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Review

A safety assessment of branched chain saturated alcohols when used as fragrance ingredients ☆

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ABSTRACT

The Branched Chain Saturated Alcohol (BCSA) group of fragrance ingredients was evaluated for safety. In humans, no evidence of skin irritation was found at concentrations of 2–10%. Undiluted, 11 materials evaluated caused moderate to severe eye irritation. As current end product use levels are between 0.001% and 1.7%, eye irritation is not a concern. The materials have no or low sensitizing potential. For individuals who are already sensitized, an elicitation reaction is possible. Due to lack of UVA/UVB light-absorbing structures, and review of phototoxic/photoallergy data, the BCSA are not expected to elicit phototoxicity or photoallergy. The 15 materials tested have a low order of acute toxicity. Following repeated application, seven BCSA tested were of low systemic toxicity. Studies performed on eight BCSA and three metabolites show no *in vivo* or *in vitro* genotoxicity. A valid carcinogenicity study showed that 2-ethyl-1-hexanol is a weak inducer of liver tumors in female mice, however, the relevance of this effect and mode of action to humans is still a matter of debate. The Panel is of the opinion that there are no safety concerns regarding BCSA under the present levels of use and exposure.

Contents

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1. Introduction

In 2006 complete literature searches were conducted on the branched chain saturated alcohol group of fragrance ingredients. This document provides a risk assessment of these materials as fragrance ingredients and is a critical evaluation of the pertinent data. The scientific evaluation focuses on dermal exposure, which is considered to be the primary route for fragrance materials. Where relevant, toxicity, metabolism and biological fate data from other exposures have been considered.

The current format includes a group summary evaluation paper and individual Fragrance Material Reviews on discrete chemicals. The group summary is an evaluation of relevant data selected from the large bibliography of studies and reports on the individual chemicals. The selected data were deemed to be relevant based on the currency of protocols, quality of the data, statistical significance and appropriate exposure. These are identified in tabular form in the group summary. Details that are provided in the tables are not always discussed in the text of the group summary. The Fragrance Material Reviews contain a comprehensive summary of all published reports including complete bibliographies (McGinty et al., 2010a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q).

2. Chemical identity, regulatory status, and exposure

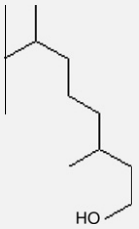
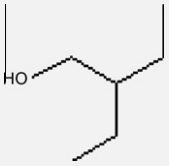
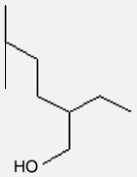
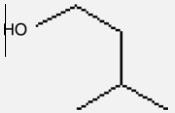
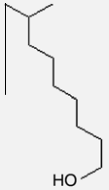
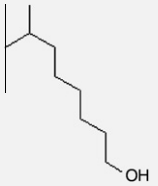
2.1. Rationale for grouping branched chain saturated alcohols together

The group consists of 12 primary, 5 secondary and 3 tertiary alcohols. Of these materials, three have been previously reviewed in RIFM's Safety Assessment on Terpene Alcohols (Belsito et al., 2008). The names and structures of the materials reviewed are shown in Table 1.[1] In addition, several noncyclic branched chain alcohols used as examples here have been reviewed in other recent RIFM publications. Information on previously reviewed substances of this group is not presented again unless it is new or required to evaluate remaining fragrance ingredients. The common characteristic structural elements of the alcohols with saturated branched chain are one hydroxyl group per molecule, a C_4–C_{12} carbon chain with one or several methyl side chains. Two members of the group, 2-ethyl-1-butanol and 2-ethyl-1-hexanol, contain an ethyl side chain. One member contains a methoxy group. Metabolism studies are lacking for this compound, however, a methoxy group is enzymatically not readily cleaved and if it were so, another primary alcohol group would be formed.

As the database for the alcohols under review is limited, additional data for some metabolites of these alcohols have been used. It was demonstrated that 4-methyl-2-pentanol, a group member, is metabolized to *4-methyl-2-pentanone* and *4-hydroxy-4-methyl-2-pentanone* is a metabolite of both substances (Gingell et al., 2003). It can also be expected that 2,6-dimethyl-4-heptanol is metabolized to *2,6-dimethylheptan-4-one*. Therefore, studies on pharmacokinetics, metabolism, genotoxicity and systemic toxicity of *4-methyl-2-pentanone*, *4-hydroxy-4-methyl-2-pentanone* and *2,6-dimethylheptan-4-one* have been added to the database. These materials are not used as fragrance ingredients. Due to their structural similarity, these alcohols also share common metabolic pathways (see below). As metabolism is crucial for pharmacokinetics and toxicity, these alcohols or their metabolites are expected to have the same primary target organs (liver, kidney, and blood) as was shown for 2-ethyl-1-hexanol, isoamyl alcohol, isotridecan-1-

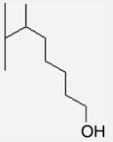
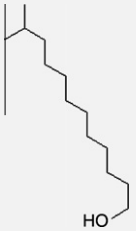
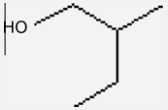
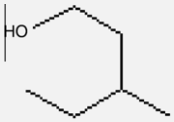
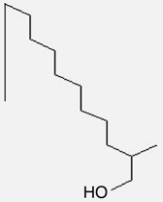
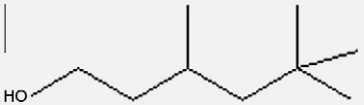
[1] Isooctan-1-ol, isononyl alcohol, isodecyl alcohol and Isotridecan-1-ol (isomeric mixture) are generic names for mixtures of isomers of primary branched alcohols with an average C-number of 8, 9, 10, or 13, respectively.

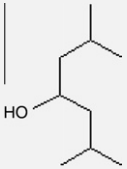
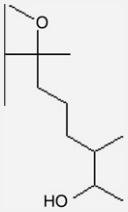
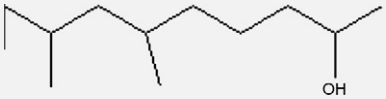
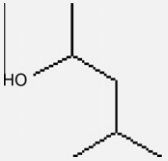
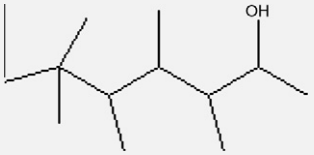
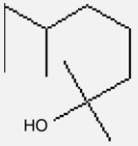
Table 1
Material identification, summary of volume of use, and dermal exposure.

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level (%)[b]
Subgroup: primary					
3,7-Dimethyl-1-octanol[c] $C_{10}H_{22}O$ CAS# 106-21-8 Henry's Law: 0.0000547 atm m^3/mol 25 °C LogK_{ow}: 3.9 at 35 °C Molecular weight: 158.29 Vapor pressure: 0.06 mm Hg 20 °C Water solubility: 175.4 mg/l at 25 °C	•Dihydrocitronellol •1-Octanol, 3,7-dimethyl- •Pelargol •Tetrahydrogeraniol		100–1000	0.0005[d]	0.02
2-Ethyl-1-butanol $C_6H_{14}O$ CAS# 97-95-0 Henry's Law: 0.0000176 atm m^3/mol 25 °C LogK_{ow}: 1.75 calc Molecular weight: 102.18 Vapor pressure: 1.0 mm Hg 20 °C Water solubility: 11,950 mg/l at 25 °C	•1-Butanol,2-ethyl- •2-Ethylbutyl alcohol •2-Ethylbutan-1-ol		<0.01	0.0005[d]	0.02
2-Ethyl-1-hexanol $C_8H_{18}O$ CAS# 104-76-7 Henry's Law: 0.000031 atm m^3/mol 25 °C LogK_{ow}: 2.73 calc Molecular weight: 130.23 Vapor pressure: 0.06 mm Hg 20 °C Water solubility: 1379 mg/l at 25 °C	•2-Ethylhexanol •1-Hexanol,2-ethyl- •2-Ethylhexan-1-ol		0.1–1	0.0005	0.008
Isoamyl alcohol $C_5H_{12}O$ CAS# 123-51-3 Henry's Law: 0.0000133 atm m^3/mol at 25 °C LogK_{ow}: 1.16 Molecular weight: 88.15 Vapor pressure: 3.84 mm Hg 25 °C Water solubility: 41,580 mg/l at 25 °C	•1-Butanol,3-methyl- •Isobutyl carbinol •Isopentanol •Isopentyl alcohol •3-Methyl-1-butanol •3-Methylbutan-1-ol		0.1–1	0.0002	0.01
Isodecyl alcohol $C_{10}H_{22}O$ CAS# 25339-17-7 Henry's Law: 0.0000547 atm m^3/mol 25 °C LogK_{ow}: 3.71 calc Molecular weight: 158.85 Vapor pressure: 0.0204 mm Hg 25 °C Water solubility: 151.8 mg/l at 25 °C	•Isodecanol •8-Methylnonan-1-ol		0.1–1	0.0005[d]	0.02
Isononyl alcohol (isomer unspecified) $C_9H_{20}O$ CAS# 27458-94-2 Henry's Law: 0.0000412 atm m^3/mol 25 °C LogK_{ow}: 3.22 calc Molecular weight: 144.58 Vapor pressure: 0.0198 mm Hg 25 °C Water solubility: 459.7 mg/l at 25 °C	•Isononanol •7-Methyloctan-1-ol		<0.01	0.11	0.3

(*continued on next page*)

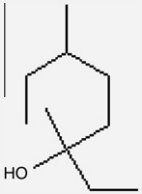
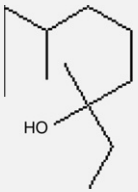
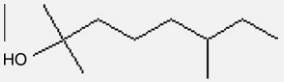
Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level (%)[b]
Isooctan-1-ol $C_8H_{18}O$ CAS# 26952-21-6 Henry's Law: 0.000031 atm m^3/mol 25 C LogK_{ow}: 2.73 calc Molecular weight: 130.31 Vapor pressure: 0.151 mm Hg 25 C Water solubility: 1379 mg/l at 25 °C	•Isooctanol •6-Methylheptan-1-ol		<0.01	0.0005[d]	0.02
Isotridecan-1-ol (isomeric mixture) $C_{13}H_{28}O$ CAS# 27458-92-0 Henry's Law: 0.000128 atm m^3/mol 25 °C LogK_{ow}: 5.19 calc Molecular weight: 200.66 Vapor pressure: 0.000462 mm Hg 25 °C Water solubility: 5.237 mg/l at 25 °C	•Isotridecanol •11-Methyldodecan-1-ol		10–100	0.04	0.7
2-Methylbutanol $C_5H_{12}O$ CAS# 137-32-6 Henry's Law: 0.0000133 atm m^3/mol 25 °C LogK_{ow}: 1.26 calc Molecular weight: 88.15 Vapor pressure: 2.5 mm Hg 20 °C Water solubility: 32200 mg/l at 25 °C	•Active amyl alcohol •1-Butanol,2-methyl- •sec-Butylcarbinol •(+/−) 2-Methyl-1-butanol •2-Methylbutyl alcohol •2-Methylbutan-1-ol		0.01–0.1	0.0002	0.001
3-Methyl-1-pentanol $C_6H_{14}O$ CAS# 589-35-5 Henry's Law: 0.0000176 atm m^3/mol 25 °C LogK_{ow}: 1.75 calc Molecular weight: 102.18 Vapor pressure: 0.7 mm Hg 20 °C Water solubility: 11,950 mg/l at 25 °C	•2-Ethyl-4-butanol •1-Pentanol,3-methyl- •3-Methylpentan-1-ol •Methyl Pentanol-3		<0.01	0.0005[d]	0.02
2-Methylundecanol $C_{12}H_{26}O$ CAS# 10522-26-6 Henry's Law: 0.0000963 atm m^3/mol 25 °C LogK_{ow}: 4.7 calc Molecular weight: 186.39 Vapor pressure: 0.0014 mm Hg 25 °C Water solubility: 16.18 mg/l at 25 °C	•1-Undecanol,2-methyl- •2-Methylundecan-1-ol		<0.01	0.01	0.04
3,5,5-Trimethyl-1-hexanol $C_9H_{20}O$ CAS# 3452-97-9 Henry's Law: 0.0000412 atm m^3/mol 25 °C LogK_{ow}: 3.11 calc Molecular weight: 144.26 Vapor pressure: 0.2 mm Hg 20 °C Water solubility: 572 mg/l at 25 °C	•1-Hexanol,3,5,5-trimethyl- •i-Nonyl alcohol •Nonylol •Trimethylhexanol •3,5,5-Trimethylhexanol •3,5,5-Trimethylhexan-1-ol •3,5,5-Trimethylhexyl alcohol		1–10	0.004	0.7

Subgroup: secondary					
2,6-Dimethyl-4-heptanol $C_9H_{20}O$ CAS# 108-82-7 Henry's Law: 0.0000412 atm m^3/mol 25 °C LogK_{ow} 3.08 calc Molecular weight: 144.26 Vapor pressure: 0.0624 mm Hg 25 °C Water solubility: 613.8 mg/l at 25 °C	•Diisobutylcarbinol •4-Heptanol,2,6-dimethyl- •2,6-Dimethylheptan-4-ol		10–100	0.0005[d]	0.02
3,7-Dimethyl-7-methoxyoctan-2-ol $C_{11}H_{24}O_2$ CAS# 41890-92-0 Henry's Law: 0.000000404 atm m^3/mol 25 °C LogK_{ow}: 2.76 calc Molecular weight: 188.31 Vapor pressure: 0.0119 mm Hg 25 °C Water solubility: 707.1 mg/l at 25 °C	•7-Methoxy-3,7-dimethyloctan-2-ol •2-Octanol,7-methoxy-3,7-dimethyl- •Osirol •Osyrol		1–10	0.09	1.3
6,8-Dimethylnonan-2-ol $C_{11}H_{24}O$ CAS# 70214-77-6 LogK_{ow}: 4.06 calc Molecular weight: 172.12 Vapor pressure: 0.000115 mm Hg 25 °C	•2-Nonanol,6,8-dimethyl- •Nonadyl		1–10	0.001	0.009
4-Methyl-2-pentanol $C_6H_{14}O$ CAS# 108-11-2 Henry's Law: 0.0000176 atm m^3/mol 25 °C LogK_{ow}: 1.68 calc Molecular weight: 102.18 Vapor pressure: 3.7 mm Hg 20 °C Water solubility: 13,800 mg/l at 25 °C	•Isobutyl methyl carbinol •Methyl isobutyl carbinol •MIC •2-Pentanol,4-methyl- •4-Methylpentan-2-ol		0.01–0.1	0.0005[d]	0.02
3,4,5,6,6-Pentamethylheptan-2-ol $C_{12}H_{26}O$ CAS# 87118-95-4 LogK_{ow}: 4.36 calc Molecular weight: 186.39 Vapor pressure: 0.0000000461 mm Hg 25 °C	•2-Heptanol,3,4,5,6,6-pentamethyl- •Koavol DH		10–100	0.14	1.7
Subgroup: tertiary *2,6-Dimethyl-2-heptanol* $C_9H_{20}O$ CAS# 13254-34-7 Henry's Law: 0.0000412 atm m^3/mol 25 °C LogK_{ow} 3.0 at 45 °C Molecular weight: 144.26 Vapor pressure: 0.2 mm Hg 20 °C Water solubility: 572 mg/l at 25 °C	•Dimetol •Freesiol •2-Heptanol,2-6-dimethyl- •Lolitol •2,6-Dimethylheptan-2-ol		10–100	0.0614	1.4

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level (%)[b]
3,6-Dimethyl-3-octanol $C_{10}H_{22}O$ CAS# 151-19-9 Henry's Law: 0.0000547 atm m^3/mol 25 °C Log K_{ow}: 3.6 calc Molecular weight: 158.29 Vapor pressure: 0.0651 mm Hg 25 °C Water solubility: 188.9 mg/l at 25 °C	•3-Octanol,3,6-dimethyl- •3,6-Dimethyloctan-3-ol		0.1–1	0.0005[d]	0.02
Tetrahydrolinalool[c] $C_{10}H_{22}O$ CAS# 78-69-3 Henry's Law: 0.0000547 atm m^3/mol 25 C Log K_{ow}: 3.6 at 45 °C Molecular weight: 158.29 Vapor pressure: 0.0713 mm Hg 25 °C Water solubility: 188.9 mg/l at 25 °C	•2,6-Dimethyl-6-octanol •3,7-Dimethyloctan-3-ol •3-Octanol, 3,7-dimethyl-		>1000	0.0005[d]	0.02
Tetrahydromyrcenol[c] $C_{10}H_{22}O$ CAS# 18479-57-7 Henry's Law: 0.0000547 atm m^3/mol 25 C Log K_{ow}: 3.6 calc Molecular weight: 158.29 Vapor pressure: 0.05 mm Hg 20 °C Water solubility: 188.9 mg/l at 25 °C	•2,6-Dimethyloctan-2-ol •2,6-Dimethyl-2-octanol •2-Octanol, 2,6-dimethyl		100–1000	0.06	0.7

[a] 2007 Volume of use survey.
[b] Skin levels were based on the assumption that the fragrance mixture is used at 20% in a consumer product.
[c] Materials have been previously reviewed by in RIFM's Safety Assessment of Terpene Alcohols.
[d] A default value of 0.02% was used to calculate dermal systemic exposure.

ol (isomeric mixture), 3,5,5-trimethyl-1-hexanol, *2,6-dimethylheptan-4-one, 4-hydroxy-4-methyl-2-pentanone*, 4-methyl-2-pentanol, and *4-methyl-2-pentanone*.

Data for 2-ethyl-1-hexanol, 2-ethylbutanol, 4-methyl-2-pentanol, isoamyl alcohol, 2-methylbutanol and *4-methyl-2-pentanone* show that the alcohols share common metabolic pathways. The major pathways of metabolism and fate are:

- conjugation of the alcohol group with glucuronic acid;
- oxidation of the alcohol group;
- side-chain oxidation yielding polar metabolites, which may be conjugated and excreted – or further oxidized to an aldehyde, a carboxylic acid, and to CO_2;
- excretion of the unchanged parent compound.

In most cases, metabolism yields innocuous metabolites. Intermediary reactive products of oxidation of primary alcohols are aldehydes, which are toxic and possibly genotoxic, although no relevant genotoxicity was shown with the primary alcohols tested.

The alcohols under review are summarized in Table 1. CAS No. and synonyms for the alcohols considered in this review are shown in Table 1. The structural formulas are provided in Table 1.

2.2. Occurrence and use

The alcohols under review are used as fragrance ingredients. They may be found in fragrances used in decorative cosmetics, fine fragrances, shampoos, toilet soaps, and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. This report summarizes and synthesizes animal and human data, including studies by various routes of exposure, and emphasizes the risk assessment for use as fragrance ingredients. The scientific evaluation focuses on dermal exposure, which is considered the primary exposure route for fragrance materials. Where relevant the metabolism, toxicity, and biological fate data of other routes of exposure have also been considered.

The selected data from published and unpublished reports were deemed relevant based on the nature of the protocols, quality of the data, and appropriate exposure. These data are presented in tabular form.

Some of the alcohols assessed in this report have been evaluated and approved for use as flavor ingredients in foodstuffs. In the United States, 2-ethyl-1-hexanol, isoamyl alcohol, and 3-methyl-1-pentanol have been approved for use as food additives or in food contact materials by the Food and Drug Administration (FDA). In addition, 2,6-dimethyl-4-heptanol, 2-methylbutanol, and 3,5,5-trimethyl-1-hexanol are listed as food additives (FDA, 2007).

The International Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated alicyclic ketones, secondary alcohols and related esters including 2,6-dimethyl-4-heptanol from the group under review and its metabolite *2,6-dimethylheptan-4-one* (JECFA, 1999). JECFA also evaluated aliphatic, branched chain saturated and unsaturated alcohols, aldehydes, acids, and related esters including 2-methylbutanol (JECFA, 2004). These materials were judged by this Committee not to present a safety concern at the current estimated intake levels.

The annual worldwide use of the individual alcohols reviewed herein varies greatly and ranges from <0.01 to 100 metric tons. Compounds with a use volume of >10 metric tons are 2,6-dimethyl-2-heptanol, 2,6-dimethyl-4-heptanol, isotricedan-1-ol, and 3,4,5,6,6-pentamethylheptan-2-ol (IFRA, 2007; Table 1).

2.3. Estimated consumer exposure

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

The fragrance industry has developed three types of approaches to estimate potential exposure for consumers to fragrance materials. All three types of exposure are summarized in Table 1. The first is volume of use. The total worldwide volume of use for fragrance materials in the branched chain saturated alcohols ranges from <0.01 to >1000 metric tons per year (IFRA, 2004). The reported volume is for the fragrance ingredient as used in fragrance compounds (mixtures) in all 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 the potential percutaneous (total 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 10 types of the most frequently used personal care and cosmetic products (antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap). The concentration of the fragrance ingredient in fine fragrances is obtained from examination of several thousand commercial formulations. The upper 97.5 percentile concentration is calculated from the data obtained. This upper 97.5 percentile concentration is then used for all 10 consumer products. These concentrations are multiplied by the amount of product applied, the number of applications per day for each product type, and a "retention factor" (ranging from 0.001 to 1.0) to account for the length of time a product may remain on the skin and/or likelihood of the fragrance ingredient being removed by washing. The resultant calculation represents the total consumer exposure (mg/kg/day) (Cadby et al., 2002; Ford et al., 2000). In view of all of the above assumptions, the total calculated consumer exposure is conservative; it is unlikely that a consumer will consistently use a number of different consumer products which are all perfumed with the upper 97.5 percentile level of the fragrance ingredient from a fine fragrance type of product (Cadby et al., 2002; Ford et al., 2000). The total consumer exposures to fragrance ingredients range from 0.0002 to 0.11 mg/kg/body weight (bw)/day for the branched chain saturated alcohols fragrance ingredients in high-end users of cosmetic products containing these materials (see Table 1) (IFRA, 2004).

The third method provides maximum skin levels. For consideration of potential sensitization, the exposure is calculated as the percent concentration of the fragrance ingredient applied to the skin based on the use of 20% of the fragrance mixture in the fine fragrance consumer product (IFRA, 2007). The maximum skin exposure levels of the branched chain saturated alcohol compounds that form part of the formulae of fine fragrances vary widely and have been report to range from 0.008% to 1.7%. The maximum skin exposure for branched chain saturated alcohols in fine fragrance products are listed in Table 1 (IFRA, 2007).

In assessing safety, the calculated dermal systemic exposure in cosmetic products can then be compared to the indices of systemic toxicity such as NOAEL and LOAEL that are obtained from the repeat dose subchronic, chronic and reproductive toxicity studies to derive a margin of exposure (MOE). Systemic exposures (i.e., the dose absorbed through the skin and available to the systemic circulation) were estimated based on dermal absorption rates. Where such data were lacking, as a conservative measure, dermal

absorption was considered to be 100% (i.e., the maximum skin exposure value was considered as the estimate of systemic exposure).

All exposure data were provided by the fragrance industry. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).

3. Metabolism

3.1. Primary alcohols

When 25 mmoles (2.55 g) of 2-ethyl-1-butanol were administered by gavage to rabbits, 40% of the dose was excreted in the urine as the glucuronide conjugate. The excretion of glucuronide was completed within 24 h (Kamil et al., 1953a). A rabbit was given 3.1 ml (2.55 g) 2-ethyl-1-butanol and the 24-h urine was collected. 2-Ethyl-1-butanol was excreted mainly as diethylacetylglucuronide and a minor amount of methyl *n*-propyl ketone was also found (Kamil et al., 1953b).

Main metabolites of 2-ethyl-1-hexanol identified in the urine of rats after oral or dermal application were 2-ethylhexanoic acid, 5-hydroxy-2-ethylhexanoic acid, 5-keto-2-ethylhexanoic acid, 2-ethyl-1,6-hexanedioic acid and 6-hydroxy-2-ethylhexanoic acid, mainly as their glucuronides, and expired carbon dioxide. Potential metabolites not detected in each study were 2-ethylhexanoic acid, 4- and 2-heptanone. One to three percent 2-ethyl-1-hexanol was excreted unchanged or as glucuronide. Metabolic saturation was seen with 500 mg/kg body weight applied (Kamil et al., 1953a,b). This metabolite pattern demonstrates the well-known metabolic pathways of primary alcohols: oxidation of the alcohol group and oxidation of the side chain at various positions, glucuronidation of the oxidation products, and decarboxylation (Fig. 1; Albro, 1975; Deisinger et al., 1993, 1994). Induction of metabolism was not seen with repeated oral dosing (Deisinger et al., 1994). In rabbits the glucuronide of 2-ethylhexanoic acid was identified as the main metabolite (87%) after oral application of 2-ethyl-1-hexanol (Kamil et al., 1953a,b). *In vitro* incubation with mammalian alcohol dehydrogenase resulted in a V_{max} of 0.30 μmol/min/mg protein and a K_m value of 0.74 mM (Albro, 1975).

Only about 9% of the administered dose was found in the form of the glucuronide when isoamyl alcohol (3-methylbutanol) or 2-methylbutanol was given to rabbits. Other metabolites were not identified (Kamil et al., 1953a). Age-dependent glucuronidation activity was demonstrated *in vitro* in the olfactory mucosa of rats with isoamyl alcohol (Leclerc et al., 2002). The glucuronidation of isoamyl alcohol and other short-chained aliphatic alcohols was investigated *in vitro* with human liver microsomes. The V_{max} value was 3.3 nmol/min/mg protein and the K_m was determined as 13.3 mM. The glucuronidation increased with chain length (C2–C5) of the alcohols studied (Jurowich et al., 2004).

Oxidation to the aldehyde and glucuronidation was demonstrated for isoamyl alcohol and 2-methylbutanol with microsomes from rats pretreated with ethanol (Iwersen and Schmoldt, 1995). The rate of oxidative metabolism of isoamyl alcohol was about 0.1 mmol/g liver in rat liver homogenate and about 0.05 mM/g perfused rat liver (Hedlund and Kiessling, 1969). The rate of oxidation of isoamyl alcohol by human skin alcohol dehydrogenase was 183.3 nM/mg protein per minute (Wilkin and Stewart, 1987). The K_m-values of isoamyl alcohol with alcohol dehydrogenase from human and horse liver were 0.07 and 0.08 mM, respectively (Pietruszko et al., 1973). After intraperitoneal application of 1000 mg isoamyl alcohol or 2-methylbutanol/kg body weight, the corresponding aldehydes could not be detected in expired air of rats (Haggard et al., 1945).

3.2. Secondary alcohols

After application of 4-methyl-2-pentanol (methyl isobutyl carbinol in Fig. 2) to rabbits 33.7% of the dose was excreted as the glucuronide (Kamil et al., 1953a). In mammals, the metabolism of secondary alcohols proceeds primarily through their respective ketones. 4-Methyl-2-pentanol is metabolized to *4-methyl-2-pentanone* (*methyl isobutyl ketone* in Fig. 2) and further to *4-hydroxy-4-methyl-2-pentanone* in rats (Fig. 2; OECD/SIDS, 2007).

Plasma levels of 4-methyl-2-pentanol, *4-methyl-2-pentanone*, and *4-hydroxy-4-methyl-2-pentanone* were determined up to 12 h after oral gavage administration of 5 mmol/kg of 4-methyl-2-pentanol or *4-methyl-2-pentanone* to male rats. After dosing rats by gavage with 4-methyl-2-pentanol or *4-methyl-2-pentanone*, the major material in the plasma for both compounds was *4-hydroxy-4-methyl-2-pentanone.* No other metabolites were detected in the plasma. The extent of metabolism of 4-methyl-2-pentanol to *4-methyl-2-pentanone* was at least 73%. The reduction of *4-methyl-2-pentanone* to 4-methyl-2-pentanol was insignificant (Gingell et al., 2003; Hirota, 1991a).

Similar results were obtained with intraperitoneal application of 4-methyl-2-pentanol and *4-methyl-2-pentanone* in mice. After intraperitoneal administration of *4-hydroxy-4-methyl-2-pentanone*, neither 4-methyl-2-pentanol nor *4-methyl-2-pentanone* could be detected in the blood and in the brain (Fig. 2; Granvil et al., 1994). This result shows that in rats and mice 4-methyl-2-pentanol is predominantly oxidized to *4-methyl-2-pentanone* and both compounds share the same principal metabolite, namely *4-hydroxy-4-methyl-2-pentanone*.

In workers exposed to mixed solvents including *4-methyl-2-pentanone* and 4-methyl-2-pentanol was identified by GC–MS in the urine. In a subject exposed to 42.3 ml pure *4-methyl-2-pentanone*/m^3 for 6 h, 0.42 mg 4-methyl-2-pentanol/g creatinine was excreted (Hirota, 1991b). This result confirms, that in humans as well, the reduction of *4-methyl-2-pentanone* is insignificant (6 h 42 ml/m^3 *4-methyl-2-pentanone* corresponds to about 320 mg at 66% retention in the lung and a minute volume of 8 l).

3.3. Tertiary alcohols

Data on the tertiary alcohols under review are not available. A tertiary alcohol group cannot be oxidized. Tertiary alcohols are expected to be excreted either via conjugation or unchanged or undergo hydroxylation of the carbon chain, which in turn may give rise to a metabolite which can be easily excreted.

4. Pharmacokinetics

4.1. Dermal route of exposure

In vitro absorption rates for 2-ethyl-1-hexanol were 0.22 ± 0.09 and 0.038 ± 0.014 mg/cm^2/h for rat and human skin, respectively, giving a rat/human ratio of 5.78. The permeability constants were $2.59 \pm 1.10 \times 10^{-4}$ cm/h for rats and $4.54 \pm 1.66 \times 10^{-5}$ cm/h for humans (Barber et al., 1992).

The dermal absorption in the rat was determined to be 5.2% of a dose of 1000 mg 2-ethyl-1-hexanol/kg body weight applied for 6 h; the absorption rate was calculated to be 0.57 mg/cm^2/h. The terminal half-life was calculated to be 77 h (Deisinger et al., 1994).

4.2. Oral route of exposure

In rats, oral administration of 2000 mg isoamyl alcohol/kg body weight led to a peak concentration of 170 mg/l blood 1 h later. The

authors calculated an oxidation rate of 5 mg/kg body weight/h (Gaillard and Derache, 1965).

After oral administration to rats, 69–75% of a dose of 500 mg ^{14}C-labeled 2-ethyl-1-hexanol/kg body weight was excreted in the urine within 96 h. About 13–15% of the dose was excreted in the feces and about the same amount was exhaled. More than 50% of the dose was excreted within 24 h (Deisinger et al., 1993, 1994).

Plasma levels of 4-methyl-2-pentanol, *4-methyl-2-pentanone*, and *4-hydroxy-4-methyl-2-pentanone* were determined up to 12 h after oral gavage administration of 5 mmol/kg of 4-methyl-2-pentanol or *4-methyl-2-pentanone* to male rats. The major material in the plasma for both compounds was *4-hydroxy-4-methyl-2-pentanone*, with similar areas under the curve (AUCs) and C_{max} at 9 h after dosing for both 4-methyl-2-pentanol and *4-methyl-2-pentanone*. *4-Methyl-2-pentanone* plasma levels and AUC were also similar after *4-methyl-2-pentanone* or 4-methyl-2-pentanol administration. 4-Methyl-2-pentanol AUC was only about 6% of the total material in the blood following 4-methyl-2-pentanol administration, and insignificant after *4-methyl-2-pentanone* administration (Gingell et al., 2003).

4.3. Respiratory route of exposure

Respiratory uptake of isoamyl alcohol was investigated in four healthy volunteers. Air concentration was 25–200 ppm and exposure duration was 10 min. The mean uptake for the last 5 min of exposure was 63% and the mean respiratory rate was 15.3 min^{-1} (Kumagai et al., 1998).

4.4. Parenteral route of exposure

After intravenous administration to rats, about 74% of a dose of 1 mg ^{14}C-labeled 2-ethyl-1-hexanol/kg body weight was excreted in the urine within 96 h. About 4% of the dose was excreted in the feces and 23% was exhaled. More than 50% of the dose was excreted within 8 h. The terminal half-life was estimated to be 60 h (Deisinger et al., 1993, 1994).

The concentration of isoamyl alcohol in blood declined within 5 h to non-detectable levels after intraperitoneal administration of 1000 mg isoamyl alcohol/kg body weight. Similar values were found for 2-methylbutanol administered at the same dose. An elimination half-life was not calculated. For isoamyl alcohol and 2-methylbutanol, 1.2% and 7.6%, respectively, were excreted via urine and expired air. Compared to other amyl alcohols tested by the authors, primary alcohols were eliminated from the blood more quickly than secondary and tertiary alcohols (Haggard et al., 1945).

5. Toxicological studies

5.1. Acute toxicity

Acute dermal toxicity studies have been performed with six primary, three secondary, and three tertiary alcohols, all but one in rabbits. The dermal LD_{50} values in rabbits and the one in rats are in the range of 1000–>5000 mg/kg body weight. In summary all the compounds are of low acute toxicity by the dermal route (Table 2-1).

Eight primary alcohols, four secondary, and three tertiary alcohols have been tested for oral acute toxicity. The oral LD_{50} values in rats, mice, and rabbits are in the range of 1000–>5000 mg/kg body weight, and therefore, all the compounds exhibit a low toxicity when administered via the oral route (Table 2-2).

Lethargy was the most often reported clinical sign after oral or dermal administration, diarrhea and ataxia after oral administration, and irritation of the skin after dermal administration. Signs of gastrointestinal irritation were noted at necropsy in acute oral toxicity tests.

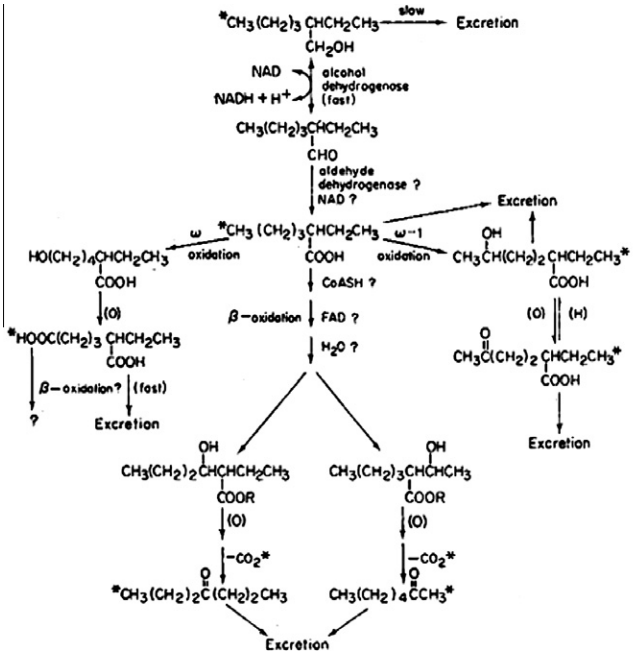


Fig. 1. Metabolism of 2-ethyl-1-hexanol in the rat (from Albro, 1975). Metabolites marked with asterisks were detected.

In inhalation tests with five primary and two secondary alcohols, no mortality was observed in rats exposed to air saturated with alcohol vapor at room temperature for as long as 8 h. LC_{50} values were not determined. Local ocular and upper respiratory tract irritation was seen with 2-ethyl-1-hexanol. However, 4-methyl-2-pentanol exposure at 2000 ml/m^3 for 8 h resulted in death at 14 days of 5/6 rats, and exposure to saturated air at 20 °C resulted in anesthesia at 4 h and death of 6/10 mice after 10 h.

Acute toxicity data obtained from studies with other than oral or dermal exposure are summarized in Table 2-3.

5.2. Repeated dose toxicity

The evaluation of repeated dose systemic toxicity is based on several oral studies with mainly primary alcohols and only one secondary alcohol. The metabolic pathways with all the materials in this group yield innocuous metabolites. The database could be strengthened by an evaluation of the systemic toxicity of a secondary and tertiary alcohol. Other studies can be found in Section 5.10.

5.2.1. Dermal studies

Dermal studies with branched chain saturated alcohols are summarized in Table 3-1.

5.2.1.1. Primary alcohols. Over a period of 12 days, rats were treated with undiluted 2-ethyl-1-hexanol (2 ml/kg body weight/day, about 1600 mg/kg body weight/day) on their shaved backs. At necropsy, the treated animals had decreased absolute and relative thymus weights, liver granulomas, bronchiectasis in the lung, renal tubular epithelial necrosis in the kidneys, edema in heart and testes, decreased spermatogenesis, and an increase in lipids in adrenals were found on day 17. These effects were reversed on day 30 (Schmidt et al., 1973).

2-Ethyl-1-hexanol was applied topically under occlusion to Fischer 344 rats for 5 days, followed by 2 days untreated, 4 days

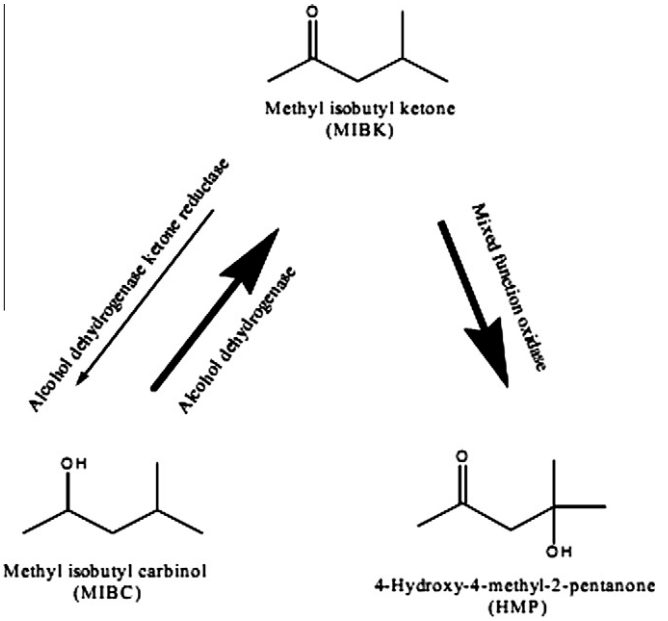


Fig. 2. Metabolism of 4-methyl-2-pentanol in the rat and mouse (OECD/SIDS, 2007).

treated with 0, 500, or 1000 mg/kg body weight/day. Treatment-related clinical signs of toxicity were restricted to the skin at the treatment site and included exfoliation (minimal severity) at both doses and transient erythema at the high dose. Serum triglycerides were increased in females at both doses. In high-dose females, peripheral blood lymphocytes and absolute spleen weight were reduced (RIFM, 1988; Weaver et al., 1989).

Albino rabbits (2/sex/dose) were treated by dermal occluded application with 0, 400, or 2000 mg/kg body weight/day of isooctanol (alcohols C7–9, branched CAS No. 68526-83-0) for 12 days with 10 applications, lasting 18–24 h each. Control animals received isopropyl alcohol. No relevant changes in appearance, behavior, body weight, hematology, and urinalysis were noted in treated animals. Necropsy and microscopic evaluation demonstrated no treatment-related findings. Moderate to severe skin irritation at the application site was noted in treated animals with necrosis in high-dose animals. The systemic NOAEL was 2000 mg/kg body weight/day (Esso, 1961a, as cited in ExxonMobil Chemical Company, 2001a).

5.2.1.2. Secondary alcohols. New Zealand White rabbits (5/sex/dose) were treated topically by occlusive application of 0 or 1000 mg/kg body weight/day of 3,4,5,6,6-pentamethylheptan-2-ol for 28 consecutive days at the same site according to OECD test guideline (TG) 410. Severe skin irritation was induced in rabbits receiving 1000 mg/kg body weight/day of 3,4,5,6,6-pentamethylheptan-2-ol. However, no alterations in general health, hematology, biochemistry, major organ weights, or histopathology were observed. For systemic effects the NOAEL was 1000 mg/kg body weight/day (RIFM, 1985c).

5.2.1.3. Tertiary alcohols. No studies are available for the members of this subgroup.

5.2.2. Oral studies

Oral toxicity studies with branched chain saturated alcohols are summarized in Table 3-2.

5.2.2.1. Primary alcohols. Three repeated dose oral toxicity studies were done with isoamyl alcohol. In a 90-day study according to OECD TG 408, isoamyl alcohol was administered in the drinking water in concentrations of 0, 1000 ppm (about 80 mg/kg/d), 4000 ppm (about 340 mg/kg/d), and 16,000 ppm (about 1250 mg/kg/d). The NOAEL of isoamyl alcohol was concluded to be 4000 ppm in males (340 mg/kg/d) by the authors because the increase of erythrocyte counts at this dose fell within the historical control range. The NOAEL for females was 16,000 ppm (1250 mg/kg/d) because the increase in prothrombin time was only seen in females and fell within the historical control range (Schilling et al., 1997). Isoamyl alcohol was tested in a 17-week toxicity study with Ash/CSE rats. The test substance was administered by gavage to 15 male and 15 female rats per group at dose levels of 0 (vehicle), 150, 500, or 1000 mg/kg body weight/day in corn oil. Observations included mortality, behavior, body weight, food and water consumption, hematology, serum analysis, urinalysis, renal concentration, organ weights, and gross pathology; microscopic pathology of 25 organs or tissues on control and top dose only. The only observed effect was a statistically significant reduced body weight in males at the highest dose level; food intake was reduced, but not statistically. The NOAEL was 500 mg/kg body weight/day for males and 1000 mg/kg body weight/day for females (Carpanini and Gaunt, 1973). Finally, isoamyl alcohol was administered to male and female Wistar rats as a 2% solution in drinking water (about 2000 mg/kg body weight/day) for 56 weeks. No treatment-related effects on body weight, liver weight, ADH, GOT, GPT activity, and protein content of the liver were found. Histological examinations of the livers, hearts, spleens, kidneys, and lungs did not show any significant abnormalities (Johannsen and Purchase, 1969).

Several studies in mice (gavage, RIFM, 1992a,b) and rats (gavage, RIFM, 1988; Weaver et al., 1989), given 2-ethyl-1-hexanol by gavage or drinking water (RIFM, 1988; Weaver et al., 1989), or feed (RIFM, 1992c) for periods of 9–11 days yielded NOAELs in the range of 100–150 mg/kg body weight/day. Doses of 330 mg/kg body weight/day and higher resulted in CNS depression, lacrimation, decreased food consumption, and body weights. 2-Ethyl-1-hexanol was administered by gavage to F344 rats and B6C3F1 mice of both sexes as an aqueous solution (0, 25, 125, 250, or 500 mg/kg body weight/day) for 13 weeks. Histopathology was undertaken on tissues recommended in US EPA guidelines. The NOAEL was 125 mg/kg body weight/day for rats and mice (Astill et al., 1996a). In a carcinogenicity study (see Section 5.4) 2-ethyl-1-hexanol was given to male and female rats and mice by gavage 5 times a week in 0.005% aqueous Cremophor EL (rats: 0 (water), 0 (vehicle), 50, 150, or 500 mg/kg body weight/day, 2 months; mice: 0 (water), 0 (vehicle), 50, 200, or 750 mg/kg body weight/day, 18 months). The NOAEL for systemic toxicity for mice was 200 mg/kg body weight/day. In rats, the NOAEL for systemic toxicity was 50 mg/kg body weight/day (Astill et al., 1996b).

An oral study according to OECD TG 422 (combined repeated dose and reproductive/developmental toxicity screening test) was conducted with 3,5,5-trimethyl-1-hexanol. Twelve SD (Crj:CD) rats per sex and dose group were gavaged with 0 (vehicle: olive oil), 12, 60, or 300 mg/kg body weight/day. Exposure duration in males was 46 days and in females from day 14 before mating to day 3 of lactation. Males of all dose groups showed alpha-2u-globulin nephropathy. In males and females dosed with 60 or 300 mg/kg body weight/day, systemic effects were seen, including reduced body weight and food consumption. On the basis of these findings, the NOAEL for repeated dose toxicity was 12 mg/kg body weight/day for male and female rats (MHW, Japan, 1997b as cited in OECD/SIDS, 2003).

In a 90-day study according to OECD TG 408 isotridecanol(iso alcohols C11–14, C13 rich, CAS No. 68526-86-3) was administered orogastrically (gavage) to Sprague–Dawley rats in doses of 0, 100, 500, or 1000 mg/kg body weight/day. No effects were observed only at the lowest dose. The NOAEL for systemic toxicity was

100 mg/kg body weight/day (Exxon Biomedical Sciences Inc., 1986 as cited in ExxonMobil Chemical Company, 2001b).

5.2.2.2. Secondary alcohols. A combined repeated dose and reproductive/developmental screening study according to OECD TG 422 is available with *4-hydroxy-4-methyl-2-pentanone*,a metabolite of 4-methyl-2-pentanol. Ten rats per sex and group were dosed by gavage with 0, 30, 100, 300, or 1000 mg 4-hydroxy-4-methyl-2-pentanone/kg body weight/day in distilled water. Males were dosed for 44 days and females from day 14 before mating to day 3 of lactation (approximately for 45 days). No effects were noted at 30 mg/kg body weight/day. Males treated with at least 100 mg/kg body weight/day showed male rat-specific alpha-2u-nephropathy. At both 300 and 1000 mg/kg body weight/day, deleterious effects were observed, including dilatation of the distal tubules and fatty degeneration of the proximal tubular epithelium in kidneys in females (300 mg/kg body weight/day) (MHW, Japan 1997, as cited in OECD/SIDS, 2007). The NOAEL was 100 mg/kg body weight/day due to kidney effects in females at 300 mg/kg body weight/day. The kidney effects in males at 100 mg/kg body weight are not relevant for humans.

2,6-Dimethyl-4-heptanol was tested in a 13-week toxicity study in rats. Male and female animals were fed a diet containing the test substance mixed with five parts of microcrystalline cellulose (16/sex/group). The daily intake of the test material was 11 mg/kg body weight/day for males and females. Female rats showed a statistically significantly lower (−12.1%) body weight gain and reduced food efficiency. The authors concluded that the reduction in body weight gain was most probably of no toxicological significance since the reduction was not associated with other toxicologically significant differences between test and control animals (Posternak and Vodoz, 1975). Because only the range of body weights at the start of the study is given, it is unclear whether the animals were adequately randomized to control and test groups based on body weight. Only one dose was tested, therefore, it cannot be judged whether the body weight gain reduction is a substance-induced effect. A NOAEL for this study for the females cannot be deduced because of the reduction in body weight gain. For males the NOAEL is 11 mg/kg body weight/day.

5.2.2.3. Tertiary alcohols. No data available.

5.2.3. Inhalation studies

Inhalation studies with branched chain saturated alcohols are summarized in Table 3-3.

5.2.3.1. Primary alcohols. Male and female Wistar rats (10/group/sex) were exposed 6 h daily on 5 days per week for 90 days to 2-ethyl-1-hexanol (purity 99.9%) in concentrations of 15, 40, or 120 ml/m^3 (highest vapor concentration at room temperature). Neither local nor systemic effects were found. The NOAEL is 120 ml/m^3 (Klimisch et al., 1998).

Three female Alderly-Park rats exposed in whole body exposure chambers for 13 six-hour exposure periods to saturated vapor of a mixture of branched chain alcohols designated isooctan-1-ol (180 ml/m^3) showed no adverse effects (Gage, 1970).

5.2.3.2. Secondary alcohols. A 9-day study in rats (10/sex/group, 5 h/day, 5 days/week) exposed to 98, 300, or 905 ml/m^3 *2,6-dimethylheptan-4-one* demonstrated increased liver weights from 300 ml/m^3 as well as alpha-2u-globulin accumulation in the kidneys of males (Dodd et al., 1987). Considering the increased liver weights as a sign of enzyme induction, the NOAEL is 98 ml/m^3.

In a 6-week inhalation study with *2,6-dimethylheptan-4-one*, groups of 30 rats (15/sex) were exposed to 0, 125, 252, 534, 925, or 1654 ml/m^3 of *2,6-dimethylheptan-4-one*, 7 h/day, 5 days/week for 6 weeks. Liver and kidney weights were increased at 252 ml/m^3 in females. At 925 ml/m^3 "increased incidence of minor pathological change" was reported. At 1654 ml/m^3 all females died during the first exposure whereas 12/15 males survived all exposures at this concentration. Among surviving males at 1654 ml/m^3 there were no major histopathological changes; "cloudy swelling" in the liver and the convoluted tubules in the kidneys and lung congestion were observed in some surviving males (Carpenter et al.,

Table 2-1
Acute dermal toxicity studies.

Material	Species	No./dose	LD_{50} mg/kg body weight[b]	References
Subgroup: primary				
2-Ethyl-1-butanol	Rabbit	4	1260 (95% C.I. 850–1870)	Smyth et al. (1954)
	Rabbit	n.f.i.	2000	Draize et al. (1944)
2-Ethyl-1-hexanol	Rabbit	10	>5000	RIFM (1977a)
	Rabbit	4 (males)	2380 (95% C.I. 1700–3340)	Smyth et al. (1969)
	Rabbit	4	>2600	Scala and Burtis (1973)
Isoamyl alcohol	Rabbit	10	>5000	RIFM (1976a)
	Rabbit	6	4000	RIFM (1979c)
	Rabbit	4 (males)	3970 (95% C.I. 2930–5370)	Smyth et al. (1969)
Isotridecan-1-ol (isomeric mixture)	Rabbit	4 (males)	7070	Smyth et al. (1962)
	Rabbit	4	>2600	Scala and Burtis (1973)
2-Methylbutanol	Rabbit	4 (males)	3540	Smyth et al. (1962)
	Rabbit	n.f.i.	3540	RIFM (1979b)
3,5,5-Trimethyl-1-hexanol	Rabbit	10	>5000	RIFM (1977a)
Subgroup: secondary				
2,6-Dimethyl-4-heptanol	Rabbit	20 (males)	4591 (95% C.I. 2036–10,383)	Smyth et al. (1949)
4-Methyl-2-pentanol	Rabbit	5	3560 (2720–4760)	Smyth et al. (1951)
3,4,5,6,6-Pentamethylheptan-2-ol	Rat	10 (5/sex)	>2000	RIFM (1985a)
Subgroup: tertiary				
2,6-Dimethyl-2-heptanol	Rabbit	10	>5000	RIFM (1976a)
3,6-Dimethyl-3-octanol[a]	Rabbit	8	>5000	RIFM (1973a)
3-Methyloctan-3-ol[a]	Rabbit	10	>5000	RIFM (1978c)

n.f.i.: no further information.
[a] No relevant use was reported.
[b] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.

1953). Considering the increased liver weights as a sign of enzyme induction at 250 ml/m^3, the NOAEL is 125 ml/m^3.

Wistar rats were whole body exposed to 0, 211, 825, or 3700 mg 4-methyl-2 pentanol/m^3 (0, 50.5, 198, or 886 ml/m^3) (purity > 98%) 6 h per day and 5 days per week for 6 weeks, 12 animals per sex and group. In females of all concentration groups and in males treated with 198 ml/m^3 or more, increased levels of ketone bodies in urine were noted. At the highest concentration, absolute kidney weights increased in males and proteinuria was detected; an increase in serum alkaline phosphatase in females was observed. There were no exposure-related histopathological effects in the kidneys or other organs. The increases in ketone bodies, kidney weight, and alkaline phosphatase were not considered adverse toxicological effects. Therefore, the NOAEL was assessed to be 3700 mg/m^3 (886 ml/m^3) by OECD/SIDs (Blair, 1982 as cited in OECD/SIDS, 2007). However, since the increase in alkaline phosphatase in high-concentration females was significantly elevated the NOAEL is judged to be 198 ml/m^3.

A 14-week inhalation study (equivalent to OECD TG 413) was performed with the metabolite of 4-methyl-2-pentanol and

Table 2-2
Acute oral toxicity studies.

Material	Species	No./dose	LD_{50} mg/kg body weight[b]	References
Subgroup: primary				
2-Ethyl-1-butanol	Rat	5	1850 (95% C.I. 1520–2240)	Smyth et al. (1954)
	Rat	n.f.i.	1850	Nishimura et al. (1994) and Bar and Griepentrog (1967)
	Rabbit	n.f.i.	1200	Draize et al. (1944)
2-Ethyl-1-hexanol	Rat	n.f.i.	2049	Nishimura et al. (1994)
	Rat	5	2460 (1820–3330)	Smyth et al. (1969)
	Rat	5-15	3200	Hodge (1943)
	Rat	males, n.f.i.	7100 (95% C.I. 5500–9199)	Shaffer et al. (1945)
	Rat	36 total	3290 (95% C.I. 2870–3790)	Schmidt et al. (1973)
	Rat	n.f.i.	3290 (95% C.I. 2870–3790)	Bar and Griepentrog (1967) and Dave and Lidman (1978)
	Rat	5	3730	Scala and Burtis (1973)
Isoamyl alcohol	Mouse	4 (2/sex)	>2000 (pre-screen for micronucleus test)	RIFM (2008)
	Rat	5 males	7100 (4820–10400)	Smyth et al. (1969)
	Rat	4/sex	males: 1300 (95% C.I. 670–2410) females: 4000 (95% C.I. 2450–6170)	Purchase (1969)
	Rat	n.f.i.	4360	Golovinskaia (1976)
	Rat	n.f.i.	1300	Nishimura et al. (1994)
	Rat	n.f.i.	>5000	RIFM (1979c)
	Rabbit	10–35	3438	Munch (1972)
Isodecyl alcohol	Rat	n.f.i.	6500	Nishimura et al. (1994)
Isotridecan-1-ol (isomeric mixture)	Rat	5 males	17,200	Smyth et al. (1962); Nishimura et al. (1994)
	Rat	5	4750 (ca)	Scala and Burtis (1973)
	Rat	3	2000	RIFM (2002a)
	Rat	n.f.i.	>2000 (50% branched, 50% linear form)	ECB (1995) as cited in Greim (2000)
	Mouse	n.f.i.	6500	RIFM (1963a)
	Mouse	n.f.i.	7257 (mixture of branched saturated primary isomers, purity > 99.7%)	ECB (1995) and Hoechst (1961a) as cited in Greim (2000)
2-Methylbutanol	Rat	5 males	4920 (95% C.I. 3750–6460)	Smyth et al. (1962)
	Rat	n.f.i.	1000	Nishimura et al. (1994)
	Rat	n.f.i.	4010	Rowe and McCollister (1982)
	Rat	10 (5/sex)	4170	RIFM (1979b)
	Rat	10 (5/sex)	>5000	RIFM (1985e)
3-Methyl-1-pentanol	Mouse	10	>2000	RIFM (1982a)
3,5,5-Trimethyl-1-hexanol	Rat	10	2300 (95% C.I. 1700–3100)	RIFM (1977a)
	Rat	n.f.i.	>2000	MHW, Japan (1997a) as cited in OECD/SIDS (2003)
Subgroup: secondary				
2,6-Dimethyl-4-heptanol	Rat	20 males (5/dose)	3560 (95% C.I. 1430–8860)	Smyth et al. (1949)
	Rat	32 total (16/sex)	4350	Posternak and Vodoz (1975)
	Rat	5–11	6500	McOmie and Anderson (1949)
	Mouse	6–14	5000 (95% C.I. 2500–7500)	McOmie and Anderson (1949)
3,7-Dimethyl-7-methoxyoctan-2-ol	Rat	5/sex	5000	RIFM (1976a)
4-Methyl-2-pentanol	Rat	n.f.i.	2950	Bar and Griepentrog (1967)
	Rat	n.f.i.	2590	Nishimura et al. (1994)
	Rat	5	2590 (2260–2970)	Smyth et al. (1951)
3,4,5,6,6-Pentamethylheptan-2-ol	Rat	10 (5/sex)	5845 (95% C.I. 5360–6375)	RIFM (1984a)
Subgroup: tertiary				
2,6-Dimethyl-2-heptanol	Rat	10	>5000	RIFM (1976a)
	Rat	n.f.i.	6800	RIFM (1979a)
3,6-Dimethyl-3-octanol[a]	Rat	10	>5000	RIFM (1973a)
3-Methyloctan-3-ol[a]	Rat	10	3400 (95% C.I: 2500–4700)	RIFM (1978c)

n.f.i.: no further information.
[a] No relevant use was reported.
[b] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.

4-methyl-2-pentanone. Male and female rats and mice (14 per species/sex/group) were exposed to 0, 50, 250, or 1000 ml *4-methyl-2-pentanone*/m^3 (0, 204, 1020, or 4090 mg/m^3) 6 h per day and 5 days per week. Slight, but statistically significant, increases in absolute and relative liver weight were observed in males of both species at the highest concentration. As there were no histopathological changes in the livers observed, the changes were considered to be of no toxicological relevance. Male rats demonstrated alpha-2u-globulin ephropathy. The NOAEL was considered to be 1000 ml/m^3 (4090 mg/m^3) for both species (Phillips et al., 1987).

In a two-generation study with rats with *4-methyl-2-pentanone* clinical signs in the form of CNS depression were noted during exposures of adults to 1000 and 2000 ml/m^3. The systemic NOAEL was 500 ml/m^3 in this study. Signs of irritation were not reported (Nemec et al., 2004).

5.2.3.3. Tertiary alcohols. No data available.

5.3. Mutagenicity and genotoxicity

5.3.1. In vitro mutagenicity studies

The available studies are summarized in Table 4-1.

5.3.1.1. Indicator studies. In a study of the cytotoxic and genotoxic effects of a number of alcohols and ketones, 2-methylbutanol

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

Material	Dose route	Species	No./dose	LD_{50} and/or clinical signs	References
Subgroup: primary					
2-Ethyl-1-butanol	Inhalation, exposure to concentrated vapors	Rat	6	Maximum time for no death: 8 h	Smyth et al. (1954)
2-Ethyl-1-hexanol	Inhalation, exposure to concentrated vapors	Rat	6	Maximum time for no death: 8 h	Smyth et al. (1969)
	Whole body exposure for 6 h to air bubbled through 2-ethyl-1-hexanol to yield a nominal chamber concentration of 227 ml/m^3	Rat, mouse, guinea pig	10/species	No mortality, irritation of eyes, nose, throat, and respiratory passages, blinking, lacrimation, preening, nasal discharge, salivation, gasping, and chewing movements	Scala and Burtis (1973)
	Intraperitoneal	Rat	5–15	LD_{50} 650 mg/kg body weight	Hodge (1943)
	Intraperitoneal	Rat	5/sex	LD_{50} 500–1000 mg/kg body weight	Dave and Lidman (1978)
	Intraperitoneal	Mouse	5–15	LD_{50} 780 mg/kg body weight	Hodge (1943)
Isoamyl alcohol	i.v.	Mouse	Not reported	LD_{50} 2.64 mmol/kg body weight (233 mg/kg body weight)	Chvapil et al. (1962)
Isotridecan-1-ol (isomeric mixture)	Inhalation, exposure to air saturated with alcohol vapor at room temperature for 8 h	Rat	6 rats/14 days	No effects	RIFM (1963c) and Smyth et al. (1962)
	Inhalation to 12 ml/m^3 (saturation concentration at 30 °C) for 6 h	Rat, mouse, guinea pig	10/species	No effects	Scala and Burtis (1973)
	Intraperitoneal	Mouse	n.f.i.	LD_{50} 600 mg/kg body weight	RIFM (1963b)
2-Methylbutanol	Intraperitoneal	Rat	n.f.i.	1000 mg/kg body weight: sedation, irritation of the peritoneum and injury of the lungs; 2000 mg/kg body weight: respiratory arrest and death	Haggard et al. (1945)
	Intraperitoneal	Mouse	10 (5/sex)	LD_{50} between 200 and 700 mg/kg body weight	RIFM (1979b)
	Inhalation, saturated atmosphere at 20 °C (calculated: 10,050 mg/m^3 bzw. 2744 ml/m^3) for 7 h	Rat	n.f.i.	No mortality, escape behavior, intermittent respiration	RIFM (1979b)
	Inhalation, saturated vapor for 8 h	Rat	6	No mortality	Rowe and McCollister (1982)
3-Methyl-1-pentanol	Intraperitoneal	Mouse	10	LD_{50} > 250 mg/kg body weight; ⩾2000 mg/kg body weight: 10/10 animals died within 30 min (respiratory depression)	RIFM (1982a)
Subgroup: secondary					
2,6-Dimethyl-4-heptanol	Inhalation, exposure to substantially saturated vapor or cooled mist (400 ml/m^3) for 8 h	Rat	12	No mortality	Smyth et al. (1949)
	Inhalation, exposure to a saturated vapor–air mixture for 12 h	Mouse	10	2.0 mg/l: no mortality	McOmie and Anderson (1949)
4-Methyl-2-pentanol	Inhalation for 8 h at 2000 ppm	Rat	6	5/6 animals died within 14 days	Carpenter et al. (1949) and Smyth et al. (1951)
	Inhalation exposure to a saturated vapor–air at 20 °C for 4–15 h	Mouse	10	Somnolence and anesthesia Mortality at 10 h (6/10) and 15 h (8/10)	McOmie and Anderson (1949)
3,4,5,6,6-Pentamethylheptan-2-ol	Intraperitoneal injection at doses of 50, 166, 500, 750, 1000, 1250, 1666, and 3000 mg/kg body weight	Mouse	2	One death at 1250 mg/kg Clinical signs observed for all mice above 1000 mg/kg	RIFM (1985d)

n.f.i.: no further information.

Table 3-1
Repeated dose toxicity studies – dermal.

Material	Method	Dose	Species (No./dose)	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	Single application/day on the shaved back for 12 days	2 ml/kg body weight/day (1600 mg/kg body weight/day)	Rat (10)	Absolute and relative thymus weights decreased, liver granulomas, bronchiectasis in the lung, renal tubular epithelial necroses, edematous heart and testes and decreased spermatogenesis	Schmidt et al. (1973)
	5 days occlusive treatment, 2 days untreated, 4 days treated	0, 500, or 1000 mg/kg body weight/day	Fischer 344 rat (10/sex)	⩾500 mg/kg body weight/day: exfoliation (minimal severity), spleen weight decreased; serum triglycerides increased (females); 1000 mg/kg body weight: transient erythema (days 4–7) (graded as barely perceptible), decreased absolute spleen weight, lymphocytes decreased	RIFM (1988); Weaver et al. (1989)
Isooctanol (alcohols C7–C9 branched CAS No. 68526-83-0)	Occlusive, 18–24 h for 12 days (10 treatments)	0 (isopropyl alcohol), 400, 2000 mg/kg body weight/day	Rabbit (Albino) (2/sex)	Systemic NOAEL: 2000 mg/kg body weight/day 400 mg/kg body weight/day: moderate to severe irritation, fissure, coriaceous skin 2000 mg/kg body weight/day:necrosis of the skin	Esso Research and Engineering Company (1961) as cited in ExxonMobil Chemical Company (2001a)
Subgroup: secondary					
3,4,5,6,6-Pentamethylheptan-2-ol	Dermal (occlusive), 6 h/day for 28 days (OECD TG 410)	0 (water), 1000 mg/kg body weight/day	Rabbit (New Zealand White) (5/sex)	Systemic NOAEL: 1000 mg/kg body weight/day 1000 mg/kg body weight/day: (f), severe dermal reactions: well defined severe erythema and edema, histopathology of the skin: acanthotic and focal ulcerative changes of epidermis, associated inflammation, hyperkeratosis, scab formation	RIFM (1985c)
	Dermal (occlusive), 6 h/day for 28 days	30, 100, 300, and 1000 mg/kg/day	Rabbit (New Zealand White) (10/sex)	Systemic NOAEL: 1000 mg/kg body weight/day Slight to moderate dermal irritation; severe irritation at high (300 and 1000 mg/kg/day) doses; reversible after 8 days	RIFM (1986b)

Abbreviations see Table 3-3.

Table 3-2
Repeated dose toxicity studies – oral.

Material	Method	Dose	Species (No./dose)	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	Gavage, 5 days/week, 22 days	0, 330, 660, 930 mg/kg body weight in sunflower oil, controls 10 ml oil/kg body weight	Rat (10)	930 mg/kg: body weight on day 17 decreased, mortality: 1/10	Schmidt et al. (1973)
	Gavage, 9 treatments in 11 days	0, 100, 330, 1000, 1500 mg/kg body weight/day, test substance undiluted	Fischer 344 rat (10/sex)	Systemic NOAEL 100 mg/kg body weight/day 330 mg/kg body weight/day: hypoactivity, ataxia, prostration, delayed righting reflex, muscle twitch, lacrimation, and urine-stained fur. Food consumption and body weights decreased (males), thymic atrophy and lymphoid cell degeneration in the thymus; 1000 mg/kg body weight/day: food consumption and body weights decreased (females), total peripheral blood leukocytes and lymphocytes, spleen weight decreased (females), absolute and relative liver weight increased without histopathological findings, absolute and relative stomach weight increased with hyperkeratosis, mucosal hyperplasia, edema, exocytosis, and gastritis; 1500 mg/kg body weight/day: total peripheral blood leukocytes and lymphocytes, spleen weight decreased (males), absolute and relative testes weights decreased, no histopathological findings in testes or kidneys at any dose	RIFM (1988); Weaver et al. (1989)
	Drinking water, 9 days	0, 308 ppm (half-saturated) and 636 ppm (saturated): 61.1 and 151.1 mg/kg body weight/day for males and 73.4 and 173.5 mg/kg body weight/day for females.	Fischer 344 rat (10/sex)	No adverse effects	RIFM (1988); Weaver et al. (1989)
	Gavage, 9 doses in 11 d	0, 100, 330, 1000, or 1500 mg/kg body weight/day, in propylene glycol	B6C3F1 mice (10/sex)	Systemic NOAEL 100 mg/kg body weight/day 330 mg/kg body weight/day: relative liver and stomach weights (male) increased; 1000 mg/kg body weight/day: relative liver and stomach weights (female) increased; 2/20 deaths; 1500 mg/kg body weight/day: ataxia, lethargy, piloerection, dyspnea, hypothermy, abdominal or lateral position and loss of consciousness, reduction in food consumption (males), relative testes weight decreased; clinical chemistry and hematology no substance-related changes. No histopathological examinations; 10/20 deaths	RIFM (1992a)
	Gavage, 9 doses in 11 d	0, 100, 330, 1000, or 1500 mg/kg body weight/day, in an aqueous emulsion in Cremophor EL	B6C3F1 mice (10/sex)	Systemic NOAEL 100 mg/kg body weight/day 300 mg/kg body weight/day: acanthosis with hyperkeratosis in the forestomach; $\geqslant$1000 mg/kg body weight/day: relative liver (males) and stomach weights (female) increased, hypertrophy of hepatocytes; 1/20 deaths; 1500 mg/kg body weight/day: ataxia, lethargy, piloerection, abdominal or lateral position and loss of consciousness; clinical chemistry and hematology, no substance-related changes; 5/20 deaths.	RIFM (1992b)
	Diet, 11 days	500, 980, 1430, or 2590 mg/kg/day (males) 540, 1060, 1580, or 2820 mg/kg/day (females)	F344 rat (10/sex)	NOAEL < 500 (m) or 540 (f) mg/kg bodyweight/day $\geqslant$500 (m) or 540 (f) mg /kg/d: relative stomach weights increased females (f); triglycerides and alanine aminotransferase decreased, males (m); feed consumption significantly decreased (m)	RIFM (1992c)

(*continued on next page*)

Table 3-2 (*continued*)

Material	Method	Dose	Species (No./dose)	Results	References
				⩾980 (m) or 1060 (f) mg/kg/d: absolute and relative liver weights increased (m,f); feed consumption decreased (m,f); water consumption significantly decreased (f); triglyceride and alanine aminotransferase decreased (m); ⩾1430 (m) or 1580 (f) mg/kg/d: food consumption reduced (m,f), hypertrophy of hepatocytes; body weight significantly reduced (m); water consumption significantly reduced (m,f); triglyceride and alanine aminotransferase decreased (males); 2590 (m) or 2820 (f) mg/kg/d: absolute and relative liver weights increased (m,f);body weight decreased (m,f); feed consumption decreased (m,f), water consumption significantly decreased (m,f); triglyceride and alanine aminotransferase decreased (m,f)	
	Gavage, 5 days/week, 13 weeks	0, 25, 125, 250 or 500 mg/kg body weight/day	F344 rat, B6C3F1 mice (10/sex)	NOAEL: 125 mg/kg body weight/day, rats and mice ⩾250 mg/kg body weight/day: relative liver, kidney (rats, both sexes) and stomach weights (female rats) increase, fat deposits in the liver cells (male rats) decrease, relative liver and stomach weights (male mice) increased; 500 mg/kg body weight/day: acanthosis of the forestomach (female mice); peroxisome proliferation (marker: cyanide-insensitive palmitoyl CoA oxidase) (rats, both sexes) increase	Astill et al. (1996a)
	Gavage, 24 months, 5 days/week	0 (water), 0 (vehicle), 50, 150, 500 mg/kg/body weight/day in 0.005% Cremophor EL	F344 rats (50/sex)	Systemic NOAEL: 50 mg/kg body weight/day ⩾150 mg/kg body weight/day: body weight gain decreased, poor clinical state, labored breathing, piloerection or urine-stained genital region	Astill et al. (1996b)
	3 weeks, oral administration	~833 mg/kg n.f.i.	Rat (n = 5)	Statistical increase (p < .05) in liver was observed	Yamada (1974)
	Gavage, 18 months, 5 days/week	0 (water), 0 (vehicle), 50, 200, 750 mg/kg body weight/day in 0.005% Cremophor EL	B6C3F1 mice (50/sex)	Systemic NOAEL: 200 mg/kg body weight/day 750 mg/kg body weight/day: increased mortality, body weight gains decreased, food consumption decreased, fatty liver, hyperplasia of the forestomach epithelium	Astill et al. (1996b)
Isoamyl alcohol	Drinking water 3 months	0, 1000, 4000, 16,000 mg/l drinking water (purity > 98.6%); estimated to be: 0, 80, 320, 1280 mg/kg body weight/day	Wistar rat (10/sex)	NOAEL females = 1280 mg/kg body weight/day NOAEL males = 320 mg/kg body weight/day 1280 mg/kg body weight (males): erythrocyte value increased; mean corpuscular volume (MCV) decreased; mean corpuscular hemoglobin (MCH) decreased 320 and 1280 mg/kg/day (females): increased prothrombin time	Schilling et al. (1997) RIFM (1991b)
	Gavage, daily for 17 weeks	0 (vehicle), 150, 500, 1000 mg/kg body weight/day, in corn oil	Ash/CSE rat (15/sex) additional 5 animals examined after 3 and 6 weeks, respectively	NOAEL females = 1000 mg/kg body weight/day NOAEL males = 500 mg/kg body weight/day 1000 mg/kg body weight/day: males: body weight gain decrease	Carpanini and Gaunt (1973)
	Drinking water, 56 weeks	0, 2% (2000 mg/kg body weight/day)	Wistar rat (20/sex)	No significant effects	Johannsen and Purchase (1969)
	Neurotoxicity: Whole body exposures with a 30 min habituation and 4 h exposure	3–4 exposures to the various solvent concentrations (between 25% and 75%)	Male albino SPF rats 16 (4/group)	The concentration that evoked a 30% depression in the recorded activity was determined to be 1700 ppm	Frantik et al. (1994)
	Neurotoxicity: Whole body exposure with a 30 min habituation and 2 h exposure	3–4 exposures to various solvent concentrations (between 25% and 75%)	Female mice of the H strain 32 (4/group)	The concentration that evoked a 30% depression in the recorded activity was determined to be 950 ppm	Frantik et al. (1994)

Isotridecanol (Alcohols, C11–14 iso, C13 rich, CAS No. 68526-86-3)	Gavage, 7 days/week, for 14 weeks, OECD TG 408	0 (distilled water), 100, 500, 1000 mg/kg body weight/day	Sprague–Dawley rat (20/sex)	NOAEL: 100 mg/kg body weight/day ⩾500 mg/kg body weight/day: food consumption decreased (m), body weight decreased (m), mean platelet counts increased (f), glucose decreased (f), liver weight increased (m, f), 1000 mg/kg body weight/day: glucose decreased (m), cholesterol decreased (f), rel. brain and testes weight increased (m), rel. adrenal weight increased (f)	Exxon Biomedical Sciences Inc. (1986) as cited in ExxonMobil Chemical Company (2001b)
3,5,5-Trimethyl-1-hexanol	Gavage, males: 14 days	144 mg/kg body weight/day	Alderly-Park Wistar rat	Increase in the relative liver weight No difference from controls in body weight, clinical, or histopathological signs. Peroxisome proliferation, hypocholesterolemia, and hypoglyceridaemia were not evident	Rhodes et al. (1984)
	Gavage, males: 46 days, females: from 14 days before mating to day 3 of lactation, OECD TG 422	0, 12, 60, 300 mg/kg body weight/day in olive oil	SD (Crj:CD) rat (12/sex)	NOAEL systemic toxicity males and females: 12 mg/kg body weight/day ⩾12 mg/kg body weight/day: renal hyaline droplets, eosinophilic bodies (m) ⩾60 mg/kg body weight/day: relative liver and kidney weight increase (m,f), renal epithelial fatty change (f); implantation index decreased (f) 300 mg/kg body weight/day: 1 f died, 3 f killed (weakness); body weights increase (m), food consumption increased (m), body weights decreased (f), food consumption decrease (f); total litter loss in 2 dams	MHW, Japan (1997b) as cited in OECD/SIDS (2003)
Subgroup: secondary					
2,6-Dimethyl-4-heptanol	Diet, 13 weeks	0, 11 (f), 11 (m) mg/kg body weight/day mixed with microcrystalline cellulose	Rat (16/sex)	No NOAEL (females) based on reductions of body weight gain systemic NOAEL (males): 11 mg/kg body weight; 11.06 mg/kg body weight/day: (females) body weight gain and food efficiency (weight gained (g)/food consumed (g) × 100, −10.8%) decrease (body weight gain −12.1%). Hematological and histological examinations without any significant differences between test and control rats	Posternak and Vodoz (1975)
4-Hydroxy-4-methyl-2-pentanone	Gavage, males: 44 days, females: from 14 d before mating to day 3 of lactation (approx. 45 days), OECD TG 422	0, 30, 100, 300, 1000 mg/kg body weight/day in water	Crj:CD(SD) rat (10/sex)	NOAEL: 100 mg/kg body weight/day ⩾100 mg/kg body weight/day: male alpha-2u-nephropathy ⩾300 mg/kg body weight/day: locomotor activity and stimulation response decrease (m,f); dilatation of the distal tubules and fatty degeneration of the proximal tubular epithelium in kidneys (f) ⩾1000 mg/kg body weight/day: hepatocellular hypertrophy (m,f), altered blood parameters (increase: platelet counts, GOT, total protein, total cholesterol, total bilirubin, blood urea nitrogen, creatinine, calcium (m); decrease: glucose) (m), dilatation of distal tubules of kidneys (m), vacuolization of the zona fasciculata of the adrenals (m); body weight gain decrease (f), rel. liver weight increase (f)	MHW, Japan (1997) as cited in OECD/SIDS (2007)

Abbreviations see Table 3-3.

and isoamyl alcohol were tested for their potency to induce DNA damage in V79 Chinese hamster fibroblasts, human lung carcinoma epithelial A549 cells and human peripheral blood cells with the alkaline comet assay. In V79 and A549 cells 2-methylbutanol and isoamyl alcohol showed DNA damage only at cytotoxic concentrations. The COMET assay could not be performed in human peripheral blood cells due to extreme cytotoxicity (cells with completely fragmented DNA) (Kreja and Seidel, 2001, 2002).

2-Methylbutanol and isoamyl alcohol gave negative results in a light absorption umu test and positive results in a luminescent umu test (Nakajima et al., 2006). These tests are based on the ability of DNA damaging agents to induce expression of the umu operon, which is responsible for chemical and radiation mutagenesis, in *Escherichia coli*. The positive result is not plausible in view of the other negative tests for genotoxicity (see below) and the overall negative results for branched chain saturated alcohols. 2-Ethyl-1-hexanol gave a negative and a positive result in two rec-assays (Saido et al., 2003; Tomita et al., 1982). The results of this test system are not considered for the evaluation of the genotoxicity of the alcohols under study because positive results were often assessed with substances, which were negative in other genotoxicity test systems. A test for induction of unscheduled DNA synthesis with 2-ethyl-1-hexanol was negative in primary rat hepatocytes (Hodgson et al., 1982).

4-Methyl-2-pentanone was negative in a vitro UDS test (no further information; IPCS, 1990 as cited in OECD/SIDS, 2004).

5.3.1.2. Mutation studies. The primary alcohols 3,5,5-trimethyl-1-hexanol, 2-ethyl-1-hexanol, isotridecan-1-ol (isomeric mixture), the secondary alcohols 4-methyl-2-pentanol, its metabolites *4-methyl-2-pentanone* and *4-hydroxy-4-methyl-2-pentanone*, 2,6-dimethyl-4-heptanol and its metabolite *2,6-dimethylheptan-4-one*, as well as a mixture of the secondary alcohol 3,4,5,6,6-pentamethylheptan-2-ol (55–80%) and 3,4,5,6,6-pentamethylheptan-2-on (20-45%) were inactive in Ames tests. Urine from Sprague–Dawley rats dosed by oral gavage for 15 days with 1000 mg 2-ethyl-1-hexanol/kg body weight/day was found to be non-mutagenic in *Salmonella typhimurium* with and without addition of rat liver microsomes or beta-glucuronidase/arylsulfatase (DiVincenzo et al., 1983, 1985). 2-Ethyl-1-hexanol was mutagenic in *S. typhimurium* TA100 using the mutation to resistance to 8-azaguanine (Seed, 1982). As this test was performed only in one *S. typhimurium* strain and the other mutagenicity tests using reversion to histidine independence were negative, this result seems to be of limited relevance.

The primary alcohols 2-methylbutanol, isoamyl alcohol, and 2-ethyl-1-hexanol were also inactive in mammalian cell systems ($TK^{+/-}$ mouse lymphoma mutagenicity assay in L5178Y cells or HPRT assay with Chinese hamster V79 fibroblast cells) (Kirby et al., 1983; Kreja and Seidel, 2002). For *4-methyl-2-pentanone*, a mouse lymphoma test was considered equivocal (no further information; IPCS, 1990 as cited in OECD/SIDS, 2004).

A *Saccharomyces cerevisiae* mitotic gene conversion assay was negative for *2,6-dimethylheptan-4-one* (OECD/SIDS, 2004).

The secondary alcohol 4-methyl-2-pentanol tested for gene mutation in *Saccharomyces cerevisiae* gave negative results (Clare, 1983 as cited in OECD/SIDS, 2007).

5.3.1.3. Chromosome aberration studies. The primary alcohols 2-ethyl-1-hexanol and 3,5,5-trimethyl-1-hexanol as well as the secondary alcohol 4-methyl-2-pentanol and *2,6-dimethylheptan-4-one*, did not induce chromosome aberrations *in vitro* when incubated with Chinese hamster ovary, Chinese hamster lung or rat liver cells (Brooks et al., 1985 as cited in OECD/SIDS, 2004; Brooks et al., 1988; Clare, 1983 as cited in OECD/SIDS, 2007; MHW, Japan, 1997d as cited in OECD/SIDS, 2003; Phillips et al., 1982). *4-Hydroxy-4-methyl-2-pentanone*, tested for chromosomal aberrations in Chinese hamster lung cells, revealed significantly increased polyploidy in the two highest doses (600 and 1200 μg/ml). Information as to whether this was done with or without S9 was not available. This test was considered negative because a trend test showed no dose-dependency (MHW, Japan, 1997 as cited in OECD/SIDS, 2007).

5.3.1.4. Micronucleus studies. The primary alcohols 2-methylbutanol and isoamyl alcohol did not induce micronuclei in V79 Chinese hamster fibroblasts, with or without addition of hepatic S9 mix from Aroclor induced rats (Kreja and Seidel, 2002).

5.3.2. In vivo studies

The available studies are summarized in Table 4-2. No indication for a covalent binding of 2-ethyl-1-hexanol to liver DNA of rats and mice was noted (Albro et al., 1982; Däniken et al., 1984). 2-Ethyl-1-hexanol was not mutagenic in the dominant lethal test (Rushbrook et al., 1982; only as abstract) and not clastogenic in a bone marrow chromosome aberration test (Putman et al., 1983), although this result is not reliable because the doses used failed to induce toxicity. 2-Ethyl-1-hexanol (Astill et al., 1986; Barber et al., 1985; only as abstract, no information on the method, and validity cannot be assessed) and 3,4,5,6,6-pentamethylheptan-2-ol were not clastogenic in the mouse bone marrow micronucleus test (RIFM, 1985d). Isoamyl alcohol showed an increase in chromosomal aberrations in bone marrow cells of rats (Barilyak and Kozachuk, 1988). The study is invalid as no information is available if a positive control group was used, the definite dose was not mentioned (1/5 of LD_{50}), only one dose was tested, the control animals did not show any chromosomal aberrations, and the purity of the substance was not given. The authors also found chromosomal aberrations with propanol, which was not genotoxic in a variety of tests (Greim, 1996). An *in vivo* mouse micronucleus assay was conducted on isoamyl alcohol (RIFM, 2008) at doses of 500, 1000, and 2000 mg/kg there was no increase in the frequency of detected micronuclei. Isoamyl alcohol was determined to be non-mutagenic in the micronucleus assay.

Additionally, *4-methyl-2-pentanone* was negative in an *in vivo* micronucleus test (no further information; IPCS, 1990 as cited in OECD/SIDS, 2004).

5.4. Carcinogenicity

The available carcinogenicity studies are summarized in Tables 5-1.

5.4.1. Cell transformation assays

In a cell transformation study with mouse epidermis-derived JB6 cells 2-ethyl-1-hexanol did not promote JB6 cells to anchorage independence (Ward et al., 1986). A cell transformation assay with BALB 3T3 cells did not induce a significant number of transformed foci (Barber et al., 1985; RIFM, 1983b).

5.4.2. Carcinogenicity studies

2-Ethyl-1-hexanol was given to male and female rats and mice by gavage 5 times a week in 0.005% aqueous Cremophor EL (rats: 0 (water), 0 (vehicle), 50, 150, 500 mg/kg body weight/day, 24 months; mice: 0 (water), 0 (vehicle), 50, 200, 750 mg/kg body weight/day, 18 months). The incidences of carcinomas and basophilic foci in the liver increased in female mice with the dose and attained statistical significance in the highest dose group compared with the vehicle control group but not with the water control group. The time-adjusted incidence of hepatocellular carcinomas in female mice (13.1%) was outside the normal range (0–2%), but in male mice (18.8%) was within the historical control range at the testing facility (0–22%). No adenomas were observed.

Table 3-3
Repeated dose toxicity studies – inhalation.

Material	Method	Concentration	Species (No./dose)	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	OECD TG 413 90 days, 6 h/day, 5 days/week	0, 15, 40, or 120 ml/m^3 (highest vapour concentration at room temperature), purity: 99.9%	Wistar rat (10/sex)	Local and systemic NOAEL: 120 ml/m^3	Klimisch et al. (1998)
Isooctanol	13 days, 6 h/day	180 ml/m^3 (highest vapour concentration at room temperature)	Alderly-Park rat (3 f)	No mortality, clinical signs, autopsy findings and histopathological changes	Gage (1970)
Subgroup: secondary					
2,6-Dimethylheptan-4-one	2 weeks, 5 h/day, 5 days/week	0, 98, 300, 905 ml/m^3	Rats (10/sex)	NOAEL: 98 ml/m^3 $\geqslant$ 300 ml/m^3: liver weight increased, alpha-2u-globulin accumulation in the kidneys (m)	Dodd et al. (1987)
	6 weeks, 7 h/day, 5 days/week	0, 125, 252, 534, 925, 1654 ml/m^3	Rat (15/sex)	NOAEL: 125 ml/m^3 125 ml/m^3: No adverse effects 252 ml/m^3: Liver and kidney weights increased (f) 534 ml/m^3: Liver and kidney weights increased (m + f) 925 ml/m^3: Liver and kidney weights increased (m + f) 1654 ml/m^3: Mortality in all females and 3/15 males. Surviving males: body weight gain decreased and liver and kidney weights increased	Carpenter et al. (1953)
4-Methyl-2-pentanone	14 weeks, 6 h/day, 5 days/w (OECD TG 413)	0, 50, 250, 1000 ml/m^3 (0, 204, 1020, 4090 mg/m^3)	Fischer 344 rat (14/sex)	NOAEL: 250 ml/m^3 $\geqslant$250 ml/m^3: hyaline droplets in proximal tubular cells (m) 1000 ml/m^3: abs. and rel. liver weight (slight but statistically significant) increase (m)	Phillips et al. (1987)
	14 weeks, 6 h/day, 5 days/w (OECD TG 413)	0, 50, 250, 1000 ml/m^3 (0, 204, 1020, 4090 mg/m^3)	B6C3F1 mouse (14/sex)	NOAEL: 50 ml/m^3 1000 ml/m^3: abs. and rel. liver weight (slight but statistically significant) increase (m)	Phillips et al. (1987)
4-Methyl-2-pentanol	12 $\times$ 4-h-exposures	0, 20,000 mg/m^3	Mouse (9)	Unclear description of effects, unclear extent of histopathology	McOmie and Anderson (1949)
	6 weeks, 6 h/day, 5 days/w (OECD TG 407)	0, 50.5, 198, 886 ml/m^3 (0, 211, 825, 3700 mg/m^3)	Wistar rat (12/sex)	NOAEL: 198 ml/m^3 $\geqslant$50.5 ml/m^3: concentration of ketone bodies in urine increased (f) $\geqslant$198 ml/m^3: concentration of ketone bodies in urine increased (m) 886 ml/m^3: abs. kidney weight increased (m), serum alkaline phosphatase increased (f)	Blair (1982) as cited in OECD/SIDS (2007)

ADH: alcohol dehydrogenase, BUN: blood urea nitrogen, GOT: glutamate oxalacetate transaminase (now renamed: AST aspartate aminotransferase), GPT: gutamate pyruvate transaminase (now renamed: ALT alanine aminotransferase), f: female, m: male, n.f.i.: no further information, n.s.: not statistically significant, s.a.: see above, s.c.: subcutaneous.

The number of basophilic liver foci was increased in male mice in the mid dose group only. The authors considered the liver tumors in the mouse to be inconclusive because the incidence of hepatocarcinoma precursors did not significantly increase with the dose. Nevertheless, they concluded that 2-ethylhexanol is weakly or questionably carcinogenic for the female mouse. Under the conditions of this study 2-ethyl-1-hexanol was not oncogenic to rats. Doses of 150 and 500 mg/kg body weight/day led to reduced body weight gains and in some animals to lethargy and unkemptness which proves that the maximum tolerated dose was reached. At the end of the study the mortality was about 52% in the high-dose group females and about 28% in the other groups (Table 5-1; Astill et al., 1996b).

5.5. Reproductive and developmental toxicity

5.5.1. Fertility

5.5.1.1. In vitro. 2-Ethyl-1-hexanol (200 μM for 24 h) had no effect on lactate and pyruvate production by Sertoli-cell-enriched cultures derived from 28-day old Sprague–Dawley rats, whereas phthalate monoesters known to cause testicular atrophy *in vivo* increased Sertoli cell lactate production and lactate/pyruvate ratio (Moss et al., 1988).

In an *in vitro* model of rat seminiferous tubules 200 μM 2-ethyl-1-hexanol did not induce dissociation of germinal cells from Sertoli cells (Gangolli, 1982).

Ethyl-1-hexanol (200 μM for 24 or 48 h) did not result in an increase of germ-cell detachment in rat testicular-cell cultures (Gray, 1986; Gray and Beamand, 1984; Sjoberg et al., 1986).

5.5.1.2. In vivo. In vivo studies of reproductive and developmental toxicity of the branched chain saturated alcohols are summarized in Tables 6-1 (dermal), 6-2 (oral), and 6-3 (inhalation).

5.5.1.3. Dermal. Effects on the reproductive organs of rats treated dermally with 1000 mg 3,4,5,6,6-pentamethylheptan-2-ol/kg body weight/day for 28 days did not occur (see also Section 5.2.1; RIFM, 1985c).

5.5.1.4. Oral.

5.5.1.4.1. Primary alcohols. 2-Ethyl-1-hexanol administered by gavage, 167 mg/kg body weight/day, had no effects on Sertoli cells and gonocytes of 3-day old CD Sprague–Dawley rats (4/group) (Li et al., 2000). Daily gavage doses of 2.7 mmol 2-ethyl-1-hexanol/kg (350 mg/kg body weight) of for 5 days did not induce testicular damage in 35-day old male Sprague–Dawley rats (Sjoberg et al., 1986).

In a 90-day gavage systemic toxicity study no effects on reproductive organs of rats and mice were noted up to doses of 500 mg 2-ethyl-1-hexanol/kg body weight/day (see Section 5.2.1.1, Astill et al., 1996a).

In combined repeated dose and reproductive/developmental toxicity screening test (OECD TG 422) with gavage application of3,5,5-trimethyl-1-hexanol (see Section 5.2.1.1) no effects on fertility were observed in males. In females a dose dependent decrease in implantation index was noted in the 60 and 300 mg/kg group (MHW, Japan, 1997b as cited in OECD/SIDS, 2003). Based on these findings, the NOAELs for fertility were 12 mg/kg body weight/day for females and 300 mg/kg body weight/day for males.

5.5.1.4.2. Secondary alcohols. In the combined repeated dose and reproductive/developmental toxicity screening test (OECD TG 422) with gavage application of *4-hydroxy-4-methyl-2-pentanone* (see Section 5.2.1.1), a metabolite of 4-methyl-2-pentanol, no statistically significant changes in any reproductive parameter at any dose were noted. According to the authors there was a tendency for lower reproductive indices (fertility and implantations, no further information) at the highest dose of 1000 mg/kg body weight/day. Therefore the NOAEL for fertility was 300 mg/kg body weight/day (MHW, Japan, 1997 as cited in OECD/SIDS, 2007).

2,6-Dimethyl-4-heptanol showed no effects on the reproductive organs of rats in a 13-week feeding study with the only tested dose of 11 mg/kg body weight/day (Posternak and Vodoz, 1975). Its metabolite 2,6-dimethylheptane-4-one given by gavage has been assessed in a reproduction/developmental toxicity screen (OECD TG 421) and did not lead to reproductive effects up to the highest tested dose of 1000 mg/kg body weight/day (Shell HSE, 1996 as cited in OECD/SIDS, 2004).

5.5.1.4.3. Tertiary alcohols. No studies were available.

5.5.1.5. Inhalation.

5.5.1.5.1. Primary alcohols. In a 90-day inhalation study in rats, no effects on the reproductive organs were seen at concentrations up to 120 ml/m^3 2-ethyl-1-hexanol (Klimisch et al., 1998).

5.5.1.5.2. Secondary alcohols. With *4-methyl-2-pentanone*, the metabolite of 4-methyl-2-pentanol, a two-generation study performed in Sprague–Dawley rats (30/sex/group) exposed to 0, 500, 1000, or 2000 ml/m^3 (0, 2050, 4090, or 8180 mg/m^3), for 6 h per day, 7 days per week. Treatment started 70 days prior to mating for the F_0 and F_1 generations, continued to the end of the mating period for males and to day 20 of gestation for females. Treatment of females resumed at day 5 of lactation. Because of CNS depression in F_1 pups upon initiation of exposures on post-natal day 22 and the death of one F_1 male pup from the 2000 ml/m^3 group, treatment was interrupted and continued on day 28. In males of all exposure groups alpha-2u-globulin nephropathy was observed. F_0 and F_1 adults of the mid and high exposure groups showed a sedative effect, which was reversible 1 h after exposure. Decreased body weight gain and slightly decreased food consumption during the first 2 weeks of exposure occurred only at the high concentration in both generations. There were no effects on reproductive and developmental parameters, or on estrous cycle and sperm parameters. The NOAEL for systemic toxicity was established at 1000 ml/m^3 (4090 mg/m^3) due to slightly reduced body weight and feed consumption at 2000 ml/m^3. The NOAEL for reproductive toxicity was 2000 ml/m^3 (8180 mg/m^3) (Nemec et al., 2004). In view of the clinical signs of CNS depression of adults during the exposures at 1000 and 2000 ml/m^3 the systemic parental NOAEL is 500 ml/m^3.

Histopathological examinations in the 6-week inhalation study with 4-methyl-2-pentanol (Blair, 1982 as cited in OECD/SIDS, 2007) showed no adverse effects on the reproductive organs of male and female rats up to the highest concentration tested (886 ml/m^3). For further details see Section 5.2.1.2.

5.5.1.5.3. Tertiary alcohols. No studies were available.

5.5.2. Developmental toxicity

5.5.2.1. Dermal. 2-Ethyl-1-hexanol (99.72% pure) was administered on the clipped dorsal skin by occlusive cover to F344 rats 6 h per day from gestation days 6–15 at doses of 0, 0.5, 1.0, 2.0, or 3.0 ml/kg body weight/day (0, 420, 840, 1680, or 2520 mg/kg body weight/day) in a range-finding study (8/group). In the main study (25/group) doses of 0, 0.3, 1.0, and 3.0 ml/kg body weight/day (0, 252, 840, or 2520 mg/kg body weight/day) were applied. Persistent exfoliation, crusting, and erythema on the application site were seen in both studies from 840 mg/kg body weight/day. Maternal weight gain was reduced at 1680 and 2520 mg/kg body weight/day. The NOAELs for maternal toxicity were 252 mg/kg body weight/day based on skin irritation and 840 mg/kg body weight/day based on systemic toxicity. The developmental NOAEL was the highest tested dose of 2520 mg/kg body weight/day (Fisher et al., 1989; Tyl et al., 1992).

Table 4-1
Mutagenicity and genotoxicity: *in vitro* studies.

Material	Test system		Concentration	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	Rec-assay	*Bacillus subtilis* H17, M45	500 μg/disk in DMSO	Negative	Tomita et al. (1982)
	Rec-assay	*Bacillus subtilis* HA101, Rec-4	Diluted in DMSO to make the inhibition circle between I.D. 9 and 40 mm	Positive	Saido et al. (2003)
	Ames assay with and without S9 activation (preincubation method)	*S. typhimurium* TA98, TA100, TA1537, TA1538, TA 1535, *E. coli* WP2*uvrA*	1–1000 μg/plate in DMSO, growth inhibition ⩾500 μg/plate	Not mutagenic	Shimizu et al. (1985)
	Ames assay with and without S9 activation (preincubation method)	*S. typhimurium* TA98, TA100, TA1535, TA1537	3.3–333 μg/plate in DMSO	Not mutagenic	Zeiger et al. (1982)
	Ames assay with and without S9 activation (preincubation method)	*S. typhimurium* TA98, TA100, TA1535, TA1537	3.3–220 μg/plate in DMSO	Not mutagenic	Zeiger et al. (1985)
	Ames assay with and without S9 activation (preincubation method)	*S. typhimurium* TA98, TA100, TA1535, TA1537, 1538, 2637	100–2000 μg/plate in DMSO, tested up to cytotoxic concentrations	Not mutagenic	Agarwal et al. (1985)
	Ames assay with and without S9 activation (method unspecified)	*S. typhimurium* (unspecified)	n.f.i.	Not mutagenic	Barber et al. (1985)
	Ames assay with and without S9 activation (preincubation method)	*S. typhimurium* TA98, TA100, TA1535, TA1537, 1538	0.01–1.0 μl/plate in DMSO, cytotoxic concentration ⩾1.0 μl/plate	Not mutagenic	Kirby et al. (1983)
	Ames assay with and without S9 activation (preincubation method)	*S. typhimurium* TA98, TA100	0.1–10.0 μM, n.f.i.	Not mutagenic	Warren et al. (1982)
	L5178Y $TK^{+/-}$ mouse lymphoma mutagenicity assay	L5178Y mouse lymphoma cells	0.013–1.0 μl/ml in DMSO, cytotoxic concentration ⩾1.0 μl/ml	Not mutagenic	Kirby et al. (1983)
	8-Azaguanine resistance assay	*S. typhimurium* TA100	0.5–1.5 μM, n.f.i.	Mutagenic	Seed (1982)
	UDS assay	Primary rat hepatocytes cultures prepared from Fischer 344 rats	Cells were treated simultaneously with test compound and tritiated thymidine for 1 h, n.f.i.	Did not induce detectable levels of UDS	Hodgson et al. (1982)
	Chromosomal aberration assay	Chinese hamster ovary cells	1.5–2.8 mM	Did not induce an increased frequency of chromosomal aberrations compared to the control; 50% kill at 2.5 mM	Phillips et al. (1982)
Urine of 2-ethyl-1-hexanol treated rats (1000 mg/kg body weight for 15 days)	Ames assay with and without S9 activation (standard plate assay)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA 1538	Up to 2 ml undiluted urine, negative and positive controls: urine of untreated rats and 8-hydroxyquinoline	Not mutagenic	DiVincenzo et al. (1985)
Isoamyl alcohol	Comet assay	Chinese hamster V79 fibroblast cells, human lung carcinoma epithelial cell line A549, and human peripheral blood cells (pB)	0, 23, 46, 91 mM	DNA damage at at cytotoxic concentrations (91 mM in V79 and A549 cells), extremely cytotoxic in pB (analyses not possible)	Kreja and Seidel (2001, 2002)
	umu test: Light absorption	*S. typhimurium* TA1535/pSK1002	Concentrations in which growth inhibition ⩽50% (n.f.i.)	Negative	Nakajima et al. (2006)
	umu test: Luminiscent	*S. typhimurium* TA1535/pTL210	concentrations in which growth inhibition ⩽50% (n.f.i.)	Positive	
	Micronucleus test with and without S9 activation	Chinese hamster V79 fibroblast cells	0, 5, 9, 23 mM	Not genotoxic	Kreja and Seidel (2002)
	HPRT test with and without S9 activation	Chinese hamster V79 fibroblast cells	Up to 51.5 mM (highest non-toxic concentration)	Not mutagenic	Kreja and Seidel (2002)
Isotridecan-1-ol (isomeric mixture)	Ames assay with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535, TA1537	20-5000 μg/plate no cytotoxicity	Not mutagenic	RIFM (1989)
2-Methylbutanol	*umu* test: Light absorption	*S. typhimurium* TA1535/pSK1002	Concentrations in which growth inhibition ⩽50% (n.f.i.)	Negative	Nakajima et al. (2006)
	umu test: Luminiscent	*S. typhimurium* TA1535/pTL210		Positive	
	Comet assay	Chinese hamster V79 fibroblast cells, human lung carcinoma epithelial cell line A549, and human peripheral blood cells (pB)	0, 45, 90 mM	DNA damage at cytotoxic concentrations (45 mM in A549, 90 mM in V79 cells), extremely cytotoxic in pB (analyses not possible)	Kreja and Seidel (2001, 2002)

(*continued on next page*)

Table 4-1 (*continued*)

Material	Test system		Concentration	Results	References
	Micronucleus test with and without S9 activation	Chinese hamster V79 fibroblast cells	0, 23, 45 mM	Not genotoxic	Kreja and Seidel (2002)
	HPRT test with and without S9 activation	Chinese hamster V79 fibroblast cells	Up to 46 mM (highest non-toxic concentration)	Not mutagenic	Kreja and Seidel (2002)
3,5,5-Trimethyl-1-hexanol	Ames assay (preincubation assay) with and without metabolic activation OECD TG 471, 472	*S. typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2*uvrA*	up to 500 μg/plate cytotoxicity: ⩾150 μg/plate (±S9)	Not mutagenic	MHW, Japan (1997c) as cited in OECD/SIDS (2003)
	Chromosomal aberration and polyploidy OECD TG 473	Chinese hamster lung cells (CHL/IU)	up to 100 μg/ml cytotoxicity: 200 μg/ml	Not genotoxic	MHW, Japan (1997d) as cited in OECD/SIDS (2003)
Subgroup: secondary					
2,6-Dimethyl-4-heptanol	Ames assay with and without S9 activation (standard plate assay)	*S. typhimurium* TA98, TA100, TA1537, TA1538, TA 1535, *E.coli* WP2*uvrA*	3.33–1000 μg/plate with S9 mix in DMSO, 1.00–500 μg/plate iwith S9 mix in DMSO, cytotoxic concentration: ⩾333 μg/plate	Not mutagenic	Mecchi (2002) as cited in DOW (2003)
2,6-Dimethylheptan-4-one	Mitotic gene conversion assay with and without S9	*Saccharomyces cerevisiae*	0.01–5.0 mg/ml, cytotoxicity at 0.5 mg/ml with S9, at 5.0 without S9	Negative	Mortelmans et al. (1986)
	Ames assay with and without S9 activation (standard plate assay)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA 1538, *E.coli* WP2*uvrA*	31.25-4000 μg/plate in DMSO, cytotoxic concentration: ⩾500 μg/plate	Not mutagenic	Brooks et al. (1985) as cited in OECD/SIDS (2004) Brooks et al. (1988)
	Ames assay with and without S9 activation (standard plate assay)	*S. typhimurium* n.f.i.	1–333 μg/plate, no cytotoxicity observed	Not mutagenic	Mortelmans et al. (1986)
	Cytogenetic assay	Rat liver cell (RL4)	62.5–500 μg/ml, cytotoxicity at the highest dose level tested	No increased incidence of chromosome aberrations	Brooks et al. (1985) as cited in OECD/SIDS (2004) Brooks et al. (1988)
4-Hydroxy-4-methyl-2-pentanone	Ames assay with and without metabolic activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2*uvr* A	313–5000 μg/plate no cytotoxicity was observed	Not mutagenic	MHW, Japan (1997) as cited in OECD/SIDS (2007)
	Chromosomal aberrations and polyploidy OECD TG 473	Chinese hamster lung cells (CHL/IU)	300–1200 μg/ml no cytotoxicity observed at the highest concentration	polyploidy increase at 600 and 1200 μg/ml, without dose-dependence not genotoxic	MHW, Japan, 1997, as cited in OECD/SIDS (2007)
4-Methyl-2-pentanone	UDS	n.f.i.	n.f.i.	Negative	IPCS, 1990 as cited in OECD/SIDS (2004)
	Ames assay	n.f.i.	n.f.i.	Negative	IPCS (1990) as cited in OECD/SIDS (2004)
	Mouse lymphoma test	n.f.i.	n.f.i.	Equivocal	IPCS (1990) as cited in OECD/SIDS (2004)
4-Methyl-2-pentanol	Ames assay with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, *E. coli* WP2*uvr* A	up to 5000 μg/plate cytotoxicity: 5000 μg/plate (±S9)	Not mutagenic	Shimizu et al. (1985)
	Ames assay with and without metabolic activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, *E. coli* WP2 *uvr* A pkm 101	31.25–4000 μg/plate no cytotoxicity was observed	Not mutagenic	Clare (1983) as cited in OECD/SIDS (2007)
	Gene mutation with and without metabolic activation	*Saccharomyces cerevisiae* JD1	10–5000 μg/plate cytotoxicity: 5000 μg/plate	Not mutagenic	Clare (1983) as cited in OECD/SIDS (2007)
	Cytogenetic assay	Rat liver cell (RL4)	0, 0.5, 1, 2 mg/ml no cytotoxicity was observed	Negative	Clare (1983) as cited in OECD/SIDS (2007)
3,4,5,6,6-Pentamethylheptan-2-ol (55–80%) and 3,4,5,6,6-pentamethylheptan-2-on (20–45%)	Ames assay with and without metabolic activation (plate incorporation test)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, *E. coli* WP2 *uvrA*	1. test: up to 1000 μg/plate 2. test: up to 100 μg/plate cytotoxicity: ⩾500 μg/plate	Not mutagenic	RIFM (1985b)

DMSO: dimethylsulfoxide, n.f.i.: no further information, n.s.: not statistically significant.

Table 4-2
Mutagenicity and genotoxicity: *in vivo* studies.

Material	Test system	Species (No./dose)	Dose/Concentration	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	DNA binding in vivo by [^{14}C] labeled 2-ethyl-1-hexanol; 16 h after the administration of the radiolabeled test substance: isolation of liver DNA and analyzing for radioactivity	2 Female Fischer 344 rats and 2 female NMRI mice	Diet containing 1% di(2-ethylhexyl) phthalate (rat) or di(2-ethylhexyl) adipate (mouse) for 4 weeks; radiolabeled [^{14}C] 2-ethyl-1-hexanol was administered by gavage (rat: 51.1 or 53.4 mg/kg body weight; mouse: 120.2 or 109.5 mg/kg body weight)	No indication for a covalent binding of 2-ethyl-1-hexanol to liver DNA of rats or mice; most if not all radioactivity in liver DNA was due to biosynthetic incorporation	Däniken et al. (1984)
	DNA binding in vivo by [^{14}C] labeled 2-ethyl-1-hexanol, 24 h after the administration of the radiolabeled test substance: isolation of liver DNA and analyzing for radioactivity	Male Fischer rat, n.f.i.	Animals were fed a diet containing 1% di(2-ethylhexyl) phthalate for 11 days ad libitum. On day 10 they were given a single oral dose of 100 μCi [1-^{14}C] 2-ethyl-1-hexanol and on day 11 they were sacrificed	No binding of the labeled test substance to liver DNA	Albro et al. (1982)
	Bone marrow micronucleus assay, n.f.i.	B6C3F1 mouse, n.f.i.	Test protocol according to standard tests performed by Litton Bionetics Inc., n.f.i.	Not genotoxic, n.f.i.	Astill et al. (1986); Barber et al. (1985)
	Cytogenetic assay with bone marrow cells	5 Fischer 344 rat/group	Oral gavage for 5 consecutive days with 0.02, 0.07, and 0.21 ml/kg body weight/day (17, 58, 174 mg/kg body weight/day) = up to 1/10 of the 5-day-LD50	No increase in chromatid and chromosome breaks compared to the controls; mitotic index was not affected, no toxicity observed, no reliable negative result	Putman et al. (1983)
	Dominant lethal test	Male ICR/SIM mouse n.f.i.	250, 500, and 1000 mg/kg body weight/day (based on 5-day-LD50) for 5 consecutive days, after treatment each male was housed with 2 virgin femals per week for 8 consecutive days, sacrifice of the females on days 14–17 of caging with the males; positive control: trimehtylenemelamine	No dominant lethal mutations; fertility indices and average numbers of dead and total implants per pregnancy were within the normal range	Rushbrook et al. (1982)
Isoamyl alcohol	Micronucleus Test with bone marrow cells	NMRI mice (5/sex/dose)	500, 1000, or 2000 mg/kg body weight/day	Non-mutagenic	RIFM (2008)
Subgroup: secondary					
4-Methyl-2-pentanone	Micronucleus test	n.f.i.	n.f.i.	Negative	IPCS (1990) as cited in OECD/SIDS (2004)
3,4,5,6,6-Pentamethylheptan-2-ol	Bone marrow micronucleus assay (i.p.), sacrified: 30, 48, 72 h after application	Mouse (5/sex/dose)	0, 900 mg/kg body weight in corn oil	Not genotoxic PCE/NCE reduced 48 and 72 h after dosing	RIFM (1985d)

n.f.i.: no further information, PCE: polychromatic erythrocytes, NCE: normochromatic erythrocytes.

5.5.2.2. Oral.

5.5.2.2.1. Primary alcohols. Wistar rats were given a single dose of 6.25 or 12.5 mmol 2-ethyl-1-hexanol/kg body weight (833 or 1666 mg/kg body weight) by gavage on day 12 of pregnancy, and underwent caesarean section on day 20 of pregnancy. At the higher dose, 22.2% of the surviving fetuses had malformations (lower dose group 2% and controls 0%). These included hydronephrosis (7.8%), tail anomalies (4.9%), malformed limbs (9.7%), and "others" (1%). In the higher dose group the average fetal weight was reduced. Implantation index, numbers of dead and resorbed fetuses were unaffected. Although the dose of 1666 mg/kg body weight is around half of the oral LD_{50}, no maternal toxicity was reported (Ritter et al., 1987).

Pregnant Sprague–Dawley rats (6/group) were gavaged with a single dose of 0, 6.25, 9.38, or 12.5 mmol 2-ethyl-1-hexanol/kg body weight (equivalent to 0, 813, 1219, and 1625 mg/kg body weight) in corn oil on gestation day 11.5, followed 8 h later by 32 μCi ^{65}Zn and killed on gestation day 12.5. From 1219 mg/kg body weight the maternal food intake was reduced, maternal liver metallothionein and ^{65}Zn concentrations were higher, whereas in the embryos the ^{65}Zn content was lower than in animals which did not receive 2-ethyl-1-hexanol. The percentage of resorptions was not affected by the test substance (Bui et al., 1998).

2-Ethyl-1-hexanol was administered daily by gavage to Wistar rats (10/group) from gestation days 6 to 19 at doses of 0, 1, 5, or 10 mmol/kg body weight/day (equivalent to 0, 130, 650, and 1300 mg/kg body weight/day). At the lowest dose no maternal and fetal effects occurred. At 650 mg/kg body weight/day, fetus weights were significantly lower and the incidence of skeletal variations and retardations was increased. At 1300 mg/kg body weight/day maternal body weight measured on days 15 and 20 was significantly reduced; clinical signs (salivation, CNS depression, nasal discharge) were observed, and 6 dams died. Post-implantation losses, resorptions, number, and percent of fetuses and litters with malformations and variations, and number and percent of fetuses with retardations were increased. The fetal weight was decreased. The maternal and developmental NOAEL were 130 mg/kg body weight/day each (Hellwig and Jäckh, 1997).

Groups of 28 CD-1 Swiss mice were given >99% pure 2-ethyl-1-hexanol microencapsulated in their diet at concentrations of 0%, 0.009%, 0.03%, and 0.09% from days 0 to 17 of pregnancy. This corresponded to calculated doses of 0.13, 43, and 129 mg/kg body weight/day. No maternal toxicity was observed and the birth rate was 93–96% in all groups. All of the litters survived and all gestational parameters were normal. There were no external, visceral, or skeletal malformations and no increase in variations occurred. The authors concluded that 2-ethyl-1-hexanol plays essentially no role in the expression of DEHP-induced maternal and developmental toxicity (NTP, 1991; Price et al., 1991). As no toxic doses were reached, no conclusion on the potential of developmental toxicity of 2-ethyl-1-hexanol in mice can be drawn from this study.

In a screening test, mice (Charles River CD-1) were given 1525 mg 2-ethyl-1-hexanol/kg body weight/day by gavage from days 7 to 14 of pregnancy (50 animals treated and 50 controls). The dams and pups were observed until day 3 of lactation. Signs of toxicity in the dams included significantly reduced body weight and movement, ataxia, hypothermia, unkempt coats, and blood in the urine. Seventeen animals died of exposure-related causes. The number of live pups and their weight were significantly reduced (Hardin et al., 1987). A NOAEL cannot be deduced from this study.

Twenty-five pregnant Wistar rats were gavaged with 0 (corn oil), 100, 500, or 1000 mg/kg body weight/day on gestation days 6–15. The test material was a mixture of C7–9 branched alcohols, with isooctyl alcohol as the main component (CAS No. 68526-83-0). In the mid- and high-dose groups statistically significant increases in the number of lumbar ribs were observed. The authors state that, due to the lack of embryotoxicity these findings were attributed to maternal toxicity observed during treatment. However, in the 500 mg/kg body weight/day group no maternal toxicity was reported. In high-dosed dams emaciation, rales, hypoactivity, decreased food consumption, and body weight gain were observed. The total number of fetuses with skeletal variations and with hypoplastic skull bones was noted. These findings exceeded the historical control range of the laboratory but were not observed with litter-based analysis. The maternal NOAEL was set at 500 mg/kg body weight/day and the fetal NOAEL at 1000 mg/kg body weight/day (EBSI, 1994a, as cited in Nishimura et al., 1994). As increased incidences of lumbar ribs were seen from 500 mg/kg body weight/day at which dose no maternal toxicity was reported, the NOAEL for developmental toxicity should better be evaluated as 100 mg/kg body weight/day.

Two different isomeric mixes of isononyl alcohol (isononanol type 1 and isononanol type 2, CAS No. 68515-81-1 for both) and isodecyl alcohol were administered by gavage to Wistar rats

Table 5-1
Carcinogenicity studies.

Material	Method	Dose	Species (No./dose)	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	Cell transformation assay with and without metabolic activation	96–180 nl/ml; survival: 31.7–72% in the concomitant cytotoxicity test, positive control: cyclophosphamide	BALB 3T3 cells	Negative	Barber et al. (1985) and RIFM (1983b)
	Cell transformation, anchorage independence, without metabolic activation	$4–77 \times 10^{-7}$ mM, no information on cytotoxicity	JB6 cell line of mouse epidermis cells	Negative	Ward et al. (1986)
	Oral (gavage), 5 days/week, 18 months	0, 50, 200, 750 mg/kg body weight/day	B6C3F1 mouse, 50/sex/group	750 mg/kg body weight/day: weak hepatocellular carcinoma increase (f), body weight gain decrease, mortality increase	Astill et al. (1996b)
	Oral (gavage), 5 days/w, 24 months	0, 50, 150, 500 mg/kg body weight/day	F344 rat, 50/sex/group	⩾150 mg/kg body weight/day: body weight gain decrease, lethargy, unkemptness 500 mg/kg body weight/day: mortality: 52% f	Astill et al. (1996b)

Table 6-1
Reproductive and developmental toxicity studies - dermal.

Material	Method	Concentration/dose	Species (No./dose)	Results	References
2-Ethyl-1-hexanol	Occlusive, 6 h/day, on gestation days 6–15, caesarean section at day 21	Range-finding study: 0, 0.5, 1.0, 2.0, and 3.0 ml/kg body weight/day (0, 420, 840, 1680, or 2520 mg/kg body weight/day) Main study: 25/group 99.72% pure 0, 0.3, 1.0, and 3.0 ml/kg body weight/day (0, 252, 840, or 2520 mg/kg body weight/day)	F344 rats (range-finder: 8 f/group; main study: 25 f/group)	NOAEL maternal toxicity: 252 mg/kg body weight/day based on skin irritation and 840 mg/kg body weight/day based on systemic toxicity NOAEL developmental toxicity: 2520 mg/kg body weight/day *Maternal*: ⩾840 mg/kg body weight/day: Persistent exfoliation and crusting and erythema at application site; maternal liver, kidney, thymus, spleen, adrenal, and uterine weights and gestational and fetal parameters were unaffected by treatment; ⩾1680 mg/kg body weight/day: weight gain decrease *Fetal*: no treatment-related increases in incidence of individual or pooled external, visceral, or skeletal malformations or variations	Deisinger et al. (1994); Tyl et al. (1992)

(10/group) daily on gestation days 6–15. The doses for the isononyl alcohols were 0, 1, 5, 7.5, and 10 mmol/kg body weight/day (0, 144, 720, 1080, and 1440 mg/kg body weight/day), for isodecyl alcohol 0, 1, 5, and 10 mmol/kg body weight/day (0, 158, 790, and 1580 mg/kg body weight/day). Isononyl alcohol 1 mainly consists of dimethyl heptanols. Isononyl alcohol 2 mainly consists of dimethyl heptanols and methyl octanols. The test procedure was according to OECD TG 414 with the exception that 10 instead of 20 animals per dose level were used. At the lowest dose of isononyl alcohol 1 there was an equivocal increase in the incidence of fetuses with hydroureter (11%, which was only slightly above the highest incidence of 4 control groups used in the study, 9.2%). The highest historical control incidence was reported to be 7.7% for studies conducted in the same time interval as the study under question. A clear dose–response was not seen. Therefore, a substance-related effect is questionable. At the lowest dose of isononyl alcohol 2 no maternal and fetal toxicity was seen. At a dose of 720 mg/kg body weight/day and more of isononyl alcohols 1 and 2, signs of maternal and developmental toxicity, including decreased body weight, increased resorption rates, and increased skeletal variations and retardations were observed. At doses of 1080 mg/kg body weight/day and more the incidences of malformations were elevated. For isodecyl alcohol, maternal toxicity (reduced body weight gain and clinical signs) was evident at 790 mg/kg body weight/day and more. Developmental toxicity including reduced mean fetal body weight and skeletal retardations were observed only in the highest dose group. The maternal NOAEL for isononyl alcohol 1 and isononyl alcohol 2 is 144 mg/kg body weight/day and for isodecyl alcohol 158 mg/kg body weight/day. The NOAEL for developmental toxicity for isononyl alcohol 1 and 2 is 144 mg/kg body weight/day and for isodecyl alcohol 790 mg/kg body weight/day. Isononyl and isodecyl alcohol are developmental toxins only at doses that produce maternal toxicity (Hellwig and Jäckh, 1997; RIFM, 1991a).

In a combined repeated dose and reproductive/developmental toxicity screening test with gavage application of 3,5,5-trimethyl-1-hexanol (OECD TG 422) (see Section 5.2.1.1) the following results concerning developmental toxicity were observed: the number of pups born alive diminished in the 60 and 300 mg/kg body weight/day groups. In the high-dose group total litter loss was observed in two dams, the viability of neonates on day 4 of lactation was lower, and male and female pups showed lower body weights on day 0 of lactation (MHW, Japan, 1997b as cited in OECD/SIDS, 2003). Therefore, the NOAEL for systemic toxicity and developmental toxicity were considered 12 mg/kg body weight/day. Skeletal and visceral effects were not investigated in the pups.

5.5.2.2.2. Secondary alcohols. In the combined repeated dose and reproductive/developmental toxicity screening test with gavage application of *4-hydroxy-4-methyl-2-pentanone* [OECD TG 422] (see Sections 5.2.1.1 and 5.5.2), a tendency for a decrease of developmental parameters was observed at the highest dose of 1000 mg/kg body weight/day. These effects included the total number of pups born, delivery index, live birth index, number of pups alive and viability index on day 4 of lactation The NOAEL for developmental toxicity was 300 mg/kg body weight/day. The NOAEL for maternal toxicity was 100 mg/kg body weight/day (MHW, Japan 1997, as cited in OECD/SIDS, 2007). OECD TG 422 does not provide for an evaluation of skeletal and visceral effects in pups.

2,6-Dimethylheptan-4-one has been assessed in a reproduction/developmental toxicity screening test 20 rats (10/sex) were given 0, 100, 300, or 1000 mg 2,6-dimethylheptan-4-one/kg body weight/day in corn oil by gavage from 2 weeks prior to mating throughout pregnancy until weaning day 5 post partum when the dams and offspring were sacrificed. Two dams at the top dose level died during lactation due to the test substance. There was no evidence of an effect on any of the reproductive parameters investigated or on any of the surviving litters. The NOAEL for developmental effects is the highest tested dose of 1000 mg 2,6-dimethylheptan-4-one/kg body weight/day, with a parental NOAEL of 300 mg/kg body weight/day (Shell HSE, 1996 as cited in OECD/SIDS, 2004). OECD TG 421 does not provide for an evaluation of skeletal and visceral effects in pups.

5.5.2.2.3. Tertiary alcohols. No studies were available.

5.5.2.3. Inhalation.

5.5.2.3.1. Primary alcohols. Pregnant Wistar rats (20–25) were whole body exposed 6 h per day on gestation days 6–15 to 0, 510, 2500, or 9800 mg isoamyl alcohol/m^3 (0, 138, 675, and 2646 ml/m^3). Body weight gain was decreased at the highest concentration between days 6 and 9 but there were no compound-related effects on conception rate, mean number of corpora lutea, implantation sites, pre- and post-implantation losses, and number of resorptions, viable fetuses, sex ratio, mean fetal, and placental weight. No external, visceral, or skeletal malformations were observed. The NOAEL for maternal toxicity was 2500 mg/m^3 (675 ml/m^3) and the NOAEL for developmental toxicity 9800 mg/m^3 (2646 ml/m^3) (Klimisch and Hellwig, 1995).

Table 6-2
Reproductive and developmental toxicity studies – oral.

Material	Method	Concentration/dose	Species (No./dose)	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	Gavage, 3 days/week, 3-day old males	0, 167 mg/kg body weight/day	CD Sprague–Dawley rats (4 m/group)	No effect on Sertoli cells and gonocytes	Li et al. (2000)
	Gavage, 5 days, 35-day old male rats	2.7 mmol/kg body weight/day (350 mg/kg body weight/day)	Sprague–Dawley rats	No testicular damage	Sjoberg et al. (1986)
	Gavage on day 12	0 (untreated), 6.25 or 12.5 mmol (833, 1666 mg/kg body weight/day), undiluted	Wistar rats (7 f/group)	*Maternal*: no maternal toxicity was reported *Fetal*: 1666 mg/kg body weight/day: 22.2% of the surviving fetuses had malformations (lower dose group 2%, controls 0%). These included hydronephrosis (7.8%), tail anomalies (4.9%), malformed limbs (9.7%) and "others" (1%); average fetal weight decreased Implantation index, average fetal weight, numbers of dead and resorbed fetuses were not affected	Ritter et al. (1987)
	Gavage, on gestation day 11.5; after 8 h intubated with 32 μCi ^{65}Zn, killed on gestation day 12.5	0, 6.25, 9.38 or 12.5 mmol 2-ethy-1-hexanol/kg body weight in corn oil (equivalent to 0, 813, 1219, 1625 mg/kg body weight)	Sprague–Dawley rats (6 f/group)	*Maternal*: ⩾1219 mg/kg body weight: maternal food intake decreased; 1625 mg/kg body weight: percentage of ^{65}Zn retained in maternal liver increase *Fetal*: the percentage of resorptions was not affected 1625 mg/kg body weight: percentage of ^{65}Zn retained in the embryos decreased	Bui et al. (1998); Taubeneck et al. (1996)
	Gavage from days 6 to 19 of pregnancy	0, 1, 5, and 10 mmol/kg body weight/day (0, 130, 650, and 1300 mg/kg body weight/day)	Wistar rats (10 f/group)	NOAEL maternal and developmental toxicity: 130 mg/kg body weight/day *Maternal*: ⩾650 mg/kg body weight/day: 1300 mg/kg body weight/day: body weight decreased; mortality increased *Fetal*: ⩾650 mg/kg body weight/day: weight decreased, skeletal variations and retardation increased 1300 mg/kg body weight/day: post-implantation loss, resorptions, number and percent fetuses and litters with malformations and variations, and number and percentage of fetuses with retardations increased; fetal weight decreased	Hellwig and Jäckh (1997)
	Days 0–17 of pregnancy	Diet: 0%, 0.009%, 0.03%, and 0.09% (microencapsulated) (0.13, 43 and 129 mg/kg body weight/day) >99% pure test substance	CD-1 Swiss mice (28 f/group)	NOAEL maternal and developmental toxicity: 129 mg/kg body weight/day but no toxic dose tested No maternal toxicity; all of the litters survived and all gestational parameters were normal	NTP (1991) and Price et al. (1991)

	Gavage from days 7 to 14 of pregnancy; the dams and pups were observed until day 3 of lactation	0, 1525 mg/kg body weight/day in corn oil	Charles River CD-1 mice (50 f/group)	NOAEL for maternal/developmental toxicity cannot be derived *Maternal*: 1525 mg/kg/d: 17/49 died (controls 0), reduced movement, ataxia, hypothermia, unkempt coats and blood in the urine, body weight and fertility and pregnancy index decrease *Fetal*: 1525 mg/kg/day: number of live pups and in their weight decrease. No further parameters were considered in this study	Hardin et al. (1987)
Isooctyl alcohol (C7–9 alcohols, branched (CAS No. 68526-83-0))	Gavage, days 6–15 p.c., according to OECD TG 414	0, 100, 500, 1000 mg/kg body weight/day in corn oil	Sprague–Dawley rat (25 f/group)	NOAEL maternal toxicity: 500 mg/kg body weight/day NOAEL developmental toxicity: 100 mg/kg body weight/day *Maternal*: 1000 mg/kg: food consumption decreased, body weight gain from GD6–9 and GD6–15 decreased, clinical signs (emaciation, rales, hypoactivity, abdominal/anogenital staining, little or no stool) *Fetal*: ⩾500 mg/kg: number of lumbar ribs increased 1000 mg/kg body weight/day: number of fetuses with skeletal variations increased, hypoplastic skull bones increased only on a per-fetus basis	EBSI (1994a) as cited in Exxon (2001a)
Isotridecan-1-ol (isomeric mixture)	Gavage, days 6–19 p.c.	0 (olive oil), 60, 250, or 750	Wistar rats (25/f/group)	NOAEL for maternal toxicity: 250 mg/kg NOAEL for developmental toxicity: 750 mg/kg *Maternal:* 750 mg/kg: transient salivation;11% reduction of food consumption (6–10 p..c); increased alanine aminotransferase values; increased triglycerides (14%) and relative liver weights (18%); decreased total protein and globulin concentrations 250 mg/kg: transient salivation *Fetal*: 750 mg/kg body weight/day: no effects	RIFM (2003b)
Isononyl alcohol (Isononanol type 1 (CAS No. 68515-81-1))	Gavage, days 6–15 p.c. according to OECD TG 414	0 (control 1: water, control 2: water with 0.005% Cremophor EL), 1, 5, and 10 mmol/kg body weight/day (0, 144, 720, and 1440 mg/kg body weight/day) in aqueous Cremophor EL Supplementary study: 0 (control 1: water, control 2: water with 0.005% Cremophor EL) and 7.5 mmol/kg body weight/day (0, 1080 mg/kg body weight/day) because of mortality of all dams at 10 mmol/kg (1440 mg/kg) body weight/day	Wistar rats (10 f/group)	NOAEL for maternal toxicity: 144 mg/kg body weight/day NOAEL for developmental toxicity: 144 mg/kg body weight/day *Maternal*: ⩾720 mg/kg: food consumption (days 6–10 p.c.) decreased, clinical signs (apathy, nasal discharge) 1080 mg/kg: severe maternal signs (n.f.i.), mortality (1/10) 1440 mg/kg: mortality (10/10) *Fetal*: 144 mg/kg body weight/day: fetuses with hydroureter (8/73; 11.0%, control 1: 0/68, control 2: 3/69, 4.3%), no further effects	Hellwig and Jäckh (1997) and EPA, 1991

(*continued on next page*)

Table 6-2 (*continued*)

Material	Method	Concentration/dose	Species (No./dose)	Results	References
				720 mg/kg body weight/day: fetuses with hydroureter (8/67, 12.0%), fetal number decreased and % fetuses with skeletal variations and retardations increased 1080 mg/kg: fetuses with hydroureter (3/37, 8.1%, control 1: 6/65, 9.2%, control 2: 2/58, 3.4%); mean uterine and fetal weights decreased, resorptions increased, post-implantation loss increased, number and % fetuses and litters with malformations increased (mainly related to the heart), number and % fetuses with retardations increase, skeletal variation increase (rudimentary-cervical rib(s) increased (11/0 control 1, 11/1 control 2)) 1440 mg/kg body weight/day: examination of fetuses not possible because of maternal death	
Isodecyl alcohol	Gavage, days 6–15 p.c., according to OECD TG 414 (10 instead of 20 recommended animals/group)	0, 1, 5, and 10 mmol/kg body weight/day (0, 158, 790, and 1580 mg/kg body weight/day) in aqueous Cremophor EL	Wistar rats (10 f/group)	NOAEL maternal toxicity: 158 mg/kg body weight/day NOAEL developmental toxicity: 790 mg/kg body weight/day *Maternal*: ⩾790 mg/kg: food consumption decreased, body weight on days 15 and 20 decreased, clinical symptoms (nasal discharge, salivation, and CNS depression) 1580 mg/kg: mortality increased *Fetal*: 1580 mg/kg: mean uterine and fetal weights decreased, resorptions increased, postimplantation loss increased, number and % fetuses with malformations and retardations increased	Hellwig and Jäckh (1997)
3,5,5-Trimethyl-1-hexanol	Gavage, males: 46 days, females: from 14 days before mating to day 3 of lactation, OECD TG 422	0, 12, 60, 300 mg/kg body weight/day in olive oil	SD (Crj:CD) rat (12/sex/dose)	NOAEL systemic toxicity males and females: 12 mg/kg body weight/day NOAEL fertility: 12 mg/kg body weight/day (females) 300 mg/kg body weight/day (males) NOAEL developmental toxicity: 12 mg/kg body weight *Parental*: ⩾12 mg/kg body weight/day: renal hyaline droplets, eosinophilic bodies (m) ⩾60 mg/kg body weight/day: rel. liver weight increase (m,f), abs. and rel. kidney weight increase (m), pale discoloration of kidneys (m), renal tubular epithelial regeneration (m), formation of granular casts in kidney (m), renal epithelial fatty change (f); implantation index decrease (f) 300 mg/kg body weight/day: 1 f died, 3 f killed (weakness); body weights increase (m), food consumption increase (m), body weights decrease (f), food consumption decrease (f); urine volume increase (m), water consumption increase (m); red blood cell counts decrease (m), hematocrit	MHW, Japan (1997b) as cited in OECD/SIDS (2003)

				decrease (m), hemoglobin decrease (m), BUN decrease (m), chloride decrease (m) abs. liver weight increase (m,f), rel. kidney weight increase (f), swelling of kidney (m), yellowish white discoloration of liver (f), irregularity in shape of follicles (m), columnar change of follicular epithelium (m), thyroid colloid decrease (m), thymus atrophy (f); total litter loss in 2 dams *Fetal*: ⩾60 mg/kg body weight/day: decreased pups born alive 300 mg/kg body weight/day: viability of neonates on day 4 of lactation decreased, body weights of male and female pups ? decreased	
Subgroup: secondary					
2,6-Dimethylheptan-4-one	Gavage, from 2 weeks prior to mating throughout pregnancy until weaning day 5 post partum (OECD TG 421)	0 (vehicle), 100, 300, 1000 mg/kg body weight/day in corn oil	Alpk:ApfsSD rats (10/sex/group)	NOAEL parental systemic toxicity: 300 mg/kg body weight/day NOAEL developmental/reproductive effects: 1000 mg/kg body weight/day *Maternal*: 1000 mg/kg body weight/day: two dams died during lactation, attributable to the test substance. There was no effect on the number of pregnancies, positive smears, litters born, number of implantations or proportion of pups born live in any dose group *Paternal*: 1000 mg/kg body weight/day: male body weight gains decrease No changes in organ weight and no significant histopathological changes in the male or female reproductive organs; no evidence of an effect on any of the reproductive parameters investigated or on any of the surviving litters	Shell HSE (1996) as cited in OECD/SIDS (2003)
4-Hydroxy-4-methyl-2-pentanone	OECD TG 422 (screening test): males: 44 days, females: from 14 days before mating to day 3 of lactation	0, 30, 100, 300, 1000 mg/kg body weight/day in water	Crj:CD(SD) rat (10/sex/dose)	NOAEL parental systemic toxicity: 100 mg/kg body weight/day NOAEL for fertility and developmental toxicity: 300 mg/kg body weight/day *Parental*: tendency for lower reproductive indices (fertility and implants) (n.f.i.) *Fetal*:1000 mg/kg body weight/day: tendency for decrease of the following parameters: total number of pups born, delivery index, live birth index, number of pups alive, viability index on day 4 of lactation (n.f.i.)	MHW, Japan (1997) as cited in OECD/SIDS (2007)

f: female, m: male, n.f.i.: no further information, n.s.: not statistically significant, p.c.: post coitum

Table 6-3
Reproductive and developmental toxicity studies – inhalation.

Material	Method	Concentration/dose	Species (No./dose)	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	Whole body exposure from day 0 to 19 of pregnancy	0, 850 mg/m^3 (160 ml/m^3) the maximum vapor concentration that could be achieved without increasing exposure chamber temperature above 80°F	Sprague–Dawley rats (15 f/group)	NOAEL 160 ml/m^3 *Maternal*: 160 ml/m^3: no maternal toxicity *Fetal*: 160 ml/m^3: no significant differences in corpora lutea per litter, resorptions per litter, numbers of females or males per litter, or fetal weight of females or males, and no external, visceral, or skeletal malformations	Nelson et al. (1989)
Isoamyl alcohol	Inhalation, days 6 through GD15, 6 h/day, caesarean section on day 20 GD, OECD TG 414	0, 510, 2500, 9800 mg/m^3 (0, 138, 675, 2646 ml/m^3)	Wistar female rat (20–25 f/group)	NOAEL maternal toxicity: 675 ml/m^3 NOAEL developmental toxicity: 2646 ml/m^3 *Maternal*: 2646 ml/m^3: body weight gain (days 6–9)decreased; no test substance-related clinical signs *Fetal*: no litter parameters affected; no gross external, soft tissue, or skeletal fetal alterations	Klimisch and Hellwig (1995) RIFM (1990a)
	Inhalation, days 7 through 19 pi, 6 h/day, caesarean section on day 29 pi OECD TG 414	0, 510, 2510, 9800 mg/m^3 (0, 138, 678, 2646 ml/m^3)	Himalayan female rabbit (15 f/group)	NOAEL maternal toxicity: 678 ml/m^3 NOAEL developmental toxicity: 2646 ml/m^3 *Maternal*: 2646 ml/m^3: body weight gain (days 7–10) decreased; eye irritation (redness, lid closure, slight discharge) *Fetal*: no litter parameters affected; no gross external, soft tissue, or skeletal fetal alterations	Klimisch and Hellwig (1995) RIFM (1990b)
Subgroup: secondary					
4-Methyl-2-pentanone	Inhalation 6 h/day, 7 days/w Two-generation study, exposure duration (F_0, F_1): Males: 70 d prior to end through mating period Females: 70 d prior to mating to day 20 of gestation, resumed at 5 days of lactation US EPA OPPTS Guideline 870-3800	0, 500, 1000, or 2000 ml/m^3 (0, 2050, 4090, or 8180 mg/m^3)	Sprague–Dawley rat (30/sex/group)	NOAEL systemic toxicity: 1000 ml/m^3 (excluding male nephropathy) NOAEL reproductive toxicity: 2000 ml/m^3 F_0 *adults*: ⩾500 ml/m^3: centrilobular hepatocellular hypertrophy only in males, abs./rel. kidney weights increase (m) 1000 ml/m^3: nephropathy (basophilic tubules with inflammation and thickening of the tubular basement membrane) (m), sedative effect (absent or reduced reaction to auditory startle stimulus (normalized 1 h after end of exposure)) 2000 ml/m^3: body weight gain decrease (f); abs. and rel. liver weights increase (m,f)	Nemec et al. (2004)

			F_1 *adults*: $\geqslant$500 ml/m^3: kidney changes (alpha-2u-globulin nephropathy) (m) $\geqslant$1000 ml/m^3: sedative effect (s.a.) (m), centrilobular hepatocellular hypertrophy (m) 2000 ml/m^3: absent or reduced reaction to auditory startle stimulus (ameliorated 1 h after end of exposure) (f); 1 m died on PND 22, clinical signs of neurotoxicity (i.e., rocking, prostration, half-closed eyelids) approx. 1 h post-exposure (PND 22) $\Rightarrow$ exposures for all groups of F1 weanlings suspended through PND 27; body weight gain (transient) decrease (m,f); abs. and rel. liver weights increase (m, f), centrilobular hepatocellular hypertrophy (m) F_1/F_2 *Offspring*: reproductive parameters unaffected	
Inhalation, days 6–15 p.c., 6 h/day, duration of study: 21 days, according to OECD TG 414	0 (air), 300, 1000, 3000 ml/m^3 (0, 1230, 4090, 123,000 mg/m^3)	Fischer 344 rat (35 f/group)	NOAEL maternal toxicity: 1000 ml/m^3 NOAEL developmental toxicity: 1000 ml/m^3 *Maternal*: 3000 ml/m^3: neuromuscular effects (e.g. loss of coordination, paresis); body weight and body weight gain decreased, food consumption decreased, rel. kidney weights increased *Fetal*: 3000 ml/m^3: body weight per litter decreased, skeletal ossification retarded, unilateral rudimentary rib at the first lumbar arch increased	Tyl et al. (1987)
Inhalation, days 6–15 p.c., 6 h/day, duration of study: 18 days, according to OECD TG 414	0 (air), 300, 1000, 3000 ml/m^3 (0, 1230, 4090, 123,000 mg/m^3)	CD-1 mice (30 f/group)	NOAEL maternal toxicity: 1000 ml/m^3 NOAEL developmental toxicity: 1000 ml/m^3 *Maternal*: 3000 ml/m^3: 3 dams died on GD 6; neuromuscular effects, abs. and rel. liver weights increased *Fetal*: 3000 ml/m^3: body weight per litter decreased, number of dead fetuses increased, visceral variations (dilated lateral ventricles of the cerebrum and dilated renal blood vessels) increased, skeletal variations (vertebrae, sternbrae, and distal limbs) increased, skeletal ossification retarded	Tyl et al., (1987)

DEHP: di(2-ethylhexyl) phthalate, f: female, GD: gestation day, m: male, s.a.: see above, n.f.i.: no further information, MEHP: mono(2-ethylhexyl) phthalate, n.s.: not statistically significant, p.c.: post-coitum, pi: post-insemination. *4-Methyl-2-pentanone* is not a fragrance material, but is structurally related.

The same test procedure was performed with 14–15 pregnant Himalayan rabbits. The animals were exposed to 0, 510, 2510, or 9800 mg isoamyl alcohol/m^3 (0, 138, 678, and 2646 ml/m^3) from day 7 to day 19 post-insemination. In dams exposed to the highest concentration body weight gain was decreased between days 7 and 10 post insemination and irritant eye effects (reddish, lid closure, and slight discharge) were noted. Histopathological examination of the dams revealed no substance-related effects. The reproduction parameters (e.g. mean number of corpora lutea, implantation sites, values calculated for the pre- and post-implantation losses, and number of resorptions) and malformations (external, visceral, or skeletal) were within the levels of the concurrent control group or of historical control groups. The maternal NOAEL was 2500 mg/m^3 (678 ml/m^3) and the NOAEL for developmental toxicity was 9800 mg/m^3 (2646 ml/m^3) (Klimisch and Hellwig, 1995).

Fifteen pregnant Sprague–Dawley rats were exposed (whole body) 7 h per day on gestation days 0–19 to 850 mg 2-ethyl-1-hexanol/m^3 (160 ml/m^3), the maximum vapor concentration that could be achieved without increasing exposure chamber temperature above 80 ° F. After caesarean section on day 20, one-half of the fetuses were examined for skeletal malformations, the other half for visceral malformations. Aside from a decrease in feed consumption in dams compared to control, there were no significant differences in maternal, reproductive, or developmental parameters (Nelson et al., 1989). The NOAEL for maternal and developmental toxicity was 850 mg/m^3 (160 ml/m^3).

5.5.2.3.2. Secondary alcohols. Thirty-five pregnant Fischer 344 rats or 30 pregnant CD-1 mice were exposed 6 h per day on gestation days 6–15 to 0, 300, 1000, and 3000 ml *4-methyl-2-pentanone*/m^3 (0, 1230, 4090, and 12,300 mg/m^3). Maternal toxicity (neuromuscular effects, e.g. loss of coordination or paresis) was observed in both species after exposure to the highest concentration. Rat dams showed reductions in body weights, body weight gain, and food consumption. The relative kidney weights were elevated. In mice, three dams died at the first exposure and the relative and absolute liver weights were increased. Reduced fetal body weight per litter and delayed skeletal ossification was observed in both species at the highest concentration. Rat fetuses showed an increased incidence of unilateral rudimentary rib at the first lumbar arch. In mice, the number of dead fetuses as well as visceral and skeletal variations was increased. The NOAELs for maternal and fetal toxicity were 1000 ml/m^3 for both species (Tyl et al., 1987 as cited in OECD/SIDS, 2007).

5.5.2.3.3. Tertiary alcohols. No studies were available.

5.6. Skin irritation

5.6.1. Human studies

Seven alcohols with saturated branched chain under review with a worldwide use of greater than 0.01 tons per year have been well studied for their potential to produce dermal irritation in humans (see Table 7-1).

The following substances did not induce skin irritation in pretests for a maximization study with single occlusive application for 48 h with the highest concentrations tested, i.e., 20% 3,6-dimethyl-3-octanol (RIFM, 1972a, 1973c), 10% 3,7-dimethyl-7-methoxyoctan-2-ol (RIFM, 1982b), 10% 2,6-dimethyl-2-heptanol (RIFM, 1976b, 1983a), 8% isoamyl alcohol (RIFM, 1976b), 8% 3,5,5-trimethyl-1-hexanol (RIFM, 1977b), and 4% 2-ethyl-1-hexanol (RIFM, 1976c).

No irritation was observed with 2% 2,6-dimethyl-2-heptanol during the induction phase of a human repeat insult patch test (HRIPT) in 10 healthy male and female volunteers (RIFM, 1969). The repeated application of 15% 3,4,5,6,6-pentamethylheptan-2-ol during the induction phase of a HRIPT led to erythema (6 grade 1 of 4, 4 grade 2 of 4) in 5 of 51 volunteers (RIFM, 1983c).

A patch test (5 min under occlusion) was conducted on 12 healthy volunteers and with 3 or 12 subjects of oriental ancestry with a 75% aqueous solution of isoamyl alcohol. Irritation reactions were observed in all volunteers (Wilkin and Fortner, 1985a,b; Wilkin and Stewart, 1987).

Further details on studies of dermal irritation in humans are provided in Table 7-1.

5.6.2. Animal studies

Twelve of the alcohols under review with a worldwide use of greater than 0.01 tons per year have been tested in animal models of skin irritation using rabbits, rats, or guinea pigs. Studies with single application are summarized in Table 7-2-1 and studies with repeated application are shown in Table 7-2-2.

A single application of neat 3,4,5,6,6-pentamethylheptan-2-ol did not produce dermal irritation in rabbits (RIFM, 1984b) and rats (RIFM, 1985a). If applied undiluted as a single application, 2-ethyl-1-butanol, 2-ethyl-1-hexanol, isoamyl alcohol, 2-methylbutanol, 3,5,5-trimethyl-1-hexanol, 2,6-dimethyl-4-heptanol, 4-methyl-2-pentanol, 2,6-dimethyl-2-heptanol, and 3,6-dimethyl-3-octanol (McOmie and Anderson, 1949; RIFM, 1973a, 1976a, 1977a; Scala and Burtis, 1973; Cornu et al., 1992, 1984, 1978) led to slight or moderate irritation in all studies with rabbits irrespectively of the method used. As an exception undiluted 2,6-dimethyl-2-heptanol was strongly irritating after 24 h occlusive application (RIFM, 1979a). The diluted substances led to no or only slight effects in rabbits or guinea pigs: 3,6-dimethyl-3-octanol 15% no to slight reactions (RIFM, 1970), 2,6-dimethyl-2-heptanol 10% no reaction (RIFM, 1981a), 3,7-dimethyl-7-methoxyoctan-2-ol 1% slight reaction (RIFM, 1973e).

Five percent 3,7-dimethyl-7-methoxyoctan-2-ol did not produce dermal irritation in guinea pigs after repeated application (RIFM, 1973d). Repeated application of neat 2-ethyl-1-hexanol led to slight dermal irritation in rats (Schmidt et al., 1973). Moderate or strong irritation was observed after repeated applications of undiluted 2,6-dimethyl-4-heptanol, 4-methyl-2-pentanol, and 3,4,5,6,6-pentamethylheptan-2-ol (also diluted) in rabbits (McOmie and Anderson, 1949; RIFM, 1985c, 1986a). Toxicity studies with repeated dermal application (see Section 5.2.1) also showed dermal irritation especially with 3,4,5,6,6-pentamethylheptan-2-ol. These studies were performed with high doses under occlusion and are therefore not representative of human exposure.

5.7. Mucous membrane irritation

5.7.1. Sensory irritation

5.7.1.1. Human data. The results of the human irritation studies are summarized in Table 8.

Human male volunteers (with and without self-reported multiple chemical sensitivity) were exposed to 2-ethyl-1-hexanol by inhalation for 4 h (exposure chamber). Fluctuating concentrations (time weighted average concentrations: 1.5 (control), 10, and 20 ml/m^3) were used in the first experiment, and similar but constant vapor concentrations in a second experiment. Olfactory- and trigeminal-mediated symptoms and intensities of odor, eye, and nasal irritation were recorded. Self-reported nasal and eye irritation and perceived odor intensity were increased and concentration-related at concentrations of 10 ml/m^3 or more. Self-reported chemical sensitivity had only minor effects on chemosensory symptoms in the second experiment (constant concentrations) and no effect on intensity ratings in either experiment (van Thriel et al., 2005).

An average of 12 subjects were exposed by inhalation to 2,6-dimethyl-4-heptanol for 15 min. At 5 ml/m^3 or more, eye irritation was observed, and at 10 ml/m^3 nose and throat irritation. The sensory response limit was reported to be less than 5 ml/m^3 (Silver-

man et al., 1946). In the same study 4-methyl-2-pentanol led to eye irritation at 50 ml/m^3 and higher concentrations resulted in nose and throat irritation. The NOEL was 25 ml/m^3 (Silverman et al., 1946).

5.7.1.2. Animal data. Sensory irritation was evaluated in 4 Swiss male mice via measurement of changes in respiratory rate during a 10-min exposure to isoamyl alcohol. The concentration of isoamyl alcohol that caused a 50% decrease in the respiratory rate (RD_{50}) of mice was 4452 ml/m^3 with 95% confidence limits of 2885–12,459 ml/m^3 (Kane et al., 1980). Another study reported a RD_{50} value of 2624 mg/m^3 (729 ml/m^3) (Korpi et al., 1999).

After a 5-min exposure to 4-methyl-2-pentanol the RD_{50} for mice was 420 ml/m^3 (6 animals/group) (Muller and Greff, 1984 as cited in Greim, 2002).

5.7.2. Eye irritation

No human studies on eye irritation are available. An overview of *in vivo* studies on eye irritation in rabbits can be found in Table 9.

Several *in vitro* tests to investigate the eye irritation potential did show an irritating effect of 2-ethyl-1-hexanol (Adriaens and Remon, 2002; Adriaens et al., 2005; Casterton et al., 1996; Gautheron et al., 1994; Gilleron et al., 1997; Goethem et al., 2006; Kennah et al., 1989a).

For 3,7-dimethyl-7-methoxyoctan-2-ol only one study with a 1% solution in propylene glycol was available, in which the substance did not cause irritating effects (RIFM, 1973e).

In 4 of 5 studies, isotridecan-1-ol (isomeric mixture) elicited no eye irritation in rabbits (Greim, 2000). Further information about the test method and the concentration were not given. The undiluted substance was moderately irritating to the rabbit eye in one study (Greim, 2000; Scala and Burtis, 1973).

Undiluted 3,6-dimethyl-3-octanol was evaluated as an eye irritant. The substance led to redness and chemosis of the conjunctiva, slight corneal opacity, and swelling of the iris. The effects were not reversible within 3 days (RIFM, 1970).

In three studies undiluted 2-ethyl-1-hexanol was moderately irritating to the rabbit eye (Carpenter and Smyth, 1946; Schmidt et al., 1973; Smyth et al., 1969). Observed effects were conjunctival redness and swelling, lacrimation, and discharge. The effects did not clear within 96 h. Corneal effects were not found (Schmidt et al., 1973). In three other studies, the undiluted substance was classified as a severe eye irritant (Kennah et al., 1989b; RIFM, 1978b; Scala and Burtis, 1973). These studies resulted in dullness and vascularization of the cornea (Scala and Burtis, 1973). The corneal effects were persistent (RIFM, 1978b). In addition, iritis, conjunctival erythema, chemosis, and discharge appeared (Scala and Burtis, 1973).

Undiluted 2,6-dimethyl-2-heptanol, 2,6-dimethyl-4-heptanol, 4-methyl-2-pentanol, and 3,4,5,6,6-pentamethylheptan-2-ol were moderate eye irritants (McOmie and Anderson, 1949; RIFM, 1979a, 1984c; Smyth et al., 1951). The substances caused conjunctivitis with edema and corneal injury. The effects disappeared within 7 days (McOmie and Anderson, 1949; RIFM, 1984c) except for those caused by 2,6-dimethyl-2-heptanol (RIFM, 1979a).

Undiluted 2-ethyl-1-butanol, isoamyl alcohol, and 2-methylbutanol were highly irritating to the rabbit eye (Smyth et al., 1954, 1962, 1969).

5.8. Skin sensitization

5.8.1. Human studies

Seven of the alcohols under review with a worldwide use of greater than 0.01 tons per year have been evaluated for their potential to induce sensitization in humans (see Tables 10-1 and 10-2).

In both subgroups of primary and secondary alcohols no evidence of a sensitizing effect in a maximization test or in a human repeated insult patch test (HRIPT) with volunteers was observed with 4% 2-ethyl-1-hexanol (RIFM, 1976c), 8% isoamyl alcohol (RIFM, 1976b), 8% 3,5,5-trimethyl-1-hexanol (RIFM, 1977b), 10% 3,7-dimethyl-7-methoxyoctan-2-ol (RIFM, 1982b), and 15% 3,4,5,6,6-pentamethylheptan-2-ol (RIFM, 1983c). In the subgroup of tertiary alcohols 2,6-dimethyl-2-heptanol did not induce positive reactions in a maximization test (10%, RIFM, 1976b) or a HRIPT (2%, RIFM, 1969). In a maximization test with 20% 3,6-dimethyl-3-octanol in petrolatum (RIFM, 1972a), 4 of 25 volunteers exhibited positive reactions 24 and 48 h after challenge. However, since these four subjects also reacted strongly to a control material it was concluded that the reactions observed were due to a "spill over" effect from the other material. In a second test with 10% in petrolatum, the positive reactions could not be confirmed (RIFM, 1973c).

With a sub-irritating concentration (no further information) of 3,7-dimethyl-7-methoxyoctan-2-ol in petrolatum, 0.9% positive reactions (2 patients) were found in patch tests with 218 patients with proven sensitization to fragrance materials (Table 10-2; Larsen et al., 2002).

5.8.2. Animal studies

Results of available animal studies are shown in Table 10-3. In comparison to humans, limited data on sensitization in animals are available. Only one secondary and one tertiary alcohol were tested.

2,6-Dimethyl-2-heptanol was negative in guinea pigs at a concentration of 10% (Watanabe et al., 1988). No delayed-type hypersensitivity was observed for 3,7-dimethyl-7-methoxyoctan-2-ol in the same species (RIFM, 1973d).

5.9. Phototoxicity and photoallergenicity

Limited data were available with regard to the phototoxicity and photoallergenicity of the alcohols with saturated branched chain (see Table 11). From human or animal studies reliable data were available only on the phototoxicity and photoallergenicity of the tertiary alcohol 2,6-dimethyl-2-heptanol.

No phototoxic reactions were observed in 6 healthy female volunteers exposed to 10% 2,6-dimethyl-2-heptanol in 1:1 ethanol/acetone, followed by irradiation by UVA (RIFM, 1983a).

In the only animal phototoxicity study, 10% 2,6-dimethyl-2-heptanol in ethanol produced no phototoxic reactions after UVA or UVB irradiation in guinea pigs (RIFM, 1981a).

No studies have been performed which investigate the photoallergic potential in humans.

2,6-Dimethyl-2-heptanol was tested for its photoallergenicity in a reliable test with guinea pigs (RIFM, 1981b). No photoallergenicity was seen in the animals induced with 10% in rectified alcohol, followed by irradiation with UVB and UVA (9 times in 18 days), and challenged after a 10-day rest with 10% of the test substance in rectified alcohol and irradiation.

As the alcohols under review do not contain double bonds, they cannot absorb UVA or UVB light. Indeed, UV spectra have been obtained for 12 materials (2-ethyl-1-hexanol, isoamyl alcohol, isotridecan-1-ol (isomeric mixture), 2-methylbutanol, 3-methyl-1-pentanol, 2-methylundecanol, 3,5,5-trimethyl-1-hexanol, 2,6-dimethyl-4-heptanol, 3,7-dimethyl-7-methoxyoctan-2-ol, 6,8-dimethylnonan-2-ol, 3,4,5,6,6-pentamethylheptan-2-ol, and 2,6-dimethyl-2-heptanol). Five materials did not absorb UV light, the remaining 5 peaked in the UVC range (<290 nm) and returned to baseline around 300 nm (see Table 12). 2-Ethyl-1-hexanol and 3,7-dimethyl-7-methoxyoctan-2-ol peaked between 200 and 215 with minor absorption returning to baseline at 400 nm. Based on

Table 7-1
Skin irritation studies in humans.

Material	Method	Concentration	Subjects	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	29 healthy male volunteers	No irritation	RIFM (1976c)
Isoamyl alcohol	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	25 healthy volunteers	No irritation	RIFM (1976b)
	5 min, occlusive	75% in water	12 volunteers	Irritation in all 12 volunteers	Wilkin and Stewart (1987)
	5 min, occlusive	75% in water	12 volunteers (oriental)	Irritation in all 12 volunteers	Wilkin and Fortner (1985a)
	5 min, occlusive	75% in water	3 volunteers (oriental)	Irritation in all 3 volunteers	Wilkin and Fortner (1985b)
3-Methyl-1-pentanol	24 h, occlusive (pre-test for a HRIPT)	0.5% in alcohol SDA 39 C	41 healthy volunteers	Little or no irritation	RIFM (1973f)
3,5,5-Trimethyl-1-hexanol	48 h, occlusive (pre-test for a maximization study)	8%, in petrolatum	25 healthy volunteers	No irritation	RIFM (1977b)
Subgroup: secondary					
3,7-Dimethyl-7-methoxyoctan-2-ol	48 h, occlusive (pre-test for a maximization study)	10%, petrolatum	27 healthy male and female volunteers	No irritation	RIFM (1982b)
3,4,5,6,6-Pentamethylheptan-2-ol	During the induction phase of a repeated insult patch test (HRIPT): 9 applications with a duration of 24 h within a 3-week period, occlusive, 0.2 ml, observations on the application days	15% v/v solution in ethanol SDA 39C (99%)	51 healthy male and female volunteers	10/48 positive reactions: 5 grade 1 reactions (erythema confined to the contact site and exceeding that of the untreated skin) and 5 grade 2 reactions (erythema confined to the contact site and definitely exceeding that of the untreated skin; papules may or may not be present)	RIFM (1983c)
Subgroup: tertiary					
2,6-Dimethyl-2-heptanol	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	25 healthy volunteers	No irritation	RIFM (1976b)
	0.025 ml/2 cm^2, occlusive, up to 72 h	10% in 1:1 ethanol/acetone	6 healthy female volunteers	No irritation	RIFM (1983a)
	Induction phase of HRIPT	2% in dimethyl phthalate	10 healthy male and female volunteers	No irritation	RIFM (1969)
3,6-Dimethyl-3-octanol[a]	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	5 healthy male volunteers	No irritation	RIFM (1973c)
	48 h, occlusive (pre-test for a maximization study)	20% in petrolatum	5 healthy male volunteers	No irritation	RIFM (1972a)
3-Methyloctan-3-ol[a]	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	29 healthy volunteers	No irritation	RIFM (1978a)

[a] No relevant use was reported.

Table 7-2-1
Skin irritation studies in animals, single application.

Material	Method	Concentration	Species	Results	References
Subgroup: primary					
2-Ethyl-1-butanol	24 h, uncovered, 0.01 ml sample on the clipped skin	Undiluted	Rabbit (n = 5)	An average reaction to a trace of capillary injection	Smyth et al. (1954)
2-Ethyl-1-hexanol	5000 mg/kg, n.f.i.	Undiluted	Rabbit (n = 10)	Moderate redness and edema in 10/10	RIFM (1977a)
	24 h, uncovered, 0.01 ml sample on the clipped skin	Undiluted or as a solution in water, propylene glycol or acetone	Rabbit (n = 5)	Moderate irritation observed	Smyth et al. (1969)
	24 h, occlusive, 0.1, 0.316, 1.0, 3.16 mg/kg body weight, on the clipped intact skin, observations daily up to 7 days	Undiluted	Rabbit (n = 4)	Moderate irritation: moderate erythema, moderate edema, atonia, blanching, desquamation, coriaceousness, necrosis, and eschar	Scala and Burtis (1973)
Isoamyl alcohol	Single application of 5.0 g/kg	Undiluted	Rabbit (n = 10)	Marked erythema and moderate edema	RIFM (1976a)
	Single application	Undiluted	Rabbit (n = 6)	Very irritating	RIFM (1979c)
	24 h, uncovered, 0.01 ml sample on the clipped skin	Undiluted or as a solution in water, propylene glycol or acetone	Rabbit (n = 5)	Irritation was observed	Smyth et al. (1969)
isotridecan-1-ol (mixed isomers)	Single occlusive patch for 24 h to intact skin of 4 rabbits	Undiluted	Rabbits	Moderately irritating	Scala and Burtis (1973)
	Single uncovered application of 0.01 ml for 24 h	Undiluted	Rabbits	Moderately irritating	Smyth et al. (1962)
	Percutaneously to the intact dorsal skin for 20 h	Undiluted	Rabbits	Severe erythema and distinct edema at 24 h distinct scarring and severe scaling at 8 days	RIFM (1963d,e)
	4-h semi-occlusive irritation	Undiluted	Rabbits	Slight to marked erythema, slight or moderate edema and scaling	RIFM (2003a)
2-Methylbutanol	24 h, uncovered, 0.01 ml sample on the clipped skin	Undiluted	Rabbit (n = 5)	Irritation defined as the least visible capillary injection from the undiluted material	Smyth et al. (1962)
	n.f.i.	Undiluted	Rabbit (n = 2)	Moderately irritating	RIFM (1979b)
3-Methyl-1-pentanol	0.5 ml application, 24 h contact, observed again at 48 h	0.5% in alcohol SDA 39C	Rabbit (n = 3)	No erythema and edema observed	RIFM (1972c)
3,5,5-Trimethyl-1-hexanol	5000 mg/kg body weight, n.f.i.	Undiluted	Rabbit (n = 10)	Redness: mild: 2/10, moderate: 4/10, severe: 4/10; edema: mild: 1/10, moderate: 9/10, severe: 0/10	RIFM (1977a)
Subgroup: secondary					
2,6-Dimethyl-4-heptanol	Neat application as part ofl LD_{50}	Undiluted	Rabbit (n = 5)	No irritation	Smyth et al. (1949)
	4 h, semi-occlusive, 3.9-9.4 ml/kg body weight on the shaved skin	Undiluted	Rabbit (n = 5)	2/5 some erythema and slight edema	McOmie and Anderson (1949)
3,7-Dimethyl-7-methoxyoctan-2-ol	24 h, occlusive, 0.5 ml, abraded and intact skin, observations after 24, 72 h	1% in propylene glycol	Rabbit (n = 6)	Mildly irritating, PII 0.5, 5/6 very slight erythema in the intact and abraded sites after 24 h, 1/6 very slight erythema in the intact and abraded sites after 72 h	RIFM (1973e)
4-Methyl-2-pentanol	Details of the method not reported	Concentration and vehicle not reported	Rabbit, n.f.i.	2/10 defined as an average reaction equivalent to a trace of capillary injection	Smyth et al. (1951)
	0.25 h, observation period of 10 days, n.f.i.	Undiluted	Rabbit (n = 3)	Immediate slight erythema and delayed moderate erythema with drying of surface	McOmie and Anderson (1949)
	7 applications (5 h) to the intact skin for 21 days	Undiluted	Rabbits (n = 2)	Erythema, flaking, and cracking of the skin with bleeding fissures by the 7th exposure	McOmie and Anderson (1949)
3,4,5,6,6-Pentamethylheptan-2-ol	4 h, occlusive, 0.5 ml, clipped skin, observations at 24, 48, 72 h	Undiluted	Rabbit (n = 6)	No irritation	RIFM (1984b)
	24 h, occlusive, 2000 mg/kg body weight, observations at 24 h, and daily for 14 days	Undiluted	Rats (n = 5/sex)	No irritation	RIFM (1985a)
Subgroup: tertiary					
2,6-Dimethyl-2-heptanol	5000 mg/kg body weight, n.f.i.	Undiluted	Rabbit (n = 10)	2/10 slight redness, 8/10 moderate redness, 1/10 slight edema, 9/10 moderate edema	RIFM (1976a)

(*continued on next page*)

Table 7-2-1 (*continued*)

Material	Method	Concentration	Species	Results	References
	1, 5, 15 min, 2, 20 h, intact and abraded skin, observations after 24 h, 48 h, 8 days; (Federal Register 38, No. 187, § 1500.41, S. 27019, 27. Sept. 1973)	Undiluted	Rabbit (n = 6)	PII 5.1, strongly irritating, after 24 h on intact skin: 6/6 strong redness, 5/6 slight edema, 1/6 strong edema, slight redness already after 5 min reversible within 8 days, redness after 24 h application not reversible within 8 days	RIFM (1979a)
	4 h, patch test, observations after 4 h, 24 h, 48 h (control of a phototoxicity study)	10% in ethanol	Albino guinea-pig (n = 8)	No irritation	RIFM (1981a)
3,6-Dimethyl-3-octanol[a]	5000 mg/kg body weight, n.f.i.	Undiluted	Rabbit (n = 8)	8/8: slight redness, 3/8: slight edema, 4/8: moderate edema	RIFM (1973a)
	24 h, occlusive, 0.5 ml, intact and abraded skin, observations at 24, 48, 72 h	Undiluted, 15% in distilled water	Rabbit (n = 6)	Undiluted PII: 3.4, very slight to moderate/severe erythema, very slight to slight edema, no observations were made after 3 days; 15% PII: 2.0, very slight to well-defined erythema no edema to very slight edema, 3/6 animals were not entirely recovered within 7 days a score of 5 or more is regarded as signifying a primary skin irritant	RIFM (1970)
3-Methyloctan-3-ol[a]	5000 mg/kg body weight	Undiluted	Rabbit (n = 10)	4/10: slight redness, 4/10: moderate redness, 2/10: slight edema, 8/10: moderate edema	RIFM (1978c)

n.f.i.: no further information, PII: primary irritation index.
[a] No relevant use was reported.

the UV spectra and review of phototoxic/photoallergy data, the materials in this group would not be expected to elicit phototoxicity or photoallergy under the current conditions of use as a fragrance ingredient.

5.10. Miscellaneous studies

To address hepatotoxicity, several miscellaneous studies were conducted. *Ex vivo* studies on the mechanism of hepatotoxicity were conducted with 2-ethyl-1-hexanol, 2-methylbutanol, and isoamyl alcohol, *in vitro* enzyme induction and peroxisome proliferation studies were conducted with 2-ethyl-1-hexanol and isoamyl alcohol and *in vivo* repeated dose toxicity studies with 2-ethyl-1-hexanol, isoamyl alcohol, isodecyl alcohol, isononyl alcohol, isooctane-1-ol (isomeric mixture) and 3,5,5-trimethyl-1-hexanol were performed. These studies are not summarized here but may be found in detail in individual Fragrance Material Reviews (McGinty et al., 2010a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q). The data show that 2-ethyl-1-hexanol is a peroxisome proliferator and that 2-ethyl-1-hexanol, 2-methylbutanol, and isoamyl alcohol induce liver enzymes.

6. Conclusion

The compounds assessed in this group have a close structural relationship, similar metabolism, and toxicity profiles.

Data on metabolism for the compounds under review are available only for the primary alcohols 2-ethyl-1-butanol, 2-ethyl-1-hexanol, isoamyl alcohol, 2-methylbutanol, and for the secondary alcohol 4-methyl-2-pentanol.

The major pathways of metabolism and fate which are common to the primary, secondary and tertiary alcohols in this group are:

- conjugation of the alcohol group with glucuronic acid;
- oxidation of the alcohol group;
- side-chain oxidation yielding polar metabolites, which may be conjugated and excreted – or further oxidation to an aldehyde, a carboxylic acid, and to CO_2;
- excretion of the unchanged parent compound.

In most cases metabolism yields innocuous substances, which are excreted in the urine and feces.

Because there is insufficient information for many of the 20 alcohols with saturated branched chain under review, the database is supplemented with studies of 3 metabolites of these alcohols.

The Panel is of the opinion that there are *no safety concerns* regarding alcohols branched chain saturated under the present declared levels of use and exposure. These materials have not been evaluated at levels other than reported in this group summary. Use of these materials at higher maximum dermal levels or higher systemic exposure levels requires re-evaluation by the Panel. This conclusion was based on the following reasons:

- No, or only minimal, evidence of skin irritation in humans was caused by 6 compounds tested at concentrations of 2–10%. Due to the structural similarities, compounds not tested for skin irritation in humans are expected to show similar properties with respect to this endpoint. Therefore, the alcohols under review pose no concern provided concentrations in end products are in the range of 2–10%, which is above the current concentrations of use.
- The 11 materials evaluated for eye irritation showed that the undiluted materials cause moderate to severe eye irritation. However, since these materials are not used undiluted they pose no concern for eye irritation at the concentrations currently in use in end products (0.001–1.7%).

Table 7-2-2
Skin irritation studies in animals, repeated application.

Material	Method	Concentration	Species	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	12 applications, over a period of 12 days, uncovered, 2 ml/kg body weight/day on the shaved skin, observations daily	Undiluted	Rat (n = 10)	After 10 days slight redness and scabbing	Schmidt et al. (1973)
Subgroup: secondary					
2,6-Dimethyl-4-heptanol	7 applications, 5–12 h duration over a period of 15–21 days, uncovered, 3.0 ml/kg on 100 cm^2, nonabraded skin, observations daily	Undiluted	Rabbit (n = 2)	definite erythema after 2nd exposure; areas of flaking after 4th exposure; cracking of skin, fissures with some bleeding after 7th exposure	McOmie and Anderson (1949)
3,7-Dimethyl-7-methoxyoctan-2-ol	10 applications, 24 h duration on alternate days during a 3-week period, occlusive, 0.2 ml, shaved skin, observations	2.5, 5% in water, applications 1–7: 5%, applications 8–10: 2.5%	Guinea pig (n = 10)	No irritation, isolated occurences of slight erythema during the treatment period	RIFM (1973d)
4-Methyl-2-pentanol	5 applications, 5–12 h duration over a period of 15–21 days, uncovered, 3.0 ml/kg on 100 cm^2, nonabraded skin, observations daily	Undiluted	Rabbit (n = 3)	Severe drying of the skin with some sloughing and cracking	McOmie and Anderson (1949)
3,4,5,6,6-Pentamethylheptan-2-ol	9–28 applications, 6 h duration over a period of 28 days, occlusive, nonabraded and clipped skin, observations daily	Undiluted, 1.5%, 5%, 15%, 50% dissolved in 1% w/v aqueous methylcellulose (ca. 30, 100, 300, 1000 mg/kg body weight/dayay)	Rabbit (n = 10/sex)	$\geqslant$30 mg/kg body weight/dayay: erythema and edema increased dose-dependently; $\geqslant$300 mg/kg body weight/dayay: after 9 treatments the treatment was terminated as a result of irritation	RIFM (1986a)
	Daily applications for 6 h, duration over 28 days, occlusive, 1000 mg/kg body weight/dayay, nonabraded skin, observations daily	Undiluted	Rabbit (n = 13/sex)	Severe and persistent irritation: dermal irritation progressed rapidly in all animals to well defined to moderate erythema and edema within one week; irritation progressed further in several rabbits becoming severe within 2 weeks of treatment, scab formation	RIFM (1985c)

Table 8
Sensory irritation studies in humans

Material	Dose route	No. subjects/ concentration group	Clinical signs	References
Subgroup: primary				
2-Ethyl-1-hexanol	Inhalation, exposure, 4 h: constant concentrations: (1.5, 10, 20 ml/m^3) or fluctuating concentrations (time-weighted average 1.5, 10, 20 ml/m^3)	Constant concentrations: 7 males without and 12 males with sMCS	$\geqslant$10 ml/m^3: self-reported nasal and eye irritation and perceived odor intensity increase; no difference between subjects with and without sMCS	van Thriel et al. (2005)
Subgroup: secondary				
2,6-Dimethyl-4-heptanol	Inhalation, exposure for 15 min	12	Eye irritation at 5 and 10 ml/m^3, nose and throat irritation at 10 ml/m^3	Silverman et al. (1946)
4-Methyl-2-pentanol	Inhalation exposure for 15 min	12	Eye irritation at 50 ml/m^3, nose and throat irritation >50 ml/m^3	Silverman et al. (1946)

sMCS: self-reported multiple chemical sensitivity.

- These materials have no or low sensitizing potential. Available data for five of the substances show that they do not possess a sensitization potential. However, for 3,6-dimethyl-3-octanol, a low sensitization potential in humans cannot be excluded. Saturated alcohols do not form hydroperoxides. They oxidize and become aldehydes or ketones. The use of these materials under the declared levels of use and exposure will not induce sensitization. For those individuals who are already sensitized, there is a possibility that an elicitation reaction may occur. The relationship between the no effect level for induction and the no effect level for elicitation is not known for this group of materials.
- Based on the lack of structures, which could absorb UVA or UVB light, and review of phototoxic/photoallergy data, the alcohols with saturated branch chains would not be expected to elicit phototoxicity or photoallergy under the current conditions of use as a fragrance ingredient.
- The 15 compounds tested have a low order of acute toxicity.
- The seven branched chain saturated alcohols and three of their metabolites (see Tables in Section 5.2) tested were of low systemic toxicity after repeated application. Changes indicative of enzyme induction in the liver (liver enlargement), peroxisome proliferation and alpha-2u-nephropathy in male rats have been observed at doses of 60 mg/kg body weight/day and more. The lowest NOAEL of all the subacute and sub-chronic oral studies available, which were performed with five of the substances under review and the metabolite *4-hydroxy-4-methyl-2-pentanone*, is 10 mg/kg body weight/day for 3,5,5-trimethyl-1-hexanol. This value is taken as representative for all members of the group as a worst-case. The database does not allow a definite conclusion that the toxicity after dermal application is lower than after oral application by gavage (oral bolus dose vs. slow uptake via the skin). However, at least 3,4,5,6,6-pentamethylheptan-2-ol had a much higher systemic NOAEL of 1000 mg/kg body weight/day in a subacute dermal study compared to the lowest oral NOAEL of 10 mg/kg body weight/day mentioned above. Several subacute and subchronic inhalation studies showed a lowest NOAEL of 120 ml/m^3 for 2-ethyl-1-hexanol corresponding to a dose of 175 mg/kg body weight/day, assuming a body weight of 261 g, a minute volume of 0.2 l for a rat (Bide et al., 2000) and 100% retention. Comparing the oral worst-case NOAEL of 10 mg/kg body weight/day to the worst-case daily uptake of 0.14 mg/kg body weight/day which was estimated for 3,4,5,6,6-pentamethylheptan-2-ol (100% dermal absorption assumed as worst-case) the margin of safety is 70 (100% oral absorption is assumed as shown with 2-ethyl-1-hexanol). For the other compounds for which systemic uptake in consumers (Table 1) has been estimated by RIFM, the margin of safety is between 90 and 50,000. There is an adequate margin of safety for the alcohols under review when applied in consumer products at the current concentrations.
- With 3,5,5-trimethyl-1-hexanol adverse effects on reproduction were noted at a rather low oral dose (60 mg/kg body weight/day) with a NOAEL of about 10 mg/kg body weight/day. For this compound the estimated systemic dose is 0.0036 mg/kg body weight for consumers (Table 1), leading to a margin of safety of 2700. 2-Ethyl-1-hexanol induced fetotoxic and teratogenic effects at high doses of 1300 mg/kg body weight/day in rats, however, none of the group members tested induced adverse effects on fertility and development at doses or concentrations that were not toxic to the parental animals. It should be noted that in a dermal study with 2-ethyl-1-hexanol no adverse effects on development in rats were seen with the highest dose of 2520 mg/kg body weight indicating, that dermal exposure is less effective in producing adverse effects than oral exposure most probably due to the different pharmacokinetic behavior for both application routes.

Table 9
Eye irritation studies in rabbits.

Material	Method	Results	References
Subgroup: primary			
2-Ethyl-1-butanol	Single application, undiluted or diluted in water of propylene glycol, grading after 18–24 h, n.f.i.	Produced an injury of necrosis to 63–87% of the eye	Smyth et al. (1954)
2-Ethyl-1-hexanol	Single application of 0.005 ml, undiluted, grading after 18–24 h, n.f.i.	Severe burn	Carpenter and Smyth (1946)
			Smyth et al. (1969)
	Single application, one drop, undiluted, 50%, 25%, 12.5% solutions in oil, observations up to 96 h, one rabbit per concentration	Conjunctival redness and swelling, lacrimation, discharge, no effects on the cornea	Schmidt et al. (1973)
		Undiluted test substance: effects not reversible within 96 h 12.5% no effect	
	Single application of 0.1 ml, undiluted, observations after 1, 4, and 24 h, 2, 3, 4, and 7 days, 6 rabbits	Severe eye irritant	Scala and Burtis (1973)
		Median scores after 24, 72 h, and 7 days: 19, 20, 0 (Draize scores) Corneal dullness, opacity (widespread corneal opacity), and vascularization, irititis, conjunctival erythema, chemosis, and discharge	
	Single application of 0.1 ml, undiluted, observations after 24, 48, and 72 h, 6 rabbits	Persistent corneal effects	RIFM (1978b)
		Draize scores 24 h: cornea: 17.5, iris: 2.5, conjunctivae: 7.0 48 h: cornea: 10.8, iris: 0.8, conjunctivae: 7.0 72 h: cornea: 7.5, iris: 0.8, conjunctivae: 5.3	
	Single application of 0.1 ml, undiluted and solution in propylene glycol or water: 110, 14, and 21 days, 6 rabbits	Draize scores	Kennah et al. (1989b)
		100% solution: 51 (severe), 30%: 35 (severe/moderate), 10%: 39 (moderate), 3%: 30 (moderate), 1%: 9 (mild) Corneal swelling in % of control: 100% solution: 192%; 30%: 190%; 10%: 162%; 3%: 151%; 1%: 94%	
Isoamyl alcohol	Single application, undiluted or solution in water or propylene glycol, n.f.i.	Severe burn	Smyth et al. (1969) RIFM (1979c)
Isotridecan-1-ol (isomeric mixture)	Single application, undiluted and observations 1, 24, 48, 72 h and 7 days after application	Irritation was observed. In one animal slight corneal opacity and loss of corneal tissue	RIFM (2002b)
	Single application, undiluted, 0.5 ml	Small area of necrosis on the eye	Smyth et al. (1962)
	Single application, undiluted and observations 1 ant 24 h after application	Slight irritation	RIFM (1963d)
			RIFM (1963f)
	Single application of 0.1 ml, undiluted, observations after 1, 4, and 24 h, 2, 3, 4, and 7 days, 6 rabbits	Moderately irritating	Scala and Burtis (1973)
2-Methylbutanol	Single application, undiluted or solution in water or propylene glycol, observations and grading after 24 h, 6 animals	Resulted in injury where corneal necrosis was observed	Smyth et al. (1962)
	Single application, undiluted and observations after 24, 48, and 72 h, 6 animals	Turbidity at the cornea, inflammation on the iris, and redness, swelling, or secretion of the conjunctivae	RIFM (1979b)
Subgroup: secondary			
2,6-Dimethyl-4-heptanol	Undiluted, 0.5 ml application, n.f.i.	An average reaction, at most a very small area of necrosis resulting from 0.5 ml of undiluted chemical in the eye	Smyth et al. (1949)
	Single application, undiluted, observations after 24 h, and 72 h, 1 animal	Moderate; some conjunctivitis with some edema and corneal injury; score 10 after 24 h, returned to score 0	McOmie and Anderson (1949)

(*continued on next page*)

Table 9 (*continued*)

Material	Method	Results	References
		within 72 h	
3,7-Dimethyl-7-methoxyoctan-2-ol	0.1 ml of a solution of 1% in propylene glycol, single application, observations after 24, 48, and 72 h, 6 animals	No irritation 5/6 animals: erythema of the conjunctiva, 1/6 animals: chemosis of the conjunctiva No corneal or iris involvement Effects cleared within 3 days	RIFM (1973b)
4-Methyl-2-pentanol	Single application, undiluted or diluted in water or propylene glycol, grading after 18–24 h, n.f.i.	Severe burn from 0.005 ml	Smyth et al. (1951)
	Single application, undiluted, observations after 1 h, 24, and 72 h, 3 animals	Moderate; some conjunctivitis with some edema and corneal injury; score 11 after 1 h, 25 after 24 h, 17 after 72 h Returned to normal within 7 days	McOmie and Anderson (1949)
3,4,5,6,6-Pentamethylheptan-2-ol	Single application, undiluted, 0.1 ml, irrigation for 5 min after 4 s or 30 s, respectively, or without irrigation, observations after 1 h, 1, 2, 3, 7 days, 3 animals/group	moderately irritating Without irrigation 3/3 animals: hyperaemia of the conjunctiva after 1 h 1/3 animals: chemosis of the conjunctiva after 1 h 2/3 animals: corneal opacity after 1 h Returned to normal after 7 days 1/3 animals was sacrificed in a moribund state after 2 days (bacterial infection) Irrigation after 30 s 3/3 animals: hyperaemia and chemosis of the conjunctiva after 1 h Returned to normal within 2 days Irrigation after 4 s 2/3 animals: hyperaemia of the conjunctiva after 1 h Returned to normal within 1 day	RIFM (1984c)
Subgroup: tertiary			
2,6-Dimethyl-2-heptanol	Single application, undiluted, observations after 24, 48, 72 h, 8 days, 6 animals	Primary irritation index (PII): 29.8, moderate irritant After 24 h: 6/6 slight corneal opacity, 2/6 slight iris effects, 5/6 moderate conjunctival redness, 6/6 moderate conjunctival swellings, 3/6 conjunctival scars, which were not reversible within 8 days	RIFM (1979a)
3,6-Dimethyl-3-octanol[a]	10% (5 animals), 15% (6 animals), 50% (1 animal), undiluted (6 animals), solutions in 1.25% Tween 20, observations at 24, 48, 72 h	primary irritation index (PII): irritant 10%: 2.8 15%: 3.6 50%: 4.0 Undiluted: 3.6, ranges of grading: corneal opacity 0–1, iris swelling 0–1, redness and chemosis of conjunctiva 1–2, not reversible within 3 days	RIFM (1970)

n.f.i.: no further information.

[a] No relevant use was reported.

Table 10-1
Skin sensitization studies in humans.

Material	Method	Concentration	Subjects	Results	References
Subgroup: primary					
2-Ethyl-1-hexanol	Maximization test	4% in petrolatum	29 healthy volunteers	No sensitization reactions	RIFM (1976c)
Isoamyl alcohol	Maximization test	8% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1976b)
3-Methyl-1-pentanol	HRIPT	0.5% in alcohol SDA 39C	41 healthy volunteers	No sensitization reactions	RIFM (1973f)
3,5,5-Trimethyl-1-hexanol	Maximization test	8% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1977b)
Subgroup: secondary					
3,7-Dimethyl-7-methoxyoctan-2-ol	Maximization test	10% in petrolatum	27 healthy volunteers	No sensitization reactions	RIFM (1982b)
3,4,5,6,6-Pentamethylheptan-2-ol	HRIPT	15% v/v solution in ethanol SDA 39C (99%)	51 healthy male and female volunteers	No sensitization reactions	RIFM (1983c)
Subgroup: tertiary					
2,6-Dimethyl-2-heptanol	Maximization test	10% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1976b)
	HRIPT	2% in dimethyl phthalate	53 healthy volunteers (18 males and 35 females)	No sensitization reactions	RIFM (1969)
	HRIPT	5% in alcohol SDA 39C	45 healthy volunteers (33 females, and 12 males)	No sensitization reactions	RIFM (1971, 1972b)
3,6-Dimethyl-3-octanol[a]	Maximization test	20% in petrolatum	25 healthy male volunteers	Inconclusive because subjects reacted to other test material on the same Panel	RIFM (1972a)
	Maximization test	10% in petrolatum	25 healthy male volunteers	No sensitization reactions (this was a retest)	RIFM (1973c)
3-Methyloctan-3-ol[a]	Maximization test	10% in petrolatum	29 healthy male volunteers	No sensitization reactions	RIFM (1978a)

HRIPT: human repeated insult patch test.
[a] No relevant use was reported.

Table 10-2
Diagnostic patch tests.

Material	Method	Concentration	Subjects	Results	Reference
Subgroup: secondary					
3,7-Dimethyl-7-methoxyoctan-2-ol	Patch test	Concentration and vehicle not reported	218 patients with proven contact dermatitis were tested with 3,7-dimethyl-7-methoxyoctan-2-ol	2 positive reactions	Larsen et al. (2002)

Table 10-3
Skin sensitization studies in animals.

Material	Method	Concentration	Species	Results	References
Subgroup: secondary					
3,7-Dimethyl-7-methoxyoctan-2-ol	According to Food and Drug Administration of the United States of America in "Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics" 1959, p. 51, except that the test material was applied topically and not injected: induction: 10 applications with 2.5 or 5% topically, challenge: 2 weeks later with 2.5% in water	Applications 1–7: 5% (irritating), applications 8–10: 2.5%	Guinea pig (n = 10)	No delayed-type hypersensitivity	RIFM (1973d)
Subgroup: tertiary					
2,6-Dimethyl-2-heptanol	Maximization test	Induction: 10% in FCA (intradermal), challenge: 20% in acetone	Guinea pig (10 in test group, 10 in control group)	No sensitization reactions	Watanabe et al. (1988)

FCA: Freund's complete adjuvant.

- Available data on genotoxicity for eight alcohols and three metabolites do not show such a potential *in vitro* or *in vivo*. Due to the structural similarities of the members of this group of alcohols, and because both terpene alcohols (Belsito et al., 2008) and unsaturated branched chain alcohols (Belsito et al., 2008) did not show a genotoxic potential, no genotoxicity is expected for the other materials of the group.
- A valid carcinogenicity study showed that 2-ethyl-1-hexanol is a weak inducer of liver tumors in female mice. Mechanistic studies showed that 2-ethyl-1-hexanol is an activator of PPAR-alpha. These substances can contribute to liver carcinogenesis by increasing tumor promotion. The relevance of this mechanism for humans is still a matter of debate. While this mechanism cannot be completely discounted, it is reasonable to assume that humans are less sensitive than rodents. In view of the low use of 2-ethyl-1-hexanol in cosmetic products (0.1–1 tons/y) and the low systemic exposure estimated by RIFM (0.0005 mg/kg body weight/day), the margin of exposure is 100,000 compared to the NOAEL for liver carcinomas in mice of 50 mg/kg body weight, which is considered to be sufficient for a non-genotoxic compound.

Conflict of interest statement

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Table 11
Phototoxicity and photoallergenicity.

Material	Method	Concentration	Species	Results	References
Subgroup: tertiary					
2,6-Dimethyl-2-heptanol	0.025 ml/test site on the back (36 test sites, 2 cm^2), covered, 30 min later the test sites were exposed to UVA irradiation (320–400 nm, 1, 2.5, 5, 10, 20 J/cm^2), observations 4, 24, 48 and 72 h after irradiation	10% in 1:1 ethanol/acetone	6 healthy volunteers (females)	Not phototoxic	RIFM (1983a)
	Patch applied 48 h, 4 h after the removal of the patches the animals did receive: Group A: UVA (320–400 nm), 30 min Group B: UVB (280–370 nm), 15 min Group C: no irradiation, Group D: not pretreated and Radiated from both light sources, observations 4, 24, 48 h after the irradiation	10% in ethanol	Albino guinea pig (n = 8/group)	Not phototoxic, after 4 h 1/8 slight reaction (in each group), which was cleared within 24 h	RIFM (1981a)
	Photoallergy test: induction: 0.1 ml on 8 cm^2 of the test area, 15 min UVB, 4 h UVA (Westinghouse black light tubes, from a distance of 25 cm) every 2nd day, total nine times in 18 days, challenge: after resting time of 10 days 0.025 ml applied on both flanks, left flank irradiated as for induction, skin reading 24 and 48 h after challenge	10% in rectified alcohol	Guinea pig (n = 8/sex)	No photoallergenicity	RIFM (1981b)

Table 12
Summary of UV spectra data.

Material	UV spectra range of absorption (nm)
2-Ethyl-1-hexanol	Peaked at 210–215 Returned to baseline at 400 (with minor absorption 290–400)
Isoamyl alcohol	Does not absorb UV light
Isotridecan-1-ol (isomeric mixture)	Does not absorb UV light
2-Methylbutanol	Peaked at 200–215 Returned to baseline at 220–225
3-Methyl-1-pentanol	Peaked at 200–210 Returned to baseline at 280–290
2-Methylundecanol	Peaked at 200–205 Returned to baseline at 270–280
3,5,5-Trimethyl-1-hexanol	Does not absorb UV light
2,6-Dimethyl-4-heptanol	Does not absorb UV light
3,7-Dimethyl-7-methoxyoctan-2-ol	Peaked at 200–210 Returned to baseline at 400 (with minor absorption 290–400)
6,8-Dimethylnonan-2-ol	Peaked at 200–210 Returned to baseline 230–240 (with minor absorption 260–320)
3,4,5,6,6-Pentamethylheptan-2-ol	Peaked at 200–205 Returned to baseline 264–271
2,6-Dimethyl-2-heptanol	Does not absorb UV light

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.

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