 Corneal opacity and 1/3 conjunctivitis, clear by day 4 (slight irritant)	RIFM (1979dd)
Acetyl cedrene	10% in Tween 80 (0.1 mL)	Rabbit (3)	1/3 Slight conjunctive erythema, clear by 24 h (non-irritant)	RIFM (1979ee)
Acetyl cedrene	2.5% In unspecified vehicle (0.1 mL)	Rabbit (3)	3/3 Moderate conjunctivitis, clear by day 7	RIFM (1965b)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	30% in DEP and 100% (0.1 mL)	Rabbit (3)	3/3 Weak to mild conjunctive irritation, clear by day 2 (30%); 3/3 Moderate conjunctive irritation, clear by day 7 (100%)	RIFM (1985b)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	100% (0.1 mL) OECD, n.f.i.	Rabbit (6)	6/6 Mild conjunctival irritation, clear by day 2	RIFM (1984b)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	100% (93.2% purity) (0.1 mL) OECD 405	Rabbit (3)	3/3 Slight erythema and watery discharge, clear by day 2 (minimally irritating)	RIFM (1999g)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	50% in DEP (0.1 g)	Rabbit (6)	5/6 Slight conjunctive irritation, clear by day 2 (non-irritating)	RIFM (1979ff)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	0.05% (1% In diethylene glycol monoethyl ether diluted 20% in water); 1% In diethylene glycol monoethyl ether (0.1 mL)	Rabbit (6)	0.05%: 0/6 1%: 6/6 Moderate irritation	RIFM (1979gg)

(*continued on next page*)

Table 7 (*continued*)

Material	Concentration (%) and Volume	Species (number/dose)	Results	Reference
2-(3,7-Dimethyl-2,6-nonadien-1-yl)cyclopentanone	0.1 mL, nfi EPA OPPTS 870.2400	Rabbit (3)	0/3	RIFM (2010d)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	100% (0.1 mL) OECD 405	Rabbit (3)	1/3 Moderate conjunctival erythema and slight swelling, 2/3 slight erythema and swelling of the conjunctiva, clear by day 2 considered a non-irritant to the eye	RIFM (1996l)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl) bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	100% (0.1 mL)	Rabbit (6)	4/6 Slight to moderate conjunctival irritation, clear by day 7	RIFM (1981b)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	100% (0.1 mL)	Rabbit (3)	3/3 Slight conjunctival erythema, clear by day 2 (minimally irritating)	RIFM (1988d)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	0.5% In PG (0.1 mL)	Rabbit (3)	3/3 Slight conjunctival irritation, clear by day 4	RIFM (1983f)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	2.5% In EtOH (0.1 mL)	Rabbit (3)	1/3 Mild conjunctival irritation, clear by day 7	RIFM (1973m)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	2.5% In EtOH (0.1 mL)	Rabbit (3)	3/3 Mild conjunctive irritation with corneal involvement, clear by day 7	RIFM (1977f)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	2.5% In propylene glycol (0.1 mL)	Rabbit (3)	0/3	RIFM (1978e)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	0.5% In propylene glycol	Rabbit (3)	0/3	RIFM (1979hh)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	100% OECD 405	Rabbit (3)	3/3 Slight conjunctival irritation, clear by 24 h (non-irritating)	RIFM (2000i)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	100%	Rabbit (3)	3/3 slight to moderate conjunctival erythema, 2/3 slight edema, clear by 24 h (non-irritating)	RIFM (2000i)
4-(2,2,3,6-Tetramethylcyclohexyl)-3-buten-2-one[b]	100% (0.1 mL)	Rabbit (4F)	4/4 Minimal conjunctival irritation at 1 h, 1/4 at 24 h Clear by day 2	RIFM (1992c)
1-(6,6,9-Trimethyl-2-methylene-4,8-cycloundecadien-1-yl)ethanone[a]	100% (0.1 g)	Rabbit (6)	0/6	RIFM (1978f)

[*] According to EEC-Guidelines 84/449/EEC and OECD 405 a substance is considered to be an eye irritant if ocular lesions arise within 72 h and persist for 24 h or longer. A lesion can be based on corneal opacity (⩾2), uvetitis (⩾1), erythema of the conjunctiva (⩾2.5), swelling of the conjunctiva (chemosis (⩾2).
n.f.i – no further information provided.
[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.

Groups of 5 male and 5 female Sprague–Dawley rats were gavaged with 0 (vehicle control), 15, 150, or 250 mg 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one per kg bw per day in corn oil in an OECD 407 guideline study for 28 days (RIFM, 1996e). Mortality, clinical signs, body weights, hematological and biochemical parameters and feed consumption were recorded. At termination, organ weights were recorded and relevant tissue samples were fixed. Tissues from the control and high-dose rats were examined microscopically. The NOAEL was 250 mg/kg bw/day, the highest dose tested. There were no statistically significant differences from control in any hematological or biochemical parameters that were considered to be treatment related; statistically significant changes in some parameters such as mean corpuscular volume, mean corpuscular hemoglobin concentration, glucose level, and creatinine, potassium, and sodium concentration were not considered treatment-related due to substantial overlap between groups, considerable variation, values within historical range and/or no dose–response. Relative liver weights of both sexes were statistically higher than controls. Livers showed minimal centrilobular hepatocyte enlargement (5/5 males, $P < 0.01$; 4/5 females, $P < 0.05$) extending to midzonal regions in 1 female. 5/5 males showed eosinophilic inclusions in proximal convoluted tubular epithelium ($P < 0.01$) and 5/5 males showed minimal basophilic cortical tubules ($P < 0.05$; incidence greater than normally seen as a background change) in renal tissue. These changes were not considered relevant to humans.

Male and female CD rats of Sprague–Dawley origin (5 per sex) were administered methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone for 28 days by gavage at doses of 0 (corn oil), 15, 150, or 1000 mg/kg body weight/day (RIFM, 1994b). At 1000 mg/kg/day, microscopic changes in the liver (hepatocyte hypertrophy), spleen (increase in splenic erythropoiesis in females), and adrenal glands (increase vacuolation in adrenal cortex of males) were observed with concurrent macroscopic changes and organ weight changes, clinical pathology changes, salivation, and effects on body weight. At 150 mg/kg/day no microscopic changes were seen, but there was decreased body weight gain in males during fourth week, and increased kidney weight at necropsy. There were decreased plasma triglyceride levels, slightly decreased myeloid:erythroid ratios in bone marrow smears and increased relative liver weights in females at this dose level. At 15 mg/kg/day, heart weight (absolute and relative) was slightly decreased in males; however, it was not consistent with the pattern of changes at the higher doses and was judged, by the authors, not to be related to treatment. The NOAEL when administered by gavage to rats for 28 days was therefore 15 mg/kg/day.

Table 8.1a
Skin sensitization studies in humans.

Material	Method	Concentration	Results	Reference
Saturated alkyl cyclic ketones				
Cyclohexyl methyl pentanone	HRIPT[c]	12% in DEP:EtOH (1:3) (14170 μg/cm^2)	0/57	RIFM (1988a)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	HRIPT[c]	5% in EtOH (3820 μg/cm^2)	0/43	RIFM (1973a)
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	HRIPT[c]	5% in EtOH (3820 μg/cm^2)	0/43	RIFM (1973b)
1-(3,3-Dimethylcyclohexyl)ethan-1-one	HRIPT[c]	5% in EtOH (3820 μg/cm^2)	0/37	RIFM (1966a)
1-(3,3-Dimethylcyclohexyl)ethan-1-one	HRIPT[c]	2.5% in EtOH (1910 μg/cm^2)	0/44	RIFM (1972b)
1-(2,5,5-Trimethylcycloheptyl)ethan-1-one	HRIPT[c]	2.5% in EtOH (1910 μg/cm^2)	0/40	RIFM (1973c)
Unsaturated alkyl cyclic ketones				
Acetyl carene	HRIPT[c]	5% in EtOH (3820 μg/cm^2)	0/41	RIFM (1971b)
Acetyl carene	Maximization[d]	10% in petrolatum (6900 μg/cm^2)	0/25	RIFM (1974b)
Acetyl cedrene	HRIPT[c]	30% in DEP:EtOH (3:1) (35430 μg/cm^2)	0/101	RIFM (2004g)
Acetyl cedrene	HRIPT[c]	5% in EtOH (3820 μg/cm^2)	0/36	RIFM (1964)
Acetyl cedrene	Maximization[d]	30% In unspecified vehicle, volume, area	0/25	Ishihara et al. (1986)
Acetyl cedrene	Maximization[d]	30% In petrolatum (20,700 μg/cm^2)	0/25	RIFM (1972c)
2-Cyclohexyl-1,6-heptadien-3-one	HRIPT[c]	2% (2500 μg/cm^2) Vehicle not stated	0/47	RIFM (2003b)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	HRIPT[c]	2% in DMP (1000 μg/cm^2)	0/53	RIFM (1996h)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT[c]	10% In petrolatum (5000 μg/cm^2)	0/51	RIFM (1977c)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT[c] FDA 21CFR parts 50,56,312	5% in DEP (2500 μg/cm^2)	0/100	RIFM (1999b)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT[c]	5% in DEP:EtOH (1:3) (2500 μg/cm^2)	0/105	RIFM (2001e)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT[c]	1% in volatile vehicle (500 μg/cm^2)	0/52	RIFM (2002e)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT[c]	1% in DEP (500 μg/cm^2)	0/102	RIFM (2003c)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT[c] (Photosensitization control)	0.5% In petrolatum (0.2 g In unspecified area)	0/50	RIFM (1979n)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	HRIPT[c]	1% in EtOH (500 μg/cm^2)	0/50	RIFM (1983c)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	HRIPT[c]	15% (vehicle not specified)	0/57	RIFM (1998)
1-(*para*-Menthen-6-yl)-1-propanone	HRIPT[c]	2% in DMP (unspecified volume and area)	0/50	RIFM (1960b)
1-(*para*-Menthen-6-yl)-1-propanone	Maximization[d]	4% In petrolatum (2760 μg/cm^2)	0/25	RIFM (1971c)
1-(*para*-Menthen-6-yl)-1-propanone	Schwartz patch [f]	100% (As supplied) (unspecified volume and area)	0/50	RIFM (1960a)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	HRIPT[c]	2% In unspecified vehicle (1000 μg/cm^2)	0/50	RIFM (1984c)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT[c]	40% in DEP:EtOH (3:1) (47,250 μg/cm^2)	0/101	RIFM (2004i)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT[c]	22.5% in DEP:EtOH (1:3) (12,400 μg/cm^2)	0/53	RIFM (1999c)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT[c]	12.5% in EtOH (1720 μg/cm^2)	0/51	RIFM (1979o)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT[c]	2.5% in EtOH (1910 μg/cm^2)	0/36	RIFM (1973d)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT[c]	2.5% in EtOH (1530 μg/cm^2)	0/44	RIFM (1977d)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	HRIPT[c]	2.5% in EtOH (1910 μg/cm^2)	0/42	RIFM (1978b)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	HRIPT[c]	2% in unspecified vehicle, volume and area	0/52	RIFM (1979ii)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	HRIPT[c]	0.1% In unspecified vehicle, 0.5 mL (125 μg/cm^2)	0/97	RIFM (2006b)

(*continued on next page*)

Table 8.1a (*continued*)

Material	Method	Concentration	Results	Reference
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	HRIPT[c]	0.1% In unspecified vehicle, 0.5 mL (125 μg/cm^2)	0/97	RIFM (2006b)
1-(3,5,6-Trimethyl-3-cyclohexen-1-yl)ethan-1-one	HRIPT[c]	0.5% In EtOH (380 μg/cm^2)	0/42	RIFM (1965a)
1-(2,2,6-Trimethylcyclohexyl)-2-buten-1-one[a]	Re-test of volunteers who reacted to 48 h closed patch test (days 18–21 and 36 after patch removal)	2%, 5% In petrolatum in unspecified volume and area	2%: 1/7 at 18–21d; 1/7 at 36d 5%: 5/7 at 18–21d; 1/7 at 36d	RIFM (2002g)
1-(6,6,9-Trimethyl-2-methylene-4,8-cycloundecadien-1-yl)ethanone[a]	HRIPT[c]	5% In petrolatum (6250 μg/cm^2)	0/50	RIFM (1975a)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.
[c] Human repeat insult patch test (HRIPT) generally consists of nine occluded induction patches (3 times/week) for 3 weeks and one occluded challenge patch. Sensitization reported during challenge phase only. Patch applications are 24 h in duration unless noted.
[d] Maximization generally consists of 5 induction 48-h 2 cm^2 patches every other day with 0.3 g or 0.3 mL at 10 times the use concentration in petrolatum (1% SLS for 24-h prior to the first patch). After 5% SLS for 30 min, challenge consists of 48-h occluded patch given 10–14 days later; recalling if necessary one week later.
[e] Modified Draize test generally consists of ten 48-or 72-h induction patches with highest tolerable concentration in petrolatum (0.2 mL or 0.2 g at highest tolerable concentration) on arm or upper back; Challenge with 72-h patch with nonirritating concentration 2 weeks later.
[f] Schwartz patch tests consist of one 48-h patch followed by challenge 1 week later.

Table 8.1b
Skin sensitization studies in humans – diagnostic patch tests.

Material	Concentration	Subjects	Results	Reference
Saturated alkyl cyclic ketones				
None				
Unsaturated alkyl cyclic ketones				
Acetyl cedrene	5% In unspecified vehicle	Patients with cosmetic dermatitis, facial melanosis and non-cosmetic dermatitis/eczema (1978–1986)	0/72 Total eczema and dermatitis (0/32 cosmetic dermatitis, 0/14 facial melanosis, 0/26 non-cosmetic dermatitis and eczema)	Itoh et al. (1986, 1988), Nishimura et al. (1984)
Acetyl cedrene	5% In petrolatum	Dermatological patients	3/1855 (0.2%)	Frosch et al. (2002)
Acetyl cedrene	1 Or 5% in petrolatum	Dermatological patients	1/100 (1%)	Frosch et al. (1995)
Acetyl cedrene	1 Or 5% in petrolatum	Dermatological patients	0/95	Frosch et al. (1995)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	5% In petrolatum	Volunteers with proven sensitization to fragrance materials	3/178, (1.7%)	Larsen et al. (2001)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	5% In petrolatum	Dermatological patients	3/1855 (0.2%)	Frosch et al. (2002)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	5% In unknown vehicle	Patients with contact allergy	0/422	An et al. (2005)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	1 Or 5% in petrolatum	Dermatological patients	1/313 (0.3%)	Frosch et al. (1995)

After a 7-day dose range oral toxicity study with rats of Sprague–Dawley origin (5 per sex), 1000 mg/kg/day was chosen as the highest dose of 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE) for a subsequent 28 day gavage study. This was based on increased mean relative liver weights in rats receiving 1000 mg/kg/day (RIFM, 1995a). Male and female CD rats of Sprague–Dawley origin (5 per sex) were administered OTNE by gavage at doses of 0 (corn oil), 15, 150, and 1000 mg/kg body weight/day in a 28-day OECD 407 guideline study (RIFM, 1997b). The control and high dose groups had another 10 animals (5 per sex) that underwent a 2-week recovery period. Centrilobular hepatocyte enlargement in male and female rats of the 1000 mg/kg/day group at the end of treatment was associated with the increase in liver weights; this change was not observed in any rats after the 2-week recovery period. Associated changes in serum liver enzymes, and biochemistry parameters were also observed, including cholesterol levels, gamma-glutamyl transferase levels and alanine transaminase (ALT) levels. Lowered ALT in males and higher cholesterol in females persisted after recovery. In males receiving 150 or 1000 mg/kg/day, a dose-related incidence and degree of eosinophilic inclusions in cortical tubules was observed at the end of treatment and persisted after the 2-week recovery period. The latter finding is consistent with alpha microglobulin nephropathy syndrome specific to the male rat and not considered to be relevant to humans (Alden, 1986). The NOEL was 15 mg/kg/day based on hematology and blood biochemistry changes at 150 mg/kg/day. These effects, reduced after recovery, and the male rat nephropathy and hepatic treatment-related findings were not considered to be adverse by the authors. The NOAEL for OTNE in this study was identified to be 1000 mg/kg/day.

Male and female CD rats of Sprague–Dawley origin (5 per sex) were administered 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one in an OECD 407 guideline study for 28 days (RIFM, 2005b). Rats were dosed (gavage) at 0 (corn oil), 50, 200, or 1000 mg/kg body weight/day. A NOAEL of 50 mg/kg/day was based on signs of toxicity at the higher dose. At 50 mg/kg/day there were increased amounts of

Table 8.2a
Skin sensitization studies in animals.

Material	Method	Induction	Challenge	Species (number/dose)	Results	Reference
Saturated alkyl cyclic ketones						
Cyclohexyl methyl pentanone	Modified Buehler[e]	25% in EtOH reduced to 10% On day 14	5% in EtOH and 2% in EtOH (rechallenge)	Guinea pig (10)	7/10 Challenge; 0/10 rechallenge	RIFM (1981a)
Cyclohexyl methyl pentanone	Maximization[c]	5% in PG ± FCA (intradermal); 25% in petrolatum (topical)	10% In petrolatum	Guinea pig (10)	3/10 Mild sensitization	RIFM (1980e)
Cyclohexyl methyl pentanone	Maximization[c] OECD 406	5% (10% In white petrolatum diluted with peanut oil or FCA) (intradermal); 10% in white petrolatum (topical)	50% In peanut oil	Guinea pig (10/sex)	0/19* (One mortality due to disease)	RIFM (1991h)
1-[1-(1-Oxopropoxy) cyclohexyl]-ethanone[a]	Delayed contact hypersensitivity test[f]	10% in alcohol SDA 39C	10% in alcohol SDA 39C	Guinea pig (15)	0/14* (One mortality unrelated to treatment)	RIFM (1980n)
Unsaturated alkyl cyclic ketones						
Acetyl cedrene	Open epicutaneous Test[d]	1%, 3%, 10%, 30% or 100% In water, acetone, alcohol, petrolatum, PEG, etc.	5% In water, acetone, alcohol, petrolatum, PEG, etc.	Guinea pig (6–8)	0/6–8	Klecak (1985)
Acetyl cedrene	Maximization[c]	10% In unspecified vehicle	10% In unspecified vehicle	Guinea pigs (n.f.i.)	"Extreme" sensitization, no further details provided	Ishihara et al. (1986)
Acetyl cedrene	Maximization[c]	0.1% In 0.01% dobs saline (intradermal); 10% in EtOH (topical)	10% in EtOH	Guinea pig (10F)	0/10	RIFM (1975b)
Acetyl cedrene	Maximization[c]	0.4% In dobs saline ± FCA (1:1) (intradermal); 40% in EtOH (topical)	10% in EtOH	Guinea pig (10)	0/10 Similar to control	RIFM (1976b)
Acetyl cedrene	Maximization[c]	0.5% In dobs saline (intradermal)	0.2% In dobs saline (intradermal); 10% in EtOH (topical)	Guinea pig (10)	3/10 At rechallenge	RIFM (1975c)
Acetyl cedrene	Maximization[c]	0.25% In 0.01% dobs saline (intradermal); 15% in EtOH (topical)	2.5% In EtOH	Guinea pig (10)	0/10 Similar to control	RIFM (1979q)
Acetyl cedrene	Maximization[c]	0.25% In dobs saline ± FCA (1:1) (intradermal); 20% in EtOH (topical)	2% in EtOH (topical)	Guinea pig (10)	0/10 Similar to controls	RIFM (1979s)
Acetyl cedrene	Maximization[c]	0.25% In dobs saline ± FCA (1:1) (intradermal); 10% in EtOH (topical)	1% in EtOH	Guinea pig (10)	5/10 Marginal reaction (after 2nd rechallenge); not considered a sensitizer under conditions of study	RIFM (1979r)
Acetyl cedrene	Photosensitizationcontrol	50% in DEP: EtoH (3:1)	15% Or 50% in DEP:EtOH (3:1)	Guinea pig (5)	0/5	RIFM (2005g)
2-Cyclohexyl-1,6-heptadien-3-one	Maximization[c] OECD 406	100% (intradermal); 100% (topical)	3% in PEG 300 (topical)	Guinea pig (10)	0/10	RIFM (2001g)
2-Cyclohexyl-1,6-heptadien-3-one	Photosensitization control[h] CFTA guidelines	15% in PEG 300 (topical)	0.5%, 1%, 3%, 5% in PEG 300 (topical)	Guinea pig (20)	0/20	RIFM (2002f)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	Maximization[c] OECD 406	5% in FCA (intradermal); 100% (topical)	75% in EtOH:DEP	Guinea Pig (20)	8/20	RIFM (1991j)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	Maximization[c] OECD 406	5% In saline: propylene glycol (1:1) (intradermal); 100% in saline: propylene glycol (1:1) (topical)	100% Topical (challenge and rechallenge)	Guinea pig (10/sex)	1/20 Challenge; 0/20 rechallenge	RIFM (1985c)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	Maximization[c](photosensitization controls)	10% in EtOH (topical)	10% in EtOH (topical)	Guinea pig (10)	0/10	RIFM (1985d)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Modified Buehler[e] OECD 406	100%	100%	Guinea pig (20)	0/20	RIFM (1999d)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Open epicutaneous Test[d] OECD 406	0.5%, 5%, or 10% in EtOH	0.1%, 1%, 5%, or 10% in EtOH	Guinea pig (6F)	0/6	RIFM (2000g)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Open epicutaneous Test[d] OECD 406	0.5%, 5%, or 10% In dipropylene glycol	0.5%, 1%, 3%, or 10% In dipropylene glycol, rechallenge with 0.5%, 1%, 3%, or 10% in EtOH	Guinea pig (6F)	First challenge = 0/6; Rechallenge with different vehicle: 3%, 10% = 1/6 0.5–1% = 0/6	RIFM (2000h)

(*continued on next page*)

Table 8.2a (*continued*)

Material	Method	Induction	Challenge	Species (number/dose)	Results	Reference
1-(5,5-Dimethyl-1-cyclohexen-1-yl pent-4-en-1-one	Maximization[c] OECD 406	5% in PEG 400 or FCA:saline (1:1) (intradermal); 100% (topical)	75% in PEG 400	Guinea pig (10M)	8/10 Sensitizing	RIFM (1999f)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Maximization[c] OECD 406	5% In mineral oil or FCA (intradermal); 100% (topical)	75% In mineral oil	Guinea pig (10)	8/10 Mild to moderate erythema persisting for >48 h Concluded that sensitization had occurred	RIFM (2003d)
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Maximization[c] OECD 406	40% in Alembicol D ± FCA (1:1) (intradermal); 100% (>95% purity) (topical)	50% in Alembicol D or 100% (>95% purity) (topical)	Guinea pig (10)	0/10	RIFM (1996i)
2-(3,7-Dimethyl-2,6-nonadien-1-yl)cyclopentanone[a]	Delayed contact hypersensitivity test[f] OECD 406	100%	100%	Guinea pig (10/sex)	0/10	RIFM (2010e)
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-[b]	Maximization[c]	5% In mineral oil (intradermal); 100% (topical)	100% (Topical)	Guinea pig (15)	0/15	RIFM (1996k)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl) bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Maximization[c]	50% In propylene glycol ± FCA (intradermal); 100% (topical)	20% In petrolatum	Guinea pig (10 M)	0/10	RIFM (1979u)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Maximization[c]	2% In 0.01% dobs saline (intradermal); 100% (topical)	50% In acetone: PEG 400	Guinea pig (10/sex)	Challenge 1: 2/20 (50%), Challenge 2: 6/20 (50%), Challenge 3: 3/20 (50%) and 1/20 (5%); weak sensitizer	RIFM (1988c)
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Maximization[c]	10% in propylene glycol ± FCA (1:1) (intradermal); 25% in petrolatum (topical)	3% and 10% in petrolatum	Guinea pig (10/sex)	2/20 (10%), 1/20 weak (3%)	RIFM (1987c)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	Open epicutaneous Test[d]	3%, 10%, 30%, 100% in EtOH	3%, 10%, 30%, 100% in EtOH on days 21 and 35	Guinea pig (6)	0/6	RIFM (1983e)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	FCAT[g]	5% in FCA (0.1 mL; intradermal)	0.1%, 0.3%, 1% (epicutaneous) on days 21 and 35	Guinea pig (10–20)	0.1%: No challenge on d 21; 5/10 reactions on d 35 0.3%: 8/10 on d 21; 9/10 on d 35 1%: 10/10 on d 21 and d 35 "strong sensitizer"	RIFM (1983g)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Guinea pig sensitization by Maguire method[h]	2.5% in EtOH	2.5% in EtOH (0.1 mL)	Guinea pig (10)	0/10	RIFM (1973i)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	Open epicutaneous Test[d]	3%, 10%, or 30% in EtOH	10% and 30% in EtOH	Guinea pig (6–8)	0/6–8	RIFM (1980f)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	FCAT[g]	5% in FCA (intradermal), 10% in EtOH (topical)	3% or 10% in EtOH	Guinea pig (20)	3%: 18/20 10%: 20/20	RIFM (1980f)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Open epicutaneous Test[d] OECD 406	1%, 5%, 10% in EtOH (topical)	0.1%, 1%, 5%, 10% in EtOH (topical)	Guinea pig (6)	0/6 at 1%, sensitizing at >1%	RIFM (2000e)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Maximization[c] OECD 406	100% (Intradermal), 100% (Topical)	5%, 25%, 100% in PEG 300 (topical)	Guinea pig (10)	9/10 at 5%, 10/10 at >5%	RIFM (2000f)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Photosensitization control[h] CFTA guidelines	1%, 10%, 100% in PEG 300 (topical)	0.5%, 1%, 2.5%, 5% in PEG 300	Guinea pig (20)	10%, 100% Induction: sensitization at all 4 challenge doses	RIFM (2001h)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Open epicutaneous Test[d] OECD 406	1%, 5%, 10% in PEG 300 (topical)	0.1%, 1%, 5%, 10% in EtOH (topical)	Guinea pig (6)	0/6 at 1%, sensitizing at >1%	RIFM (2000e)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Maximization[c] OECD 406	100% (intradermal), 100% (topical)	5%, 25%, 100% in PEG 300 (topical)	Guinea pig (10)	9/10 at 5%, 10/10 at >5%	RIFM (2000f)

Table 8.2a (*continued*)

Material	Method	Induction	Challenge	Species (number/dose)	Results	Reference
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Photosensitization control[h] CFTA guidelines	10%, 100% in PEG 300 (topical)	0.5%, 1%, 2.5%, 5% in PEG 300	Guinea pig (20)	10%, 100% Induction. ⩾0.5% challenge – sensitizing	RIFM (2001h)
4-(2,2,3,6-Tetram-ethylcyclohexyl)-3-buten-2-one[b]	Delayed contact hypersensitivity test[f]	25% Liquid paraffin or FCA and distilled water (intradermal)	50% in EtOH or 100% (Topical)	Guinea pig (20)	0/20	RIFM (1992d)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.
[b] A captive material.
[c] Maximization – Guinea pigs induced with intradermal injections of test material ± Freund's adjuvant/oleum arachidis on day 1 then with a closed patch test topical application on day 7; challenge is with closed patch test on day 21.
[d] OET – Guinea pigs inducted daily for 3 weeks with open topical applications of the test material; challenge by open application of the threshold irritating concentration and read after 24 h.
[e] Modified Buehler – Guinea pigs induced with 0.5 mL test material to 4 cm^2 occluded patch for 6 h repeated 1/week for 3 weeks; 2 weeks later primary challenge.
[f] Delayed contact hypersensitivity test – Guinea pigs induced 1/week for 3 weeks with 6-h semi-occlusive patch; challenge 14 days later in same manner; rechallenge 8 days later.
[g] FCAT – Guinea pigs inducted with 0.1 mL intradermal injection of 5% in FCA 3 times (day 1, 5 and 9) or 5 times (day 0, 2, 4, 7, or 9) on 8 cm^2; Challenge by open epicutaneous application in appropriate vehicle (water, acetone, alcohol, petrolatum, polyethylene glycol, etc.) at days 21 and 35.
[h] Photosensitization control – 24 h closed patch topical every other day for 2 weeks (6 total) followed by challenge on day 22.
[i] Draize – Guinea pigs inducted with 10 intradermal injections of the test material at the ICC over a 3 week period; challenge with injection of same concentration.
[j] Modified Draize – Guinea pigs inducted day 1 with 4 intradermal injections of 2.5× ICC (injection challenge concentration) gives a slight but perceptible irritation with no edema); challenge on day 14 performed with intradermal injection of ICC on one flank and topical application of the (application challenge concentration) is the highest open topical concentration which caused no irritation in the pretest); rechallenge performed at day 21.
[k] Modified CCET (cumulative contact enhancement test) – induction consists of FCA id injection and 24-h patch 2X at an interval of 4–6 days followed by non-occlusive patches 3 weeks later.
[l] Guinea pig sensitization by the Maguire method – occlusive application on day 1, 2, 4, and 7; on day 4 dermal application accompanied by injection of FCA. Challenge on day 18.

hyaline droplets in the males related to test article exposure. However, due to the male rat predisposition for hyaline droplet formation, it was not considered toxicologically relevant. At 200 mg/kg/day, signs of toxicity included: piloerection, salivation, sedation, hunched posture, prostration, significant reduction of reflexes, emaciation, elevation in cholesterol, triglyceride, alanine aminotransferase, gamma glutamyltransferase and phospholipids, changes in electrolytes, elevated calcium levels in males and elevated potassium levels in females.

5.3. Mutagenicity and genotoxicity

5.3.1. In vitro mutagenicity studies

Two saturated ACK fragrance materials (cyclohexyl methyl pentanone and 1-(3,3-dimethylcyclohexyl)ethan-1-one) and eleven unsaturated ACK fragrance materials (acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene); acetyl cedrene; 2-cyclohexyl-1,6-heptadien-3-one; 1-(2,4-dimethyl-3-cyclohexenyl)2,2-dimethylpropan-1-one; 1-(5,5-dimethyl-1-cyclo hexen-1-yl)pent-4-en-1-one;1-(3,3-dim 1-[5(or 6)-methyl-7(or 8) -(1-methylethyl) bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one; methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone; 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one; 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone; 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one) were inactive when tested for reverse mutation in at least one Ames test with *S. typhimurium* TA97, TA98, TA100, TA1535, TA1537, TA1538 with or without metabolic activation (Table 4.1). In *E. coli* WP2 uvrA cells, reverse mutation was reported with methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone, but was not observed with the saturated ACK, 1-(3,3-dimethylcyclohexyl)ethan-1-one, nor with the following unsaturated ACKs: acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene); 2-cyclohexyl-1,6-heptadien-3-one; 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one; 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one; or 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (Table 4.1).

Studies in mammalian cell systems showed negative genotoxic results. Chromosomal aberrations were not induced with three of the unsaturated ACK fragrance materials with cultured human lymphocytes, nor were aberrations induced with the unsaturated alkyl cyclic ketone, acetyl cedrene, with Chinese Hamster ovary cells. 2-Cyclohexyl-1,6-heptadien-3-one and 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one failed to induce chromosomal aberrations in Chinese Hamster V79 cells (Table 4.2). There were no mammalian cell system studies with saturated ACK fragrance materials. In the forward mutation assay with mouse lymphoma L5178Y ±TK cells, the unsaturated ACK, acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene), did not induce mutations with or without metabolic activation (Table 4.2).

5.3.2. In vivo mutagenicity studies

The unsaturated ACK fragrance ingredients, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one and 2-cyclohexyl-1,6-heptadien-3-one, were assessed for their effect on the incidence of micronucleated polychromatic erythrocytes in mice, see Table 4.3. CD-1 mice (15 per sex) mice were gavaged with 5000 mg/kg 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one in a single dose and bone marrow smears were taken (5 per sex) at 24, 48, and 72 h (RIFM, 1990). The ratio of polychromatic to normochromatic erythrocytes was assessed by examination of at least 1000 erythrocytes from each animal. There was no evidence of mutagenic potential in this *in vivo* test procedure. Likewise, NMRI mice (6/sex/dose) were gavaged with 0 (corn oil), 500, 1000, or 2000 mg/kg body weight of 2-cyclohexyl-1,6-heptadien-3-one in a single dose and bone marrow smears taken (5 per sex) at 24 and 48 (high dose only) h

Table 8.2b
Skin sensitization studies in animals – mouse local lymph node assay.

Material	Method	Dose	Species (number/dose)	Results	Reference
Saturated alkyl cyclic ketones					
None					
Unsaturated alkyl cyclic ketones					
Acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)	LLNA OECD 429	10%, 25%, 50% In acetone:olive oil (4:1)	CBA/Ca female mice (4)	EC_3 = 20.71% (5025 μg/cm^2)	RIFM (2007j)
Acetyl cedrene	LLNA OECD 429	2.5%, 5%, 10%, 25%, or 50% aged/oxidized test material in DEP: EtOH (3:1)	CBA/J female mice (4)	EC_3 = 13.93% (3480 μg/cm^2)	RIFM (2005h)
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	LLNA	1%, 10%, 30% in acetone	CBA/CA male mice (5)	EC_3not calculated SI values increased greater than 3-fold at 10 and 30%, indicating a potential for contact sensitization	RIFM (1995b)
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	LLNA OECD 429	0.1%, 1%, 10% or 100% in acetone:olive oil (4:1)	CBA/CaOlaHsd female mice (4)	EC_3 = 2.99% (ca) (748 μg/cm^2)	RIFM (2001i), Natsch et al. (2007), Natsch and Gfeller (2008)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	LLNA OECD 429	2.5%, 5%, 10%, 25%, or 50% aged/oxidized test material in DEP: EtOH (3:1)	CBA/J female mice (5)	EC_3 = 14.2% (3550 μg/cm^2)	RIFM (2008a)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	LLNA OECD 429	2.5%, 5%, 10%, 25%, or 50% high purity test material in DEP: EtOH (3:1)	CBA/J female mice (5)	EC_3 = 6.07% (1517.5 μg/cm^2)	RIFM (2008b)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	LLNA OECD 429	2.5%, 5%, 10%, 25%, or 50% in DEP:EtOH (3:1)	CBA/J female mice (4)	EC_3 = 25.14% (6285 μg/cm^2)	RIFM (2005i)
1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one	LLNA OECD 429	2.5%, 5%, 10%, 25%, 50% in EtOH:DEP (1:2)	CBA/CA female mice (5)	EC_3 = 14.4% (3600 μg/cm^2)	RIFM (2010f)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	LLNA OECD 429	0.1%, 1%, 10% Or 100% in acetone:olive oil (4:1)	CBA/CaOlaHsd female mice (4)	EC_3 = between 1% and 10% (250–2500 μg/cm^2)	RIFM (2001j)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	LLNA OECD 429	0.1%, 1%, 10% Or 100% in acetone:olive oil (4:1)	CBA/CaOlaHsd female mice (4)	EC_3 = between 1% and 10% (250–2500 μg/cm^2)	RIFM (2001k)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	LLNA OECD 429	0.1%, 1%, 10% or 100% In acetone:olive oil (4:1)	CBA/CaOlaHsd female mice (4)	EC_3 = between 1% and 10% (250–2500 μg/cm^2)	RIFM (2001j)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	LLNA OECD 429	0.1%, 1%, 10% Or 100% in acetone:olive oil (4:1)	CBA/CaOlaHsd female mice (4)	EC_3 = between 1% and 10% (250–2500 μg/cm^2)	RIFM (2001k)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.

Table 9.1a
Phototoxicity studies – humans.

Material	Test System	Concentration and frequency	Energy	Results	Reference
Saturated alkyl cyclic ketones					
None					
Unsaturated alkyl cyclic ketones					
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Human (20)	0.5% In petrolatum	1.68 mW/cm^2 at 38.1 cm for 15 min	0/20 (During induction of HRIPT)	RIFM (1979n)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Human (28)	12.5% in EtOH, 1×/week for 3 weeks	UVA/UVB for 12 min (3× Minimal erythema dose[a])	0/28	RIFM (1980h)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Human (10)	12.5% in EtOH (0.1 mL) single application	UVA/UVB 31.5 mW/cm^2 for 12 min	0/10	RIFM (1980i)

[a] MED – minimal erythema dose is the determined as time of light exposure necessary to cause minimal reddening of the skin after 24 h
[b] RB – Robertson–Burger SUV meter unit.

(RIFM, 2005f). The ratio of polychromatic to normochromatic erythrocytes was assessed by examination of at least 2000 erythrocytes from each animal. No evidence of mutagenic potential was found.

5.4. Reproductive and developmental toxicity

No one- or two-generation reproductive studies have been performed with any of the ACK fragrance ingredients. However the

Table 9.1b
Phototoxicity studies – animals.

Material	Test System	Concentration and frequency	Energy	Results	Reference
Saturated alkyl cyclic ketones					
Cyclohexyl methyl pentanone	Rabbit (6)	10% in EtOH	UVA at 20.3 cm For 60 min	6/6 Similar to control, not phototoxic	RIFM (1980d)
Unsaturated alkyl cyclic ketones					
Acetyl cedrene	Guinea pig (5) (2 h patch)	15% or 50% in DEP:EtOH (3:1)	UVB ~900 RB for 2.25 h (2.25 MED)	0/5	RIFM (2005g)
Acetyl cedrene	Rat (10)	30% in EtOH	12 J/cm^2 At 32 cm for 149 min	10/10 Slight phototoxic activity	RIFM (1982b)
Acetyl cedrene	Mouse (4)	0, 1.5, 5, 17, 60, 200, 660 mg/kg bw In olive oil (intraperitoneal)	18 J/cm^2 At 33 cm for 245 min	0/10	RIFM (1982d)
Acetyl cedrene	Balb/c 3T3 cells, neutral red uptake OECD 432	IC_{50}(μg/ml): 11.13 (+UV) 24.51 (−UV)	Cells irradiated at room temperature for ~50 min. through the lid of the 96 well plate with a 5 J/cm^2 dose of radiation (non-cytotoxic)	PIF: 2.203 MPE: 0.325 Phototoxic	RIFM (2010g)
2-Cyclohexyl-1,6-heptadien-3-one	Guinea pig (4) CFTA guidelines	3%, 5%, 10%, 15% in PEG 300	UVA (20 J/cm^2) at 16 cm for 30 min	0/4	RIFM (2002f)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	Guinea pig (10)	10% in EtOH (with 2% DMSO)	20 J/cm^2 UVA	0/10	RIFM (1985e)
1-[5(or 6)-Methyl-7(or 8)-(1-			methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Rabbit (6)	10% or 25% in EtOH
UVA at 20.3 cm for 60 min	6/6 Average higher than control until day 4	RIFM (1981b)			
1-[5(or 6)-Methyl-7(or 8)-(1-			methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Guinea pig (5)	25% in EtOH
maximization induction	UVA at 25 cm for 30 min	0/5	RIFM (1981c)		
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	Guinea pig (10)	3% in DMSO	UVA at 20 J/cm^2	0/10	RIFM (1983h)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Hairless Mouse (12M)	10% in EtOH	(1) UVA from blacklight 800 μW at 35 cm for 60 min; (2) UVA 200 RB [2] at 1 m for 60 min	0/24	RIFM (1980j)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	Guinea pig (10) CFTA guidelines	10% in EtOH (with 2% DMSO)	20 J/cm^2 UVA	0/10	RIFM (1982c)

PIF: Photo irritation factor.
MPE: Mean photo effect.
[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.

Table 9.2a
Photosensitization studies – humans.

Material	Test System	Concentration	Energy	Subjects	Results	Reference
Saturated alkyl cyclic ketones						
None						
Unsaturated alkyl cyclic ketones						
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	HRIPT photosensitization	Induction: 0.2 g of 0.5% in petrolatum (24 h patch) Challenge: 0.5% in petrolatum	1.68 mW/cm^{2}at 38.1 cm for 15 min	Human (20)	0/20	RIFM (1979n)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	Human Photosensitization (Induction with 2 semiocclusive patches 1/wk for 3 wks)	12.5% in EtOH	UVA/UVB 3× MED[a]of for 12 min (induction) and 3 min (challenge)	Human (28)	0/28	RIFM (1980h)

[a] MED – minimal erythema dose is the determined as time of light exposure necessary to cause minimal reddening of the skin after 24 h.
[b] RB – Robertson–Burger SUV meter unit.

developmental toxicity of two ACK fragrance ingredients, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE) and acetyl cedrene have been evaluated, see Table 5.

5.4.1. Reproductive studies

Though a full reproductive study has not been performed, some reproductive endpoints have been measured in other toxicology studies. In the 13-week dermal toxicity study with acetyl cedrene in rats discussed above, no changes in the female reproductive endpoint estrous cyclicity and male reproductive endpoints sperm mean percent motility, total sperm count, and sperm morphology were observed at doses up to 300 mg/kg/day (RIFM, 2002a). The toxicokinetic study with OTNE described above (RIFM, 2001b) indicated that little to no radioactivity was detectable in the fetus or placenta after repeated dosing during pregnancy.

5.4.2. Developmental studies

In a preliminary range-finding study, the results suggested that the unsaturated ACK fragrance material, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE), was

Table 9.2b
Photosensitization studies – animals.

Material	Test System	Concentration	Energy	Results	Reference
Saturated alkyl cyclic ketones					
Cyclohexyl methyl pentanone	Guinea pig (15)	Induction: 10% in EtOH Challenge: 2.5% in EtOH	UVA at 35 cm for 15 min	0/15	RIFM (1980k)
Unsaturated alkyl cyclic ketones					
Acetyl cedrene	Guinea pig (5)	Induction: 50% in DEP EtOH (3:1) Challenge: 15% or 50% in DEP:EtOH (3:1)	UVB ~900 RB for 2.25 h (2.25 MED)	0/5	RIFM (2005g)
2-Cyclohexyl-1,6-heptadien-3-one	Guinea pig (20)	Induction: 15% in PEG 300 (topical) Challenge: 0.5%, 1%, 3%, 5% in PEG 300 (topical)	UVA (10 J/cm^2) at 16 cm UVB (1.8 J/cm^2) at 5 cm	0/20	RIFM (2002f)
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone[a]	Guinea pig (10)	Induction: 10% in EtOH Challenge: 10% in EtOH	10 J/cm^2 UVA (duration not specified)	0/10	RIFM (1985d)
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Guinea pig (10)	Induction: 25% in EtOH (5 days) Challenge: 12.5% in EtOH	UV (Hanovia Fluorescence lamp, model 11) 30 min. at 25 cm	0/10	RIFM (1981c)
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	Guinea pig (10)	Induction: 10% in EtOH Challenge: 3% in DMSO	10 J/cm^2 UVA	0/10	RIFM (1983i)
1-(2,4,4,5,5-Pentalmethyl-1-cyclopenten-1-yl)ethan-1-one	Guinea pig (4/sex)	Induction: 10% in EtOH Challenge: 10% in EtOH	UVB at 38 cm for 15 min followed by UVA at 25 cm for 4 h	0/8	RIFM (1980l)
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	Guinea pig (20)	Induction: Undiluted or 10% in PEG 300 (topical) Challenge: 0.5%, 1%, 2.5%, 4% in PEG 300 (topical)	UVA (10 J/cm^2) at 16 cm UVB (1.8 J/cm^2) at 5 cm	0/20	RIFM (2001h)
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one[a]	Guinea pig (20) CFTA guidelines	Induction: Undiluted or 10% in PEG 300 (topical) Challenge: 0.5%, 1%, 2.5%, 4% in PEG 300 (topical)	UVA (10 J/cm^2) at 16 cm UVB (1.8 J/cm^2) at 5 cm	0/20	RIFM (2001h)

[a] This material is not one of the materials being reviewed as it is not used in fragrances; but it is included in this table because it is structurally related.

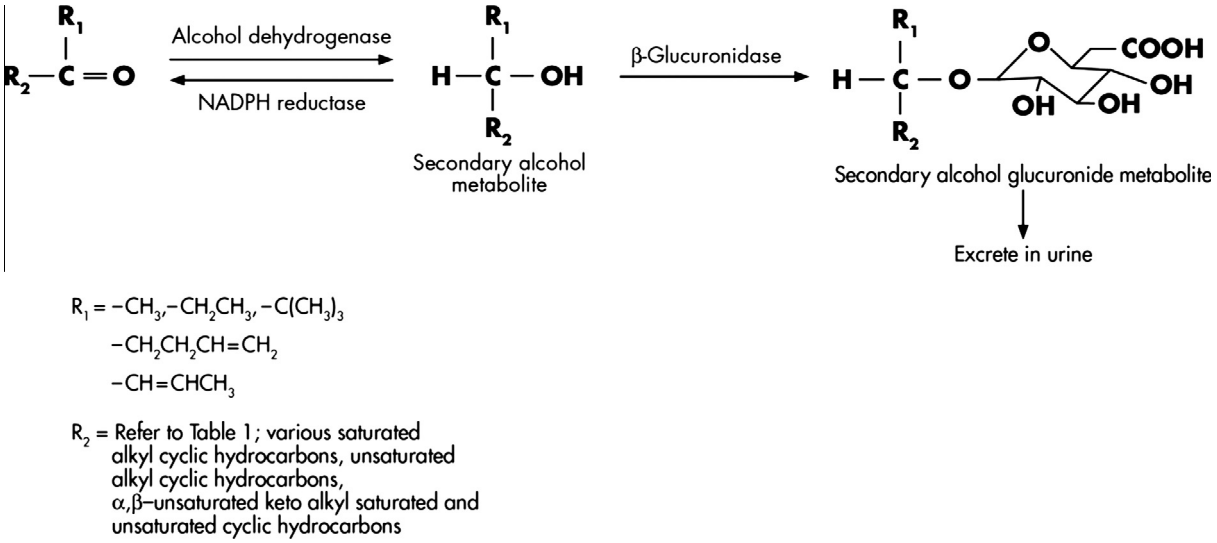


Fig. 1. Proposed primary ACK carboxyl reduction metabolism.

not a developmental toxicant at maternal doses up to 1920 mg/kg body weight/day; however, this dosage did produce maternal mortality and dams were subjected to marked reductions in feed consumption and body weight gains at dosages greater than or equal to 960 mg/kg/day during gestation (RIFM, 2002c). Therefore, female rats presumed to be pregnant were administered 0 (water), 96, 240, or 480 mg/kg/day of OTNE by gavage on GD 7–17 (Politano et al., 2009). At dosages of 96–480 mg/kg/day, litter and fetal parameters were unaffected by OTNE, except for a minimal (not statistically significant) downward trend in fetal body weights. Dams that received 480 mg/kg/day showed a prolonged significant decrease in feed consumption and body weight gains during the entire gestation period. In the 96 or 240 mg/kg/day groups there was transient decreased maternal body weight during GD 7–10. The maternal and developmental NOAEL of 240 mg/kg/day was established based on these effects.

Acetyl cedrene was studied for its potential to produce developmental toxicity in Sprague–Dawley rats. Initially, a dose range finding study measured maternal and developmental effects after gavage of 8 pregnant rats with 0 (corn oil) 50, 100, 250, 500, 1000, or 2000 mg/kg body weight/day (RIFM, 2002b) during GD 7–17. All rats in the high dose group were found moribund and sacrificed. Maternal clinical changes related to acetyl cedrene exposure occurred at $\geqslant$500 mg/kg/day. Decreased body weight loss and body weight gains were noted in all treated surviving dams. Fetal body weights were reduced at doses of 500 and 1000 mg/kg/day. Based on these findings, acetyl cedrene was then administered to pregnant rats (25 per group) via gavage at dosages of 0 (corn oil), 25, 50, or 100 mg/kg body weight/day on GD 7–17 (RIFM, 2004d; Lapczynski et al., 2006). All rats were observed daily for viability, clinical signs, abortions, and premature deliveries. Cesarean-section and necropsy were performed on GD 21 in order to examine uteri. At 100 mg/kg/day, absolute feed consumption during GD 7–12 and relative feed consumption values during GD 9–12 were decreased and accompanied by decreased maternal body weight gain during GD 7–10. No cesarean-section, fetus, or

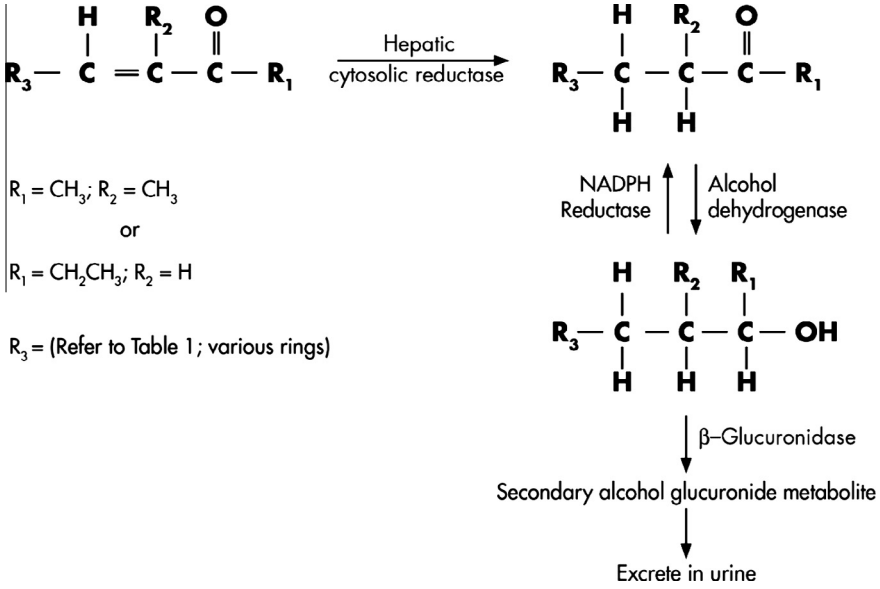


Fig. 2. Proposed ACK α,β-unsaturated ketone metabolism.

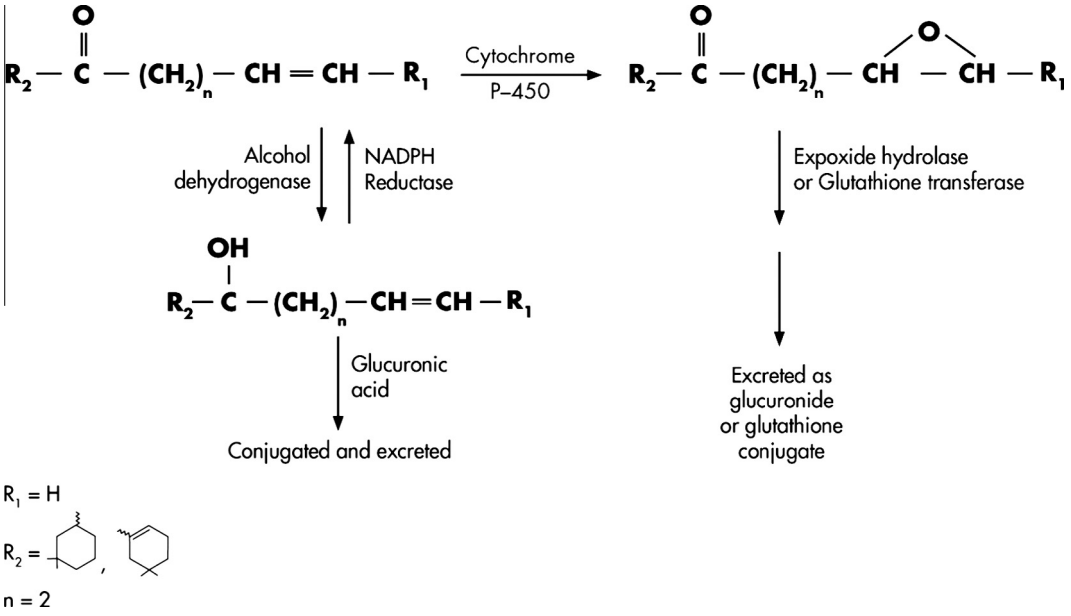


Fig. 3. Proposed ACK isolated alkyl double bond epoxidation and carbonyl reductase metabolism.

litter parameters were affected by the acetyl cedrene at these concentrations. The maternal NOAEL was 50 mg/kg/day based on decreased weight gain and the developmental NOAEL was 100 mg/kg/day, the highest dose tested.

5.5. Skin irritation

5.5.1. Human Studies

Fifteen of the 23 ACK fragrance materials have been evaluated for skin irritation in a total of approximately 1875 male and female volunteers (Table 6.1). Four materials were reported to induce mild skin irritation in at least one volunteer in at least one study.

5.5.1.1. Saturated ACKs. Among the four saturated ACK materials studied, three fragrance materials did not induce irritation in humans. Cyclohexyl methyl pentanone produced mild irritation in 11 of 106 volunteers tested during the repeat application induction period of a repeat insult patch test (HRIPT); the irritation was characterized as persistent in 5 of the 11 volunteers who reacted (RIFM, 1988a).

5.5.1.2. Unsaturated ACKs. Eight of eleven unsaturated ACK fragrance materials did not produce irritation. The unsaturated ACK fragrance material 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE), was tested on a total of 375 subjects in eight studies with concentrations ranging from 2.5% to 75%. Five of these studies produced no irritation in the subjects tested (RIFM, 1973d, 1977d, 1978b, 2004i,h); two of three of the studies that used 12.5% or higher formulations produced mild irritation in a small number of subjects (RIFM, 1999c, 2004i). No study with 2.5%, resulted in irritation. 1-(3,5,6-Trimethyl-3-cycloh-

Table 10
Summary of UV spectra data.

Material	UV spectra range of absorption (nm)	Molar extinction coefficient ($L\ mole^{-1}\ cm^{-1}$)
Acetyl cedrene	Absorbance at 205–210 nm, with minor absorbance at 250–260 nm, and returns to base line at 350 nm	9257.40
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Absorbance at 205–210 nm and returns to base line at 250 nm	8670.01
1-(3,3-Dimethylcyclohexyl)ethan-1-one	Absorbance at 205–210 nm and returns to base line at 250 nm	1157.45
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	Absorbance at 205–210 nm and returns to base line at 250 nm	9361.62
Methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone	Absorbance at 205–210 nm and returns to base line at 330 nm	N/A
1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one	Peaks at 225–230 nm and returns to baseline at 350 nm	N/A

Table 11
Calculated margin of safety.*

Material	Dermal systemic exposure (mg/kg/day)	No effect level (mg/kg body weight/day)	Method	Result = no effect level/systemic exposure (assumes 100% dermal absorption)	References[c]
Saturated alkyl cyclic ketones					
Cyclohexyl methyl pentanone	0.0068	15[b]	n/a	>2000	n/a
1-(3,3-Dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one	0.0005[a]	15[b]	n/a	30,000	n/a
1-(3,3-Dimethylcyclohexyl)ethan-1-one	0.0086	15[b]	n/a	>1000	n/a
1-(2,5,5-Trimethylcycloheptyl)ethan-1-one	0.0005[a]	15[b]	n/a	30,000	n/a
Unsaturated alkyl cyclic ketones					
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene	0.0358	150	4 week gavage in rats	>4000	RIFM, 2007b
Methyl 2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone	0.1	15	4 week gavage in rats	150	RIFM, 1994b
1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl)bicycle[2.2.1]oct-5-en-2-yl]ethan-1-one	0.0025	15[b]	n/a	6000	n/a
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	0.4604	1000	4 week gavage in rats	>2000	RIFM, 1997b
1-(1,2,3,4,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one	0.0005[a]	15[b]	n/a	30,000	n/a
1-(1,2,3,5,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one	0.0005[a]	15[b]	n/a	30,000	n/a
Acetylcarene	0.0010	15[b]	n/a	15,000	n/a
1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one	0.0005[a]	15[b]	n/a	30,000	n/a
1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one	0.0003	15[b]	n/a	50,000	n/a
1-(*para*-Menthen-6-yl)-1-propanone	0.0019	15[b]	n/a	>7000	n/a
1-(3,5,6-Trimethyl-3-cyclohexen-1-yl)ethan-1-one	0.0005[a]	15[b]	n/a	30,000	n/a
Acetyl cedrene	0.1368	50	Developmental toxicity study – gavage GD 7–17 in rats	>300	RIFM, 2004d,e Lapczynski et al., 2006
2-Cyclohexyl-1,6-heptadien-3-one	0.0005[a]	200	4 week gavage in rats	400,000	RIFM, 2004b
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	0.0014	250	4 week gavage in rats	>100,000	RIFM, 1996e
1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one	0.0005[a]	15[b]	n/a	30,000	n/a
1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one	0.0005[a]	50	4 Week gavage in rats	100,000	RIFM, 2005b
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one	0.0005[a]	15[b]	n/a	30,000	n/a
1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one	0.0348	15[b]	n/a	>400	n/a

* Margin of safety for materials that have no reported use as fragrances or are considered captive ingredients, were not calculated; no effect levels from their repeat dose studies were not used as a representative for the group.
[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 reliable no effect level was not available, hence there is no study to cite.

exen-1-yl)ethan-1-one produced a mild persistent irritation during the induction period of an HRIPT in 1 of 42 subjects (RIFM, 1965a, 53551). Acetyl cedrene produced equivocal results in four different studies. Irritation was observed in 5.1% and 3% of the volunteers during the repeat application period of induction of an HRIPT (RIFM, 1964, 2004g); however, irritation was not observed in a maximization test (Frosch et al., 1995) or in two modified primary dermal assays (RIFM, 2004f).

The preponderant finding of no irritation for these materials indicates that these compounds are not skin irritants in humans at relevant exposure levels for consumers.

5.5.2. Animal studies

Four saturated ACK fragrance ingredients and fifteen unsaturated ACK fragrance ingredients were evaluated for irritation in guinea pigs, rabbits, and rats. Reactionsranged from none to severe (Tables 6.2a and 6.2b). Irritation studies with animals included observations from acute dermal toxicity tests, primary irritation tests on the skin of rabbits and rats, and preliminary irritation tests to find the dose range for maximization tests with guinea pigs.

Single application of neat ACK fragrance materials (Table 6.2a) resulted in no irritation to severe irritation. Most caused slight to moderate irritation that tended to clear within 1–2 weeks. However, 1-[5(or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one resulted in moderate to severe irritation that did not clear. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one, in one of eight studies, resulted in moderate to severe irritation that did not clear. In the other 7 studies, this material resulted in much milder reactions. One fragrance material, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE), did not produce any irritation in multiple acute tests. In other protocols varying from 4 h to 48 h occlusive or semi-occlusive patch durations at concentrations of 5% or less, no irritation occurred or mild reactions were reported to clear quickly. However, repeated applications of the ACK fragrance materials during the induction of Maximization, Buehler, or Open Epicutaneous Tests (Table 6.2b) often resulted in an increase in the severity and duration of irritation.

5.6. Mucous membrane irritation – eye irritation

Eye irritation studies in humans were not identified. Studies of eye irritation in rabbits can be found in Table 7. The potential for eye irritation from 15 of the ACK fragrance materials has been evaluated by the Draize eye test in rabbits. These compounds produce a mild to severe conjunctivitis and erythema upon contact with the eye, usually with a recovery by day 7. Of note are the severe reactions produced by the saturated ACK, 1-(3,3-dimethylbicyclo[2.2.1]hept-2-yl)ethane-1-one in ethanol, and by the unsaturated ACK, acetyl cedrene in Tween 80; in both irritation was reported to persist. For acetyl cedrene this could be a result of the vehicle as the results over 14 studies range down to no incidence of irritation.

No sensory irritation studies were identified.

5.7. Skin sensitization

The recently revised IFRA (2009), IFRA, 2008, IFRA (2011) and IFRA, 2007, respectively Standards on 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one; 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone; 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one; and 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one are based on the dermal sensitization quantitative risk assessment (QRA) approach for fragrance ingredients (Api et al., 2008). The RIFM Expert Panel reviewed the critical effect data for 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 2500 μg/cm^2. For 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-napht halenyl) ethanone they established the No Expected Sensitization Induction Level (NESIL) as 47,200 μg/cm^2. The NESIL for 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)ethan-1-one is 1000 μg/cm^2, which is a default value based on the LLNA data. Finally, after reviewing the critical effect data for 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one, a NESIL of 71,000 μg/cm^2. For each of these materials, they recommend limits for the 11 different product categories, which are the acceptable use levels in the various product categories.

5.7.1. Human studies

5.7.1.1. Induction of human sensitization. Human sensitization data from approximately 1750 volunteers in total are available for the 4 saturated ACK fragrance ingredients and 11 unsaturated fragrance ingredients, see Table 8.1a. None of the 15 fragrance materials for which there are human sensitization data had a positive result. Overall as a class, it can be concluded that these compounds are not likely to induce sensitization.

5.7.1.2. Elicitation of human sensitization. No elicitation studies were available for the ACK fragrance ingredients.

5.7.1.3. Diagnostic patch-test studies. Diagnostic patch-test studies that tested 100 or more dermatological patients (approximately 3,035 volunteers, in total) have been reported for only two ACK fragrance materials, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE) and acetyl cedrene (Table 8.1b). The prevalence of positive skin reactions among dermatological patients for OTNE ranged from 0.2% to 1.7% (An et al., 2005; Larsen et al., 2001; Frosch et al., 1995, 2002). Sensitivity to acetyl cedrene was also identified by Frosch et al. (1995, 2002) in 0.2–1% of the patients tested. For these two substances, 1.7% was the highest frequency reported in patients.

5.7.2. Animal Studies

Thirteen ACK fragrance ingredients were evaluated for sensitization potential in guinea pigs using various test methods such as the Magnusson–Kligman maximization test, the Buehler delayed hypersensitivity test, the Freund's complete adjuvant test, and a modified Draize test (Table 8.2a).

There are data for one saturated ACK material. One of the three sensitization studies with cyclohexyl methyl pentanone showed mild sensitization.

Six of twelve unsaturated ACK fragrance ingredients did not induce sensitization in Maximization-like tests with guinea pigs. The two studies with methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone resulted in weak sensitization reactions, there was some indication that sensitization incidence was reduced with decreasing concentrations (RIFM, 1987c, 1988c). Three studies with 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one resulted in sensitization reactions at doses greater than 5% in a maximization study (RIFM, 2000f), greater than 1% in an open epicutaneous test (RIFM, 2000e), and greater than 0.5% in a photosensitization control study (RIFM, 2001h).

Three of the nine studies performed with acetyl cedrene resulted in sensitization reactions ranging from marginal to "extreme" (no further details provided) sensitization (RIFM, 1979r; RIFM, 1975c; Ishihara et al., 1986); the six other studies reported no sensitization reactions. Equivocal results were reported for 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (5 studies) and 1-(2,4,4,5,5-pentalmethyl-1-cyclopenten-1-yl)ethan-1-one (2 studies) in which results ranged from not sensitizing to partially sensitizing.

Sensitization in mice was also evaluated for seven unsaturated alkyl cyclic ketones using the local lymph node assay (Table 8.2b). The concentration giving rise to greater than a threefold increase (EC_3) in lymphocyte proliferation was identified for all of the compounds tested except 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one which had a calculated EC_3 of 2.99, which is on the cusp of a threefold increase (RIFM, 2001i; Natsch et al., 2007; Natsch and Gfeller, 2008), thus it would be labeled as a weak sensitizer. In an LLNA with 1-(2,4-dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one, EC_3 was not calculated, but stimulation index values increased greater than 3-fold indicating the potential for contact sensitization (RIFM, 1995b). The other compounds had an EC_3 of 20.71 (acetic acid, anhydride (reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene)), 13.93 (acetyl cedrene) and from 6.07–25.14 (various studies with 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2- naphthalenyl)ethanone). For two LLNA studies done with 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one an EC_3 value of between 1% and 10% was approximated (RIFM, 2001j,k).

5.8. Phototoxicity and Photosensitization

Limited phototoxicity and photosensitization data were available (Tables 9.1a, 9.1b, 9.2a and 9.2b) for saturated and unsaturated ACK fragrance ingredients.

5.8.1. Phototoxicity

5.8.1.1. Humans. Human irritation to ACKs after UV exposure has been evaluated for 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE) and 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one. OTNE irritation after UVA and/or UVB irritation has been measured after a single application (RIFM, 1980i) or multiple application induction (RIFM, 1980h). Exposures with or without UV radiation did not result in phototoxicity. Likewise, 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one exposure did not result in phototoxicity to humans after induction from a repeat insult patch test followed by exposure to UV radiation (RIFM, 1979n), see Table 9.1a.

5.8.1.2. Animals. In rabbits, guinea pigs, or mice exposed to single or repeat applications of cyclohexyl methyl pentanone; acetyl cedrene; 2-cyclohexyl-1,6-heptadien-3-one; 1-[5(or 6)-methyl-7(or 8)-(1-methylethyl) bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one;1-(2,4,4,5,5-pentalmethyl-1-cyclopenten-1-yl)ethan-1-one;3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-3-en-2-one; 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone; or 1-(2,4,4,5,5-pentalmethyl-1-cyclopenten-1-yl)ethan-1-one followed by exposure to UV radiation, phototoxicity did not result. However, all ten rats exposed to 30% acetyl cedrene in EtOH followed by UVA at 12 J/cm^2 at 32 cm for 149 min did show evidence of slight phototoxic activity. Furthermore, in an *in vitro* 3T3 Neutral Red Uptake test of phototoxicity, acetyl cedrene was considered phototoxic (RIFM, 2010g, 62349). The test evaluates photo-cytotoxicity by the relative reduction in viability of cells (Balb/c 3T3 mouse fibroblasts) exposed to the chemical (acetyl cedrene) in the presence versus absence of light (UVA at 5 J/cm^2 for 50 min). Cytotoxicity in this test is expressed as a concentration dependent reduction in the uptake of the vital dye Neutral Red when measured 24 h after treatment with the test material and irradiation. Under the conditions of the test, acetyl cedrene was considered phototoxic, see Table 9.1b.

5.8.2. Photosensitization

5.8.2.1. Humans. Human photosensitivity to ACK fragrance materials has been evaluated for two materials, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE) and 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one (Table 9.2a). A repeat insult patch test was performed with 20 volunteers using UV radiation exposure of 1.68 mW/cm^2 at 38.1 cm for 15 min after each patch with 12.5% OTNE. Neither the control nor the UV irradiated skin showed sensitization. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one was applied with a semi-occlusive patch once a week for 3 weeks each followed by 12 min of UV irradiation. Upon challenge and UV exposure (3 min) none of the volunteers showed signs of photosensitization.

5.8.2.2. Animals. Cyclohexyl methyl pentanone; acetyl cedrene; 2-cyclohexyl-1,6-heptadien-3-one; 1-[5(or 6)-methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one; 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent03-en-2-one; 1-(2,4,4,5,5-pentalmethyl-1-cyclopenten-1-yl)ethan-1-one; and 1-spiro[4.5]dec-7-en-7-yl-4-penten-1-one were tested in the guinea pig maximization test followed by UV radiation for 15 min up to 4 h (Table 9.2b). None of these compounds induced photosensitization.

UV spectra were conducted according to OECD 101 and under GLP conditions, and have been obtained for 6 materials (acetyl cedrene; 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one; 1-(3,3-dimethylcyclohexyl)ethan-1-one;1-(3,3-dimethylcyclohexyl) pent-4-en-1-one; methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone; and 1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one). In general, they did not absorb UVB light (290–320 nm), although. acetyl cedrene, 1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-pent-1-en-3-one and methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone did not return to baseline until 350, 350 and 330 nm, respectively. However, peak absorbance for all the tested materials was between 205 and 210 nm, well within the UVC range (see Table 10). Molar extinction coefficients, the measurement of how strongly a chemical species absorbs light at a given wavelength, are also presented in Table 10. Based on the UV spectra, molar extinction coefficients, and review of phototoxicity and photosensitization data, most materials in this group, with the possible exception of acetyl cedrene, would not be expected to elicit phototoxicity or photosensitization under the current conditions of use as fragrance ingredients.

6. Conclusion

The ACK fragrance ingredients are structurally diverse and include saturated alkyl cyclic ketones (4) and unsaturated alkyl cyclic ketones (19). Metabolism is postulated for the three categories of ACK fragrance ingredients based on published studies for compounds with similar chemical functionality. The predominant primary metabolic pathway for all of the saturated and unsaturated ACK fragrance ingredients is reduction of the ketone by alcohol dehydrogenases and NADH/NADPH-dependent cytosolic carbonyl reductases to generate a secondary alcohol metabolite, which may either be converted back to the parent ketone (and excreted unchanged) or conjugated with glucuronic acid and excreted. Overall, it is unlikely that the metabolism of the ACK fragrance ingredients, particularly at relevant exposure levels, produces toxic metabolites.

Although not all materials have been tested, the available data are deemed to be sufficient for all the materials in the group. It is the opinion of the Expert Panel that the available data indicate that there should be no safety concerns regarding the ACK fragrance ingredients under the presently declared levels of use and exposure. Use of these materials at higher maximum dermal levels or higher systemic exposure levels, other than those currently reported in this group summary, require re-evaluation of safety by the RIFM Expert Panel. For the compounds for which systemic uptake in consumers (Table 1) has been estimated by RIFM, the margin of safety is currently between 150 and >2000. There is an adequate margin of safety

for the ACKs under review when applied in consumer personal care products at the currently recommended concentrations.

This recommendation was based on the following rationale:

- Testing results for 16 compounds indicate that the ACK fragrance materials have low acute oral and dermal toxicity.
- Low systemic repeat dose toxicity was generally observed for ACK fragrance materials (see Table 3.2). The lowest NOAEL of the six compounds tested in sub-chronic oral studies is 15 mg/kg/body weight/day for methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl-ketone. This value could be considered as the worst case representative for all the ACK fragrance materials.
- Based on repeat dose rat developmental studies at GD 7–17 for two ACK fragrance materials (1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2- naphthalenyl)ethanone and acetyl cedrene) fetal toxicity does not occur in the absence of maternal toxicity. The lowest observed maternal NOAEL and developmental NOAEL were 50 and 100 mg/kg body weight/day, respectively.
- Chronic carcinogenicity data were not available for the ACK family. However, *in vitro* and *in vivo* evaluation of thirteen ACK fragrance materials did not result in either genotoxic or clastogenic effects.
- In the 15 of 23 ACK fragrance ingredients evaluated, overall results indicated that they are considered non-irritating to human skin; a few compounds produced mild irritation, most of which were equivocal or resulted from doses greater than are used in consumer products.
- Evaluation of 15 ACK fragrance ingredients from both categories for eye irritation showed mild to moderate irritation with complete recovery for all but two compounds, 1-(3,3-dimethylbicyclo[2.2.1] hept-2-yl)ethane-1-one and acetyl cedrene. Because the ACK fragrance ingredients are diluted to lower concentrations in personal care end products, these compounds pose minimal concern for eye irritation at the concentrations currently used in the marketplace.
- Available data for 15 of the ACK fragrance materials from both categories show that these materials are unlikely to induce sensitization.
- Moreover, because ACK fragrance materials do not form hydroperoxides *in vivo* (and can be reversibly oxidized to and from alcohols) at the reported use levels and exposure in personal care products, the ACK fragrance ingredients would be unlikely to induce sensitization. However, for those individuals who are already sensitized, there is a possibility that an elicitation reaction may occur because the relationship between the no effect level for induction and the no effect level for elicitation is not known for this group of materials.
- On the basis of UVA or UVB light data, molar extinction coefficients, and review of existing phototoxicity and photosensitization data, most of the ACK fragrance ingredients, with the possible exception of acetyl cedrene, are not expected to elicit phototoxicity or photosensitization at the concentrations currently used in consumer products.
- With the exception of one subchronic dermal study for acetyl cedrene in which a higher systemic NOAEL of 150 mg/kg body weight/day was reported, the RIFM database currently does not include sufficient data to draw firm comparative conclusions about dermal route of exposure versus oral (gavage) route of exposure in terms of toxicity (that is, slow uptake via the skin versus oral bolus dose).
- To calculate margin of safety, the lowest NOAEL of 15 mg/kg body weight/day (for 4 week oral repeat dose toxicity study with methyl-2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone, see Table 3.2) is used as a representative worst-case scenario for the group. The reported systemic exposure for this material is 0.1 mg/kg bw/day (see Table 1); the margin of safety is calculated to be 150. For the other compounds for which systemic uptake in consumers (Table 1) has been estimated by RIFM, the margin of safety is between 150 and 400,000 (Table 11).
- Using the highest systemic exposure for the group (0.46 mg/kg body weight/day for 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2- naphthalenyl)ethanone) and the NOAEL for this material (1000 mg/kg bw/day from 4 week gavage in rats) again, as a representative worst-case scenario, and assuming 100% dermal absorption, the margin of safety is calculated to be >2000. If a margin of safety of 100 were used, the maximum allowable exposure would be 0.10 mg/kg body weight/day.

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 the Research Institute for Fragrance Materials, an independent group of experts who evaluate the safety of fragrance materials. Members of the Expert Panel are paid an honorarium in recognition of their time spent at the Panel meetings.

Acknowledgement

The Panel wishes to express its sincere appreciation to Dr. A.E. Rogers for her help and guidance in the preparation of this manuscript.

Appendix A. Materials in this assessment without a corresponding Fragrance Material Review (FMR)

Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene, CAS# 144020-22-4
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone, CAS# 22463-19-0
2-(3,7-Dimethyl-2,6-nonadien-1-yl)-cyclopentanone, CAS# 1206769-45-0
1-(6,6,9-trimethyl-2-methylene-4,8-cycloundecadien-1-yl)-ethanone, CAS# 55987-49-0
1-[1-(1-Oxopropoxy) cyclohexyl]-ethanone, CAS# 82721- 48-0
Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel-, CAS# 185429-83-8
1-(4-Methoxy-2,2,6,6-tetramethyl-3-cyclohexen-1-yl)ethan-1-one, CAS# 16556-48-2
5-Acetyl-2,2,8-trimethyltricyclo (6.2.2.01,6) dodec-5-ene, CAS# 32388-56-0

1-(2,3,4,7,8,8a-Hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)ethan-1-one, CAS# 68039-35-0
1-Spiro[4.5]dec-6-en-7-yl-4-penten-1-one, CAS# 224031-71-4
4-(2,2,3,6-Tetramethylcyclohexyl)-3-buten-2-one, CAS# 54992-90-4
1-(2,2,6-Trimethylcyclohexyl)-2-buten-1-one, CAS# 39 900-18-0

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RIFM (Research Institute for Fragrance Materials, Inc.), 1990a. 1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one: Bacterial mutation assay. Unpublished report from International Flavors and Fragrances, Report number 48162 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1990b. Mouse micronucleus test on 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one. Unpublished report from International Flavors and Fragrances, Report number 48251 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991a. 1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one (chrysantheme): Acute dermal toxicity (Limit Test) in the rat. Unpublished report from Symrise, 30 May. Report number 59223 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991b. Acute dermal toxicity study of 3-buten-2-one, 4-(2,2,3,6-tetramethylcyclohexyl)- in the rat. Unpublished report from Firmenich Incorporated, 17 October. Report number 41837 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991c. Acute oral toxicity test of cyclohexyl methyl pentanone in rats. Unpublished report from Dragoco Gerberding and Co. GmbH, Report number 37768 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991d. 1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one (chrysantheme): Acute oral toxicity (Limit Test) in the rat. Unpublished report from Symrise, 29 May. Report number 59219 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991e. Mutagenicity study of 1-(2,4-dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one (chrysantheme) in the Salmonella typhimurium/mammalian microsome reverse mutation assay (Ames Test). Unpublished report from Symrise, 22 March. Report number 59222 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991f. Bacterial reverse mutation assay with 3-buten-2-one, 4-(2,2,3,6-tetramethylcyclohexyl). Unpublished report from Firmenich Incorporated, 27 September. Report number 41841 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991g. Acute dermal irritation/corrosion test of cyclohexyl methyl pentanone in rabbits. Unpublished report from Dragoco Gerberding and Co. GmbH, Report number 37770 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991h. Guinea pig maximization test of skin sensitization with cyclohexyl methyl pentanone. Unpublished report from Dragoco Gerberding and Co. GmbH, Report number 37771 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991i. Assessment of the skin irritant effect of 1-(2,4-dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one (chrysantheme) in rabbits. Unpublished report from Symrise, 9 April. Report number 59220 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991j. 1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one (chrysantheme): Magnusson & Kligman maximization study in the guinea pig. Unpublished report from Symrise, 24 May. Report number 59221 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991k. Acute eye irritation/corrosion test cyclohexyl methyl pentanone in rabbits. Unpublished report from Dragoco Gerberding and Co. GmbH, Report number 37769 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1992a. Acute oral toxicity study of 3-buten-2-one, 4-(2,2,3,6-tetramethylcyclohexyl)- in the rat. Unpublished report from Firmenich Incorporated, 13 January. Report number 41836 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1992b. Acute dermal irritation/corrosion study of 3-buten-2-one, 4-(2,2,3,6-tetramethylcyclohexyl)- in rabbits. Unpublished report from Firmenich Incorporated, 17 February. Report number 41838 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1992c. Acute eye irritation study of 3-buten-2-one, 4-(2,2,3,6-tetramethylcyclohexyl)- in rabbits. Unpublished report from Firmenich Incorporated, 06 April. Report number 41839 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1992d. Guinea-pig maximisation test with 3-buten-2-one, 4-(2,2,3,6-tetramethylcyclohexyl). Unpublished report from Firmenich Incorporated, 01 February. Report number 41840 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1993a. Report on cyclohexyl methyl pentanone. RIFM Report number 20500, (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1993b. Methyl 2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone: Acute dermal toxicity to the rat. Unpublished report from Quest International, 28 July. Report number 45816 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1993c. Methyl 2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone: Mutagenicity study in Salmonella typhimurium. Unpublished report from Quest International, 23 August. Report number 45815 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1993d. Methyl 2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone: In vitro cytogenetics study in human lymphocytes. Unpublished report from Quest International, 10 January. Report number 45814 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1994a. Ethanone, 1-(3,3-dimethyl-1-cyclohexen-1-yl)- (Artemone): Acute oral toxicity (limit) test in

rats. Unpublished report from Givaudan, Report number 56211 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1994b. Methyl 2,6,10-trimethylcyclododeca-2,5,9-trien-1-yl ketone: 28 day subacute oral toxicity study in rats. Unpublished report from Quest International, 31 January. Report number 45813 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1994c. Evaluation of the perfumery ingredient ethanone, 1-(3,3-dimethyl-1-cyclohexen-1-yl)- (artemone) for mutagenic activity in the Ames Test. Unpublished report from Givaudan, Report number 56223 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1994d. Ethanone, 1-(3,3-dimethyl-1-cyclohexen-1-yl)- (Artemone): Acute dermal irritation test in rabbits. Unpublished report from Givaudan, Report number 56209 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1995a. Iso E super - Seven day oral toxicity study in the rat. Unpublished report from International Flavors and Fragrances, 08 February. Report number 31710 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1995b. 1-(2,4-Dimethyl-3-cyclohexenyl)-2,2-dimethylpropan-1-one (chrysantheme): Local Lymph Node Assay. Unpublished report from Symrise, 20 December. Report number 59224 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996a. Partition coefficient n-octanol/water of 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8.8-tetramethyl-2-naphthalenyl)ethanone. Unpublished report from Givaudan, 4 December. Report number 33494 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996b. 1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one (galbaniff): Acute dermal toxicity to the rat. Unpublished report from International Flavors and Fragrances, Report number 47585 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996c. Acute dermal toxicity study with ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood) in rats. Unpublished report from Givaudan, 11 November. Report number 58391 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996d. Acute oral toxicity study in the rat with ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood). Limit Test. Unpublished report from Givaudan, 16 February. Report number 58390 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996e. 1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one: Twenty-eight day oral toxicity study in the rat. Unpublished report from International Flavors and Fragrances, Report number 48024 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996f. Mutagenicity evaluation of ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood) in the Ames Test. Unpublished report from Givaudan, 18 September. Report number 58392 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996g. 1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one: Metaphase chromosome analysis of human lymphocytes cultured in vitro. Unpublished report from International Flavors and Fragrances, Report number 48245 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996h. Clinical safety evaluation of ethanone, 1-(3,3-dimethyl-1-cyclohexen-1-yl)- (artemone): Repeated insult patch test. Unpublished report from Givaudan, 3 July. Report number 56225 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996i. 1-(3,3-Dimethylcyclohexyl)pent-4-en-1-one: Skin sensitisation in the guinea pig. Unpublished report from International Flavors and Fragrances, Report number 47894 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996j. Primary skin irritation study with ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood) in rabbits (4-hour semi-occlusive application). Unpublished report from Givaudan, 07 November. Report number 58388 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996k. Contact hypersensitivity to ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood), in albino guinea pigs maximization-test. Unpublished report from Givaudan, 14 November. Report number 58387 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1996l. Primary eye irritation study with ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood) in rabbits. Unpublished report from Givaudan, 07 November. Report number 58389 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1997a. Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood): Four-week oral (gavage) toxicity study in rats. Unpublished report from Givaudan, 03 March. Report number 58385 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1997b. Iso E super - Four week oral toxicity study in the rat with two week recovery period. Unpublished report from International Flavors and Fragrances, 13 October. Report number 31713 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1997c. Iso E super - Bacterial mutation assay. Unpublished report from International Flavors and Fragrances, 08 October. Report number 31711 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1997d. Chromosome analysis in cultured Chinese hamster V79 cells treated with ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood) in the presence and abscence of a metabolic activation system.Unpublished report from Givaudan, 04 February. Report number 58393 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1997e. Iso E super - Metaphase chromosome analysis of human lymphocytes cultured in vitro. Unpublished report from International Flavors and Fragrances, 12 August. Report number 31712 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1998. Ethanone, 1-[(1R,2S)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (georgywood): Repeated insult patch test. Unpublished report from Givaudan, 03 March. Report number 58386 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1999a. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one: Acute oral toxicity study, limit test, in rats. Unpublished report from Firmenich Incorporated, 27 January. Report number 42137 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1999b. Repeated insult patch test of 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one. Unpublished report from Firmenich Incorporated, 29 June. Report number 42138 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1999c. Repeated insult patch test with 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone. Unpublished report from IFF Incorporated, 22 April. Report number 47085 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1999d. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one: Delayed contact hypersensitivity modified Buehler method. Unpublished report from Firmenich Incorporated, 01 March. Report number 42136 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1999e. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one: Primary skin irritation study in rabbits (4-hour semi-occlusive application). Unpublished report from Givaudan, 15 July. Report number 42070 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1999f. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one: Study of skin sensitization in albino guinea pigs maximization-test. Unpublished report from Givaudan, 20 August. Report number 42076 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1999g. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one: Primary eye irritation study in rabbits. Unpublished report from Givaudan, 23 July. Report number 42071 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000a. 4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone): Acute oral toxicity study in rats. Unpublished report from Givaudan, 29 May. Report number 60581 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. 2-Week dermal toxicity range-finding study with acetyl cedrene and alpha-methyl-3,4-methylene-dioxy-hydrocinnamic aldehyde in rats. RIFM Report number 35257 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000c. Salmonella typhimurium reverse mutation assay with 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone). AMENDMENT ATTACHED. Unpublished report from Givaudan, 13 June. Report number 60591 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000d. 4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone): Primary skin irritation study in rabbits (4-hour semi-occlusive application). Unpublished report from Givaudan, 23 June. Report number 60590 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000e. 4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone): Study of skin sensitization in the guinea pig; Open Epicutaneous Test (ethanol as vehicle). Unpublished report from Givaudan, 31 March. Report number 60599 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000f. 4 4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone): Contact hypersensitivity in guinea pigs, maximization-test. Unpublished report from Givaudon, 25 September. Report number 60595 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000g. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one: Study of skin sensitization in the guinea pig; Open Epicutaneous Test (ethanol as vehichle). Unpublished report from Givaudan, 31 March. Report number 42074 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000h. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one: Study of skin sensitization in the guinea pig; Open Epicutaneous Test. Unpublished report from Givaudan, 10 January. Report number 42075 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2000i. 4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone): Primary eye irritation study in rabbits. Unpublished report from Givaudan, 30 May. Report number 60589 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. In-vitro human skin penetration of methyl eugenol, estragole, acetyl cedrene and OTNE. RIFM Report number 37084, April 01 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. (14)C-OTNE: Investigation of the transfer across the placenta and into milk of rats

during and after pregnancy following repeated oral administration. RIFM Report number 38108 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001c. 1,6-Heptadien-3-one, 2-cyclohexyl- (pharaone): Acute oral toxicity study in rats. Unpublished report from Givaudon, 08 October. Report number 59371 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001d. Salmonella typhimurium reverse mutation assay with 1,6-heptadien-3-one, 2-cyclohexyl- (pharaone). [Amendment Attached] Unpublished report from Givaudon, 16 November. Report number 59404 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001e. Repeated insult patch test with 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one. Unpublished report from International Flavors and Fragrances, 29 October. Report number 51118 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001f. 1,6-Heptadien-3-one, 2-cyclohexyl- (pharaone): Primary skin irritation study in rabbits (4-hour semi-occlusive application). Unpublished report from Givaudon, 19 October. Report number 59379 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001g. 1,6-Heptadien-3-one, 2-cyclohexyl- (pharaone): Contact hypersensitivity in albino guinea pigs, maximization-test. Unpublished report from Givaudon, 04 December. Report number 59410 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001h. 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone): Determination of photoallergenicity in albino guinea pigs (including information about allergenicity, photoirritation and irritation). Unpublished report from Givaudon, 15 November. Report number 60593 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001i. 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one: Local Lymph Node Assay (LLNA) in mice (identification of contact allergens). Unpublished report from Givaudan, 16 May. Report number 42073 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001j. 4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone) non-stabilized: Local Lymph Node Assay (LLNA) in mice (identification of contact allergens). Unpublished report from Givaudon, 16 May. Report number 60597 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001k. 4-Penten-1-one, 1-spiro[4.5]dec-7-en-7-yl- and 4-penten-1-one, 1-spiro[4.5]dec-7-en-7-yl-(spirogalbanone) stabilized with 0.1% alpha-tocopherol: Local Lymph Node Assay (LLNA) in mice (identification of contact allergens). Unpublished report from Givaudon, 16 May. Report number 60598 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002a. 13-Week dermal toxicity study with acetyl cedrene in rats with a 4-week recovery. RIFM Report number 40242, April 29 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002b. Oral (gavage) dosage-range developmental toxicity study of acetyl cedrene in rats. RIFM Report number 44880, May 17 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002c. Oral (gavage) dosage-range developmental toxicity study of 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE) in rats. RIFM Report number 39734 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002d. Oral (gavage) developmental toxicity study of 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE) in rats. RIFM Report number 39733 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002e. Clinical safety evaluation repeated insult patch test of 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one. Unpublished report from Givaudan, 11 June. Report number 42072 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002f. 1,6-Heptadien-3-one, 2-cyclohexyl- (pharaone): Determination of photoallergenicity in albino guinea pigs (including information about allergenicity, photoirritation and irritation). Unpublished report from Givaudon, 15 February. Report number 59408 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002g. 2-Buten-1-one, 1-(2,2,6-trimethylcyclohexyl)-: Human patch test. Unpublished report from Takasago International Corporation, 12 July. Report number 50541 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. In vitro mammalian chromosome aberration test with acetyl cedrene. RIFM report number 43491, November 21 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Repeated insult patch test with 1,6-heptadien-3-one, 2-cyclohexyl- (pharaone). Unpublished report from Givaudon, 24 Januuary. Report number 59411 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2003c. Repeated insult patch study of 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one at 1% in diethyl phthalate (DEP). Unpublished report from Firmenich Incorporated, 25 February. Report number 42658 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2003d. Dermal sensitization test with 1-(5,5-dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one – Magnusson–Kligman Method (OECD 406). Unpublished report from Firmenich Incorporated, 18 December. Report number 44320 (RIFM, Woodcliff Lake, NJ, USA).
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