FOREWORD INTRODUCTION

LINALOOL

CAS N°: 78-70-6

SIDS Initial Assessment Report

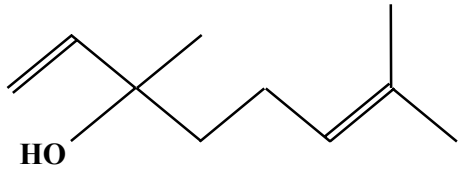
For

SIAM 14

26–28 March 2002, Paris, France;

1. Chemical Name:	Linalool
2. CAS Number:	78–70–6
3. Sponsor Country:	Switzerland
	National SIDS Contact Point in Sponsor Country: Dr Georg Karlaganis Swiss Agency for the Environment, Forests and Landscape CH–3003 Berne, Switzerland georg.karlaganis@buwal.admin.ch
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	The chemical was chosen by the Sponsor Company and the Swiss authorities in the frame of the ICCA Initiative. no testing (×) testing ( )
7. Review Process Prior to the SIAM:	
8. Quality check process:	
9. Date of Submission:	Deadline for Circulation: 1 February 2002
10. Date of last Update:	Date of Circulation:11 February 2002 (To the OECD Secretariat)
11. Comments:	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-70-6
Chemical Name	Linalool
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Linalool has an acute oral mammalian LD_{50} close to 3,000 mg/kg bw; the acute dermal toxicity is ≥ 2,000 mg/kg bw. After inhalation exposure of mice and man, slight sedative effects were observed; however a dose response characteristic could not be determined. Linalool is irritating to the skin, based on animal studies, and is a mild irritant from human experience. It may be moderately irritant to the eyes at the same concentration where it produces nasal pungency. Linalool is considered not to be a sensitizer. The incidence of dermal reaction to Linalool is below 1% in naïve probands (not knowingly pre-sensitized) while in subjects pre-sensitised to fragrances it is up to 10%.

In a 28-day oral rat study (72.9% linalool) findings were increased liver and kidney weight, thickened liver lobes and pale areas on the kidneys and in females only hepatocellular cytoplasmic vacuolisation. Other findings were related to local irritation of the gastro-intestinal tract. Based on the effects on liver and kidney a NOAEL of 160 mg/kg bw/d (equivalent to 117 mg/kg bw/d linalool) was derived. In this study no effects on male and female gonads were found.

Linalool was not mutagenic in seven out of eight bacterial tests nor in two (one *in vitro* and one *in vivo*) mammalian tests; the one positive bacterial result is estimated to be a chance event.

Linalool (72.9%) was tested in a reproduction screening test (non-OECD). The NOAEL for maternal toxicity based on clinical signs and effects on body weight and food consumption was 500 mg/kg bw/d (equivalent to 365 mg/kg bw/d linalool). The NOAEL on reproduction toxicity and developmental toxicity is 500 mg/kg bw/d (equivalent to 365 mg/kg bw linalool), based on the decreased litter size at birth and pup morbidity/mortality thereafter.

Linalool seems not to be an immunotoxicant according to one animal study.

Environment

Linalool is a liquid with a vapour pressure of approx. 0.2 hPa (at 23.5 degree C), a water solubility of 1589 mg/l (at 25 degree C) and a Log Kow of 2.97 (at 23.5 degree C).

Most linalool, both natural and synthetic, is released to the atmosphere, where it is rapidly degraded abiotically with a typical half-life below 30 minutes. In the aquatic compartment, linalool is readily biodegraded under both aerobic and anaerobic conditions, the same is predicted for soil and sediment. Linalool does not bioaccumulate to a major extent.

In acute aquatic ecotoxicity tests Linalool had a 96 hours LC_{50} value of 28 mg/l in fish, an 48 hours EC_{50} for

daphnia of 20 mg/l and for algae an 96 hours EC_{50} of 88 mg/l. It had low toxicity to micro-organisms, from activated sludge to various species of bacteria and fungi, with most reported NOECs ≥ 100 mg/l. Based on the lowest acute EC_{50} for daphnia, an aquatic freshwater a PNEC of 200 µg/l is derived.

The NOEL of linalool on the germination and initial growth of terrestrial plants was 100 mg/l. A host of data show both contact and fumigant toxicity against insects; as an acetylcholinesterase inhibitor, it paralyses and ultimately kills insects at high concentrations. These effects are not easily quantifiable

Exposure

Worldwide, approximately 12,000 t linalool *per annum* are estimated by industry to be produced, while natural biosynthesis through plants, mostly herbs, spices, trees and citrus fruits, is higher by dimensions. More than 95% of synthetic linalool is used for its fragrance and odorant qualities in cosmetics, soaps, perfumes, household cleaners, waxes and care products, while only approximately 1% is added to food and beverages for aroma and flavouring. Only two measured environmental concentrations have been located, one for water from a relatively polluted European river, of up to 0.11 µg/l, and one for air from boreal forests in Finland, of up to 120 ppt during the summer peak of biogenic linalool release.

Chemical production workers are rarely exposed to linalool, due to *quasi*-closed synthesis; where direct contact is possible, standard occupational hygiene measures limit exposure. The public, in contrast, is widely exposed to linalool, both from natural and synthetic sources, as an ingredient of formulated food and beverages, cosmetics and household products, but also as a natural constituent of fruits and spices. Oral exposure to linalool from formulated food products was estimated at up to 72 µg/kg/d for Europe and the USA; adding linalool from natural sources may possibly double this, resulting in an estimated maximal daily intake of 140 µg/kg/d. This maximum corresponds to approximately one-quarter of the upper limit of the ADI. Inhalative exposure to linalool cannot be reasonably quantified, particularly for urban and indoors environments. Due to its odorant or fragrance function, short-term inhalative exposure will be above the olfactory threshold of approximately 1 ppm, but this is predicted to decline rapidly due to abiotic degradation.

NATURE OF FURTHER WORK RECOMMENDED

Currently not a candidate for further work.

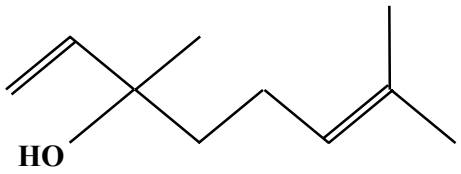
SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number:	78–70–6	dl-Linalool
	126–90–9	d-Linalool; (S)-(+)-Linalool
	126–91–0	l-Linalool; (R)-(–)-Linalool

IUPAC Name: Linalool
Molecular Formula: C_{10} H_{17} OH
Structural Formula:



Molecular Weight: 154.24 g/mol
Synonyms: 3,7-Dimethyl-1,6-octadien-3-ol

Linalyl alcohol
allo-Ocimenol
2,6-Dimethyl-2,7-octadien-6-ol
Licareol (l-Linalool)
Coriandrol (d-Linalool)

1.2 Purity/Impurities/Additives

≥ 96% w/w (synthetic dl-linalool, minimum specification)

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value
Physical state	
Melting point	< 20 °C
Boiling point	198 – 199 °C
Relative density	0.858 – 0.868 g/cm^3
Vapour pressure	~ 0.2 hPa (23.5 °C)
Water solubility	854 mg/l (23.5 °C) – 1589 mg/l (25 °C)
Partition coefficient n-octanol/water (log value)	log P_{OW} = 2.97 (23.5 °C)
Henry's law constant	$1.9 \cdot 10^{-5}$ atm·m^3/mol
BCF Bioconcentration Factor	28 (QSAR estimate)
Surface Tension	20.969 mN/m (20 °C)
Flash Point	55 °C

Linalool is an appreciably water-soluble organic compound, liquid at room temperature. It is a natural substance, a terpenoid alcohol that is biosynthesised as d-, l- or dl-linalool by a host of plants, specifically many herbs, spices and fruits. Linalool has been produced for many years in high volumes, either from natural precursors or through total chemical synthesis. It is used in vitamin E synthesis, added to processed food and beverages, to perfumes, cosmetics and soaps as well as to household detergents and waxes for its flavouring and fragrant properties. Linalool, mainly from natural sources, is also used traditionally for stored-food pest control.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Production. Linalool can be either a) extracted from linalool-biosynthesising plants respectively distilled from their essential oils or b) part-synthesised from natural pinene extracts or c) totally chemically synthesised.

a) Extraction of linalool is based on fractional distillation of essential oils of mainly bois de rose, shiu (Chinese camphor) or coriander.

b) Partial synthesis is based either on α- or β-pinene. α-Pinene is hydrated selectively to *cis*-pinane and subsequently oxidised to a *cis/trans* mixture of pinane hydroperoxide, which is in turn reduced to pinanols and the latter finally pyrolysed to the respective d- or l-linalools.

c) Total chemical synthesis of linalool is by way of 2-methyl-2-hepten-6-one. It may start from reaction of acetylene with acetone resulting in 3-methyl-1-butyn-3-ol, which is hydrated over a palladium catalyst to 3-methyl-1-buten-3-ol, that is in turn reacted with either diketene or acetic acid ester to the acetoacetate and the latter thermally reacted to 2-methyl-2-hepten-6-one. Alternatively, 3-methyl-1-buten-3-ol is reacted with isopropenyl methyl ether to 2-methyl-2-hepten-6-one. In a third synthetic pathway, isoprene hydrochloride is reacted with acetone in the presence of either an alkaline condensating agent or organic bases as catalysts to 2-methyl-2-hepten-6-one. 2-Methyl-2-hepten-6-one is finally reacted with acetylene to dehydrolinalool, which is partially hydrogenated. Industrial linalool is generally the dl-racemate.

Volumes. The industry estimate for worldwide linalool production in the year 2000 is 12,000 t. Over half of this, approx. 6,600 t/a, is reckoned to be made through chemical synthesis while the rest, approx. 5,400 t/a, is produced from natural plant terpenes. Most of the chemically synthesised linalool and practically all of the extracted is used as a fragrance or flavouring agent. (Use in vitamin E synthesis, as listed in some reference works, does not normally involve linalool but its precursor dehydrolinalool, continuing by way of isophytol.) A recent (1999) FAO/WHO Joint Expert Committee on Food Additives (JECFA) publication assesses the amount of terpene alcohols used for food and beverage flavouring in the USA and Europe at approx. 75 t/a, most of which would consist of linalool and its ester, linalyl acetate. Based on these data, it is estimated that more than 95% of the total worldwide linalool production is used for its fragrance and odorant properties, in perfumes, cosmetics, soaps, household detergents, furniture care products and waxes. In addition, some linalool has insecticidal use in formulated sprays and dips for pet ectoparasite control. Traditionally, a lot of linalool, beside other terpene compounds, has been (and still is) used in the form of natural products such as dried herbs as a fumigant for the storage of cereals and pulses against insect pests; however, this use cannot be reasonably quantified. Nor is the overall natural biosynthesis and release of linalool easy to estimate. Over 200 species of plants produce d-, l- or dl-linalool, mainly from the families Lamiaceae (mints, scented herbs), Lauraceae (laurels, cinnamon, rosewood) and Rutaceae (citrus fruits), but also birch trees and other plants, from tropical to boreal climate zones. It was also found in some fungi. There are recent (2000) quantitative measurement data of monoterpene and linalool emissions from boreal forests in Finland, based on which an overall estimate for linalool emissions from such forests in the northern hemisphere can be conservatively extrapolated to 93,000 t/a. While this does not take account of biosynthesis by mediterranean, subtropical and tropical vegetation types on all continents, where most of the plants listed above belong, it stands to reason that natural linalool biosynthesis is larger by dimensions than industrial production.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

At 20 °C linalool is a liquid with an appreciable water solubility (850–1590 mg/l), a relatively low vapour pressure (~ 0.2 hPa) and, correspondingly, a rather small Henry's law constant of 1.9×10^{-5} atm×m^3/mol; in confirmation of the latter, the modelled water-air partition coefficient is 1081. In aqueous solution linalool will not be ionised at any environmentally relevant *p*H range. In addition, based on four experimental values, the *n*-octanol/water partition coefficient is ~ 2.95 (2.84–3.1). The calculated organic-carbon/water partition coefficient (K_{OC}) is in the range of 15–60, similar to both the modelled bioconcentration factor of 28 and a fish-water partition coefficient of 46.7. Based on these essential distribution data, linalool is predicted to partition mainly to the aquatic and soil compartments, depending on the original entry into the environment, while both sediment and biota are considered of secondary importance (see also table 2).

Table 2: Dynamic environmental distribution of Linalool using a level III generic fugacity model [Mackay *et al.:* Level III, Fugacity-based Environmental Equilibrium Partitioning Model, v. 2.2 (1999). Environmental Modelling Centre, Trent University, Canada].

Compartment	Release			
	100 % to air	100 % to water	100 % to soil	33 % each to air, water and soil
Air	82.6%	0.01%	0.002%	0.1%
Water	2.7%	99.8%	1.5%	42.9%
Sediment	0.005%	0.2%	0.003%	0.1%
Soil	14.7%	0.02%	98.5%	56.9%

The atmospheric compartment is a special case, as most of the industrial linalool is used for its fragrance respectively odorant qualities and as the predominant part of natural linalool is released by plants into the air. A set of ambient air measurements from biogenic release in Finnish forests ranged from 5–10 pptv in spring to 50–120 pptv in summer to 10–15 pptv in autumn. For global environmental exposure the atmosphere is certainly the most important compartment. However, empirical and modelled fate data for linalool show rapid physico-chemical degradation for linalool in air; an experimental atmospheric fate study concluded that "at typical ozone concentrations ... atmospheric half-lives ... are ≤ 30 min for linalool". The high reaction rate with both ozone and hydroxyl and nitrate radicals is the reason why for linalool, in spite of a high initial loading, the atmosphere is not considered a compartment of concern, whereas water and soil potentially are.

Based on the partition constants, non-degraded atmospheric linalool will distribute to moist soil and water while nearly all the linalool released to water or soil will remain there. In the aquatic compartment, linalool may be expected to be rapidly eliminated as it is known to be well and ultimately biodegradable from several ready and inherent aerobic as well as an anaerobic test (table 3). The sterile, abiotic control of the Modified MITI I test shows no substance loss at all, indicating that the elimination observed was due to genuine biodegradation. Additional studies show good biodegradation rates and pathways of linalool by the common mold *Aspergillus niger* and the bacterium *Pseudomonas incognita*.

Table 3: Biodegradation test data for Linalool.

Test system	Results	Notes
Modified MITI Test I	**65% (10 d, 100 mg/l)** **80% (28 d, 100 mg/l)**	**readily biodegradable***
Closed Bottle Test	**64.2% (28 d, 2 mg/l)**	**readily biodegradable**
BOD_5/COD Ratio	BOD_5 = 1531 mg/g COD = 2808 mg/g BOD_5/COD = 0.55	readily biodegradable
Aerobic Test	0% (100 h, 40 mg/l) ≥ 95% (160 h, 40 mg/l)	readily biodegradable after a lag phase of ~100 h using soil extract as inoculum
Zahn-Wellens Test	26% (3 h, 400 mg DOC/l) 100% (13 d, 400 mg DOC/l)	well inherently biodegradable
Aerobic Test	90% (28 d, 100 mg/l, BOD) 99 % (28 d, 100 mg/l, TOC) 100% (28 d, 100 mg/l, GC)	full primary degradation as evidenced by GC and very high mineralisation rate as measured by BOD and TOC
Anaerobic Test	low degradation rate in the absence, but high degradation rate in the presence of nitrate (10 d, 0.5 mg/l)	anaerobically well degradable in the presence of nitrate, using activated sludge and mud as inoculum

* Note. The studies considered most reliable are indicated in bold.

The prediction of rapid biodegradation is corroborated by environmental monitoring data showing over 98% elimination through filtration of river water through a natural river bank and a similar rate for aerobic slow sand filtration. Even in the case of a sewage treatment plant with unsatisfactory overall degradation performance, linalool was only detected twice in the undiluted effluent at a concentration of 0.25 respectively 0.11 µg/l. Regarding aquatic environmental concentrations, there is one relatively recent (1995) determination of 0.11 µg/l from a river in the heavily populated and industrialised Ruhrgebiet in Germany. In an older (1976) overview, linalool was reported from drinking water, however, without any concentration nor analytical method given.

In conclusion, linalool is considered to be well biodegradable in sewage works and in the aquatic compartment itself.

One published environmental concentration from a relatively polluted stretch of a European river is 0.11 µg/l. No data have been located regarding environmental fate or concentrations of linalool in seawater.

No environmental monitoring data could be retrieved for the soil compartment. However, in one semi-field study where soil samples were mixed with sewage sludge and terpenes including linalool, then stored outside with regular collection of the leachate and analysis of the soil at the end of the study, linalool was never detected, neither in the soil nor in the leachate. The authors speculate that elimination "may be due to volatilisation losses"; they are more positive that "leaching does not appear to be a significant fate process". However, taking into account the relatively low vapour pressure on one hand and, on the other, the biodegradation results using extracts from two forest soils (table 2), which show rapid and nearly complete microbiological elimination of linalool subsequent to a 100-hour lag phase, biogenic removal of linalool from soils seems at least as likely. This proposed elimination process is supported by tests with the common mold *A. niger* and the bacterium *P. incognita,* both of which have been shown to readily metabolise linalool. Therefore, while it is uncontested that soil is the receiving compartment for a substantial part of linalool rel-

eased into the environment, no major concentrations are expected due to rapid biological degradation or, possibly, evaporation processes. No monitoring data have been found for freshwater or marine sediments.

2.3 Human Exposure

2.3.1 Occupational Exposure

Industrial releases of linalool may occur from the sites of production and through use in industrial processes. In the case of the Lalden, Switzerland, plant producing linalool for the reporting company F. Hoffmann-La Roche Ltd, total synthesis of linalool proceeds in dedicated closed systems. Liquid and gaseous waste streams, including the distillation residues, are incinerated in approved installations, aqueous effluents are treated in an industrial sewage works and spent catalysts are returned to the producer for recycling.

Exposure of workers to linalool is possible during sampling, manual extraction of spent catalyst and filling of storage or transport containers. Standard industrial hygiene measures, *viz.,* safety goggles, protective clothing and gloves, respiratory protection and local exhausts, are being routinely applied during these activities.

For downstream industrial processes, *e.g.,* chemical synthesis or incorporation in cosmetics or household products, safety data sheets give professional users advice on substance properties and exposure protection. There are no recommended occupational exposure limits for linalool.

2.3.2 Consumer Exposure

Consumers, in contrast, are directly exposed to linalool. It is an ubiquitous component of both natural products, *e.g.,* citrus or other fruits, spices and herbs, but also grapes and wines, as well as consumer goods containing linalool, from processed food and beverages to perfumes, cosmetics, soaps, detergents and waxes. Due to this wide dispersive use, consumers will be exposed to linalool both by oral and inhalative route. In general, oral exposure will depend heavily on geographic and cultural background, as the use of agrumes and other fruits and particularly fresh spices in daily nutrition varies with availability, acceptance and culinary tradition. Additionally, linalool is known to be rapidly formed by enzyme-catalysed or aqueous hydrolysis from its esters, some of which are also ubiquitous plant terpenoids and important flavours and odorants in their own right. In a recent (1999) publication, it was estimated that approximately one-third of total dietary linalool exposure was due to such ester hydrolysis.

There are two recent (1999, 2001) estimates of human exposure to linalool added to food and beverages for Europeans and North Americans: Based on production and use volumes of linalool and eight of its common esters in food and beverages, the daily *per capita* intake of total linalool in the 1999 study was extrapolated to 72 µg/kg/d for Europeans, respectively 21 µg/kg/d for US Americans. The 2001 estimate, based on data published by the FAO/WHO Joint Expert Committee on Food Additives (JECFA), calculated a daily intake of 0.0438 mg/kg/d for both US and EU populations, which falls right in-between the former values. Exposure to linalool from natural sources (citrus fruits, herbs and spices) is even harder to estimate considering variability of intake, but on average probably not higher than the above amounts. This would set a tentative upper limit for daily intake at roughly 40–140 µg/kg/d for Europe and the US. In 1999, JECFA revised its Acceptable Daily Intake for the sum of alicyclic and acyclic terpenoid alcohols in food and beverages, with the new value of 0–0.5 mg/kg/d, doubling the former upper limit of 0.25 mg/kg/d.

Regarding inhalative exposure, no quantitative monitoring data have been located for linalool concentrations in indoor air. In volatilisation tests with furniture waxes, linalool was indentified in the headspace of both wax- and water-based compounds, showing some (unquantified) distribution to air. In a very brief abstract in the 1995 Annual Report from the EU JRC Environment Institute, subsequent to spraying a liquid mixture of terpenoids and octane containing 9% linalool in a room, a linalool concentration corresponding to slightly above 4% (i.e., nearly half of the original) was detected in the room air and approx. 2% (not quite a quarter) in the house dust; although the time interval between spraying and sampling is not stated in the abstract, the findings are taken to reflect rapid partitioning between air and house dust and to show appreciable abiotic atmospheric degradation. Regarding ambient air, biogenic terpenoid emissions from boreal forests were monitored in Finland; peak linalool air concentrations within the forest in summer were approximately 50–120 ppt by volume. No other outdoors air monitoring data have been found.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Terpenoids are a large and highly varied group of phytochemicals that are produced in huge quantities by plants from boreal to tropical ecosystems for defense against herbivores and parasites. Such chemicals must by needs have an effect on the target animals, meaning that some toxicity is only to be expected. On the other hand, many edible fruits, herbs and spices are highly estimated precisely because of their contents of flavouring compounds; moreover, many are traditionally used for their pharmacological properties. This also holds for linalool, which is produced in high amounts for its flavour and fragrance qualities. A relatively large body of diverse toxicity data exists for synthetic and extracted linalool. Some of these are straightforward toxicity tests while others give circumstantial information relating to metabolism, physiological adaptation and pharmacological effects.

Based on experiments with rats using ^{14}C-labelled substance, linalool is rapidly absorbed from the intestinal tract following oral uptake respectively gavage; judging from the delay in faecal excretion, intestinal absorption is complete. Subsequent to absorption, linalool is metabolised rapidly, with urinary excretion of ^{14}C activity starting without delay. Several hours after gavage, substantial amounts of radioactivity were detected in the expired air as $^{14}CO_2$, evidencing complete intermediary metabolism. Faecal excretion of radioactivity was delayed and found mostly between 36 and 48 hours after dosing, suggesting entero-hepato-biliary re-circulation; this re-circulation was confirmed in a second experiment involving cross-linking a treated and an untreated rat with a biliary-to-intestinal cannula and subsequent radio-analysis. Overall, approximately 60% of the total excreted dose was found in urine over 72 hours after administration; approximately 23% of activity was detected in exhaled air and approximately 15% was found in the faeces; there is no indication of tissue accumulation of linalool whatsoever. The study suggests that large doses of oral linalool will be metabolised in the rat by conjugation and excretion in urine and bile, while a substantial proportion will enter intermediary metabolisms up to the formation of carbon dioxide and pulmonary excretion. Entero-hepato-biliary re-circulation may have the effect of enhancing the metabolic load on the liver over a certain period.

Conclusion

The relatively rapid overall excretion of linalool and its metabolites suggests no long-term hazard from chronic concentrations normally found in foods.

3.1.2 Acute Toxicity

Studies in Animals

Route/Species	Results	Notes
oral:		
Rat	LD_{50} = 2790 mg/kg bw (2440–3180, 95% CL)	old (1964) but detailed study with statistical evaluation
Mouse	LD_{50} = 3120 mg/kg bw	
Mouse	LD_{50} = 3000 mg/kg bw	
inhalative:		
Mouse	sedative effects but no deaths	detailed study using essential lavender oil (cont. 37.3% linalool, 41.6% linalyl acetate); however, no measured concentrations are given
NA	LC_{50} < 2.95 mg/l	no other information given
dermal:		
Rat	LD_{50} = 5610 mg/kg bw	
Rabbit	LD_{50} > 5000 mg/kg bw	
Rabbit	LD_{50} = 2000 mg/kg bw	
NA	LD_{50} ~ 3578–8374 mg/kg bw	
other routes:		
Rat, i.p.	LD_{50} = 307 mg/kg bw	
Mouse, i.p.	LD_{50} = 340 mg/kg bw	
Mouse, s.c.	LD_{50} = 1470 mg/kg bw	
Mouse, i.m.	LD_{50} = 8000 mg/kg bw	

Three acute oral LD_{50} values for rat and mouse are in the narrow range of 2,790–3,120 mg/kg bw. No reports regarding human intoxication due to linalool have been located.

The only inhalative LC_{50} located, from a 1985 EPA Fact Sheet, is given as < 2.95 mg linalool/l air, corresponding to just below 0.2% both by mass and volume, or just below 2,000 ppm; there is no indication of species, time of exposure or NOEC. The same source, however, gives a probably inhalative avian LC_{50} > 5,620 ppm, clearly higher but again without circumstantial data. In a behavioural inhalative study with mice using essential oil of lavender containing 37.3% linalool and 41.6% linalyl acetate, sedative effects were noted but not a single death occurred; while the experimental setup is described in detail there are no measurements or extrapolations of linalool concentration, either. On the other hand, it was shown in this study that linalyl acetate is rapidly hydrolysed to linalool.

Studies in Humans

In a recent (1998) EEG study in human subjects, a tendency of decreasing β-waves (evidencing sedation) was seen during inhalation of l- and dl-linalool-enriched air, but a contrary tendency of increase was noted with d-linalool.

Conclusion

In conclusion, while inhalative effects of linalool can be qualitatively described, no unambiguous quantitative effect concentrations can be derived due to lack of dependable data.

Reported dermal LD_{50} values range from 2000 to possibly over 8000 mg/kg bw, which is comparable to the oral span. However, due to the very brief references lacking detail, none of these results could be fully validated.

For other routes, the two subcutaneous and intramuscular data bracket the oral toxicity range while two intraperitoneal LD_{50}s show an approximately 10-fold higher toxicity in comparison with oral administration, which again seems reasonably consistent with the oral data.

3.1.3 Irritation

Skin Irritation

Species	Results	Notes
Rabbit	Irritating	OECD 404, ECETOC Irritation Chemical Reference Databank
Rabbit	severely irritating	nonstandard detailed test
Rabbit	"mild" effects	500 mg, 24 h
Rabbit	"severe" effects	100 mg, 24 h
Rabbit	irritating	occlusive, 24 h, intact and abraded skin
Rabbit	not irritating	occlusive, 24 h, intact and abraded skin
Guinea pig	moderately irritating	nonstandard detailed test
Guinea pig	moderate	100 mg, 24 h
Minipig	not irritating	nonstandard detailed test
Man	mildly irritating	nonstandard detailed test, 32% in acetone
Man	"mild"	48 mg, 48 h
Man	"not irritating"	occlusive, 48 h, 20 % in petrolatum
Man	"not irritating"	occlusive, 0.4–20 % in different solutions
Man	"not irritating"	occlusive, 48 h, 8 % in petrolatum

Primary skin irritation scores were compiled and scrutinised by ECETOC experts for the Irritation Chemical Reference Databank (1996). While this does not constitute an original source, the original data were received from participating companies and may themselves be confidential. In order to ensure the quality of the tests and data, ECETOC defined and applied stringent criteria, which is why these results are accepted here. In all three reported OECD 404 tests, linalool was irritating to rabbit skin, with Primary Irritation Indices above 3 in two instances and above 2 in the third. This conclusion is confirmed by four out of five other rabbit data located, although only one of these five results is based on a regular publication that can be evaluated, while the other four are two data points from RTECS (citing an older Czech publication) and two internal reports from the cooperating company; only one of these reports gives "not irritating". In guinea pigs, linalool is moderately irritating while in miniature pigs it is not irritating. In man, out of five tests, three using up to 20% concentration resulted in "not irritating", while two other tests including a detailed publication showed mild irritation. As in the rabbit, the standard species for the OECD skin irritation test, the criteria for irritation were consistently fulfilled, and as, in addition, two human studies were also positive.

In conclusion, linalool must be regarded as a skin irritant and should be seen as mildly irritant for man.

Eye Irritation

Linalool caused no irritation in an OECD 405 test. In contrast, in another, not fully referenced test, linalool caused "moderate" eye irritation at a dose of 0.1 ml. In a relatively recent study with human anosmic (loss of sense of smell) and normosmic (normal sense of smell) volunteers, linalool produced eye irritation at a measured vapour concentration of ~ 320 ppm; incidentally, this was also the approximate threshold for nasal pungency in anosmics. While there was no significant difference between normosmics and anosmics in their reaction, linalool failed to produce an eye irritation threshold in more than 30% of both groups.

In conclusion, linalool is at most a moderate eye irritant; moreover, in about a third of human subjects it did not cause any eye irritation at 320 ppm.

Respiratory Tract Irritation

Apart from the data on nasal pungency reported above, with a threshold of ~ 320 ppm, no data were located regarding irritation of the respiratory pathways. The olfactory threshold is reported to be far lower, at ~ 1 ppm.

3.1.4 Sensitisation

Species	Results	Notes
Guinea pig	"not sensitising"	
Man	0.5% positive/792 patients	patch test series, 10% linalool in petrolatum
Man	1 positive/119 patients	patch test series, 10% linalool in petrolatum
Man	3 positive/1781 patients	patch test series, a total of 37/1781 were positive for fragrances
Man	1 positive/16 sensitised to Peru balsam; 2 positive/253 controls	
Man	0/25 patients	maximisation test
Probably man	"not a sensitiser"	
Man	"not sensitising"	maximisation test, 20% in petrolatum
Man	"not sensitising"	maximisation test, 8% in petrolatum
Man	"extremely weak potency"	human sensitisation potency class
Mouse	"weak"	local lymph node assay class
Man	Unclear	
Probably man	2-linalool caused contact sensitisation	

In a 1972 series of Draize tests with fragrance materials, linalool was not a sensitiser in guinea pigs. This conclusion is borne out by a host of patch tests performed in a Dutch dermatology/allergy clinic: less than 1% (0.17–0.8%) of naïve (i.e. not pre-sensitized) subjects reacted positive to linalool while among patients pre-sensitised to some fragrance materials the incidence was nearly 1 in 10. In confirmation, linalool at concentrations up to 20% was consistently found not to be a sensitiser in maximisation tests. In a review that assigned human sensitisation potency classes based on literature data, linalool was characterised as being of "extremely weak potency"; in the same publication, this human potency class was compared with allergenic potency based on murine local lymph node assays, where again linalool had "weak" potency. There is one report of sensitisation to

the chemically related 2-linalool. In conclusion, while there are some cases of confirmed allergy to linalool, the incidence of dermal reactions is below 1% in patch challenges and it was not a sensitiser in three maximisation tests. This confirms negative findings in guinea pigs and "weak" potency in mouse *ex vivo* tests.

In conclusion, linalool is considered not to be a sensitizer.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Species	Results	Notes
Rat, males	NOAEL = 500 mg/kg bw/d	linalool, gavage, 64 d; effects were limited to changes in liver enzymes, which is interpreted as physiological adaptation
Rat	NOAEL = 160 mg/kg bw/d LOAEL = 400 mg/kg bw/d	72.9% linalool in essential oil, gavage, 28 d; effects were limited to changes in serum proteins and liver and kidney histology, all considered of low severity
Rat	LOAEL = 50 mg/kg bw/d	mix with unknown proportion of linalool, feed admixture, 84 d; effect limited to "slight growth retardation in males"
Rat	LOAEL = 1500 mg/kg bw/d	linalool, gavage, 5 d
Mouse	LOAEL = 375 mg/kg bw/d	linalool, gavage, 5 d; effects at this dose described as "minimal"
Mouse	MTD = 125 mg/kg bw/d	linalool, i.p., 14 d

In a repeated dose study, Crl:CD/BR rats received 160, 400 or 1000 mg/kg bw/d linalol (72.9% linalool in essential oil) during 28 days. One male and one female of the high-dose group were found dead. Total protein/albumin was increased in males at 400 mg/kg bw/d and in both sexes at 1000 mg/kg bw/d. Calcium was increased at 1000 mg/kg bw/d in males only. Serum glucose levels were decreased in males at 400 and 1000 mg/kg bw/d. Liver weight was increased dose related and significantly at 400 and 1000 mg/kg bw/d. Kidney weight was increased in males at 400 mg/kg bw/d (relative kidney weight) and in all animals at 1000 mg/kg bw/d (absolute). Macroscopically this was accompanied by thickened liver lobes and pale areas on the kidneys. All treated female groups showed hepatocellular cytoplasmic vacuolisation while the high-dose males had an increase in degenerative lesions in the renal cortex. Thickening of the stomach mucosa with concomitant lesions in the nonglandular part of the stomach, with some erosion, subacute inflammation and acanthosis were reported in middle- and high-dose animals. The NOAEL derived was 160 mg/kg bw/d (equivalent to 117 mg/kg bw/d linalool) based on effects in liver and kidney.

In a single dose study focusing on effects of linalool on drug metabolizing enzymes, rats received 500 mg/kg bw/d linalool by gavage for 64 days. A NOAEL of 500 mg/kg bw/d based on changes to liver enzymes was derived. This value is considered reliable because this study, albeit old (1974), used pure linalool as a test substance, was reported in detail with a lot of information about methodology and full description of effects including statistics. The significant effects were limited to biphasic changes in liver enzymes and a slight increase in liver mass toward the end of the study. Based on detailed reasoning in the discussion of this publication, these effects are interpreted as a physiological adaptation to metabolise this load of linalool, rather than overt toxicity. This conclusion is supported by a detailed ADME study from 1974 using radiolabelled linalool (see Full SIDS Summary), where it was shown that subsequent to rapid absorption after oral administration,

linalool is metabolised by three pathways, one catabolic with complete intermediary metabolism leading to 23% of the radioactivity being exhaled as $^{14}CO_2$, another through glucuronidation and urinary excretion of approx. 60% and the third involving extensive hepato-biliary-enteric re-circulation with, eventually, approx. 15% excreted faecally. Urinary and pulmonary excretion start immediately respectively within few hours after dosing, whereas hepato-enteric re-circulation causes faecal excretion to be delayed for more than 24 hours. The authors expected this re-circulation of linalool to prolong and enhance the metabolic load on the liver.

From a 84 days study a LOAEL of 50 mg/kg bw/d was reported based only on a slight retardation in growth restricted to the young male rats. However, in this study mixed alcohols with an unknown proportion of linalool was used. Two short-term, 5-day oral repeat toxicity studies report LOAELs of 1500 mg/kg bw/d in rats and 375 mg/kg bw/d in mice, with the observed effects at the latter dose being described as "minimal". A 14-day intraperitoneal study finds a maximal tolerated dose of 125 mg/kg bw/d, which is consistent with the oral data.

The design of the other studies mentioned above are considered not to be representative for a repeated dose study due to the duration of the exposure or in case of the 84 days repeated dose toxicity study no clear information about the concentration of linalool used, is avaible.

Conclusion

In conclusion the lowest reliable NOAEL of 160 mg/kg bw/d (equivalent to 117 mg/kg bw/d linalool) could be derived from the 28-day rat study. This value is based on effects in liver and kidney (weight and macroscopically effects), whereas the NOAEL of 500 mg/kg bw/d from the 64 days repeated dose study was based only on effects on drug metabolizing liver enzymes.

Studies in Humans

In a recent (2001) review of human exposure through food, the NOEL for linalool was set at 500 mg/kg bw/d based on data for linalyl cinnamate, because certain findings for linalool proper arguing for a limit of 50 mg/kg bw/d were discounted. This NOEL of 500 mg/kg bw/d is also supported by the upper limit of the UN Joint FAO/WHO Expert Committee on Food Additives ADI for total terpenoid alcohols in food products of 0–0.5 mg/kg bw.

No occupational health problems related to linalool have been reported from the Lalden production plant.

3.1.6 Mutagenicity

Species	Results	Notes
Bacterial, *in vitro:*		
Bacillus subtilis, M45 (rec–), H17 (rec+)	positive	recombination assay, 10 µl/disc, no data re metabolic activation
B. subtilis, M45 (rec–), H17 (rec+)	negative	recombination assay, up to 17 µl/disc, no data re metabolic activation
Salmonella typhimurium, TA92, TA94, TA100, TA1535, TA1537	negative	Ames test, up to 0.25 mg/ml, with (S-9) and without metabolic activation
S. typhimurium, TA100	negative	Ames test, no concentration given, with and without metabolic activation
S. typhimurium, TA98, TA100	negative	Ames test, 100 µl, with (S-9) and without metabolic activation
S. typhimurium, TA98, TA100, TA1535, TA1537, TA1538	negative	Ames test, up to 1.5 µl/ml, with (S-9) and without metabolic activation
Escherichia coli, WP2 uvrA (trp–)	negative	reverse mutation assay, 0.125–1.0 mg/ plate, no data re metabolic activation
NA	negative	"NBP test" for alkylating activity
Non-bacterial, *in vitro:*		
Chinese hamster fibroblast cell line	negative	cytogenetic assay, 0.25 ml/ml, with (S-9) and without metabolic activation
Non-bacterial, *in vivo:*		
Mouse	negative	OECD 474, 1500 mg/kg (gavage, 48 h)

In vitro Studies

Apart from a single *Bacillus subtilis* recombination assay all other nine bacterial and non-bacterial tests located are negative. Specifically, a second *B. subtilis* assay, with the same strain characterisation as in the first positive test, also proved negative at even higher doses. Considering the overwhelming negative evidence from bacterial and a non-bacterial test systems (chromosomal aberration test), it is assumed that the positive result in the first recombination assay was a chance event.

In vivo Studies

In a mouse micronucleus assay linalool Swiss CD-1 mice received one single dose of 500, 1000 and 1500 mg/kg bw/d linalool. Mice were sacrified and samples were taken at 24 h and for the highest dose in addition at 48 h. As positive control 50 mg/kg bw/d of cyclophosphamide was used. There was no significant difference between any of the vehicle control and linalool dosages groups.

Conclusion

In conclusion, linalool in all probability has no mutagenic activity.

3.1.7 Carcinogenicity

In a 1973 carcinogenicity test in mice with a detailed protocol, thrice-weekly intraperitoneal administration and four different negative and positive controls groups, with 8 weeks exposure and 16 weeks post-exposure, no increased incidence of pulmonary tumours was observed at any linalool dose up to a maximum total of 3 g/kg. In an older (1960) co-carcinogenicity test with mice, one of three tumour promotors per group was administered dermally at a dose "sufficient to initiate skin tumour formation but, generally speaking, inadequate for complete carcinogenesis"; starting three weeks later, essential oil of bergamot (containing linalool as one of the principal alcohols) or 20% linalool in acetone were also administered dermally once a week for 30 weeks (total duration 33 weeks). While the essential bergamot oil did not further tumour development, 20% linalool in acetone "elicited a weak tumour-promoting response". In a more recent (1989) co-carcinogenicity test using female rats, with a detailed protocol and statistics, mammary tumours were induced with a single dose of the tumour-promoting agent DMBA and linalool was administered orally by feed (1%) over a total of 20 weeks. The linalool experimental group had both a lower incidence of mammary tumours and a longer median latency, but both effects were not statistically significant. The discrepancy between the co-carcinogenicity studies, "weak tumour-promoting response" *vs* a slight but non-significant tumour-inhibiting effect of linalool, cannot be unambiguously resolved due to the lack of detail in the older, weakly positive test. Specifically, there being no clear description of a full control (initial DMBA treatment plus vehicle administration) nor a statistical evaluation, but only one sentence stating the weakly positive outcome for linalool, the validity of this conclusion is doubted. Based on the far better documented 1973 intraperitoneal carcinogenicity and the 1989 oral feed co-carcinogenicity tests, both with ample details, comprehensive control groups and statistical data, there is no reason to suspect linalool of carcinogenic activity.

3.1.8 Toxicity for Reproduction

In a 1989 reproductive and developmental screening test according to old (1966) FDA guidelines under GLP, using essential oil of coriander with 72.9% linalool and 22.3% other identified terpenoids diluted with maize (corn) oil, female rats were treated once daily by gavage from 7 days premating for a maximum of 40 days (all animals killed at 4–5 days postpartum) while the males were not treated. In the dams, all dosages caused excess salivation, which was significant in the middle- (500 mg/kg bw/d) and high-dose (1000 mg/kg bw/d) groups. A significant number of high-dose dams had urine-stained fur. One or two of the high-dose group showed ataxia or decreased motor activity during treatment, which are considered toxic (pharmacological) effects of linalool. During the premating period, body weight gain and feed consumption were decreased in the high-dose group, but during gestation significant increases in absolute and relative body weight gain were seen in all three treatment groups including the low-dose group (250 mg/kg bw/d). Based on these results, 500 mg/kg bw/d is proposed as the maternal NOAEL while the NOEL was below 250 mg/kg bw/d. On the offspring side, negative effects were only noted in the maternal high-dose group, with foetal deaths *in utero,* a concomitant decrease in live litter size and a significant increase in pup morbidity and mortality during the first four or five days postpartum. However, even at the highest dose administered to dams, there were no effects on length of gestation, pup sex ratio, pup body weight or gross morphology. Based on this evidence, 500 mg/kg bw/d was the NOEL for the offspring. While at 1000 mg/kg bw/d there was significant foetal and pup mortality, there were no gross signs of teratogenicity in the pups, as stated by the authors.

From the same study, but specifically regarding fertility parameters, the following main results were reported: In dams, dosages up to 1000 mg/kg bw/d did not adversely affect the reproductive performance, as stated by the authors of that study: There were no significant differences regarding duration of cohabitation, incidence of pregnacy or averages of implantation in all three treatment groups compared with the controls. From a 28-day subchronic toxicity study with the same

essential oil of coriander, no remarkable effects on the primary reproductive organs in both females (ovaries and uteri) and males (testes and epididymides) was noted in any animal from any dosage group up to 1000 mg/kg bw/d, both macroscopically at dissection and also microscopically during histopathology of every single (10 male, 10 female) high-dose animal. The NOEL for effects on fertility is set at 500 mg/kg bw/d (equivalent to 365 mg/kg bw/d linalool).

Conclusion

In conclusion, from the reproductive and developmental study, using an essential oil of coriander with 72.9% linalool, 22.3% other terpenoids and < 5% unidentified ingredients, a maternal NOAEL of 500 mg/kg bw/d (equivalent to 365 mg/kg bw/d linalool) based on clinical signs and effects on body weight, could be derived. For the offspring, a NOAEL of 500 mg/kg bw/d (equivalent to 365 mg/kg bw/d linalool) based on decreased litter size at birth and pub morbidity/mortality thereafter, could be derived.

In several studies, *e.g.,* the behavioural inhalative test with mice or the reproductive screening test, sedative effects of linalool were consistently or sporadically noted, described mainly as a decrease in motor activity. At least for l- and dl-linalool, sedation was confirmed recently (1998) in an inhalative study with EEG monitoring of human subjects and also in a psychopharmacological evaluation in rats in a dose-dependent fashion. In a 1988 study with insects, linalool was shown to be an effective, reversible inhibitor of acetylcholinesterase; using electric eel acetylcholinesterase and acetylthiocholine iodide as a substrate, an inhibition constant K_i of 5.5 m*M* was determined for pure linalool. The specific toxic effect of linalool on animals is therefore likely to be caused by its neurotoxic respectively neuropharmacological mode of action. In turn, this may explain the use of linalool-containing natural products (aromatic herbs and spices or their essential oils respectively extracts) in traditional medicinal systems, specifically for their sleep-inducing and anticonvulsant purposes. Moreover, it also accounts for the widespread traditional use of herbs containing linalool for stored-food pest control for the use of linalool-containing extracts as a pet flea insecticide.

A specific immunotoxicity test with mice with a detailed protocol found no negative effect of linalool on the immune performance as measured by an IGM antibody plaque-forming cell (PFC) assay and by a host resistance assay against the pathogenic bacterium *Listeria monocytogenes*. On the contrary, the middle dose (188 mg/kg bw/d) significantly enhanced the PFC counts.

3.2 Initial Assessment for Human Health

In view of quasi closed production systems in Switzerland, production workers will be exposed during filling of containers and irregular work at the installations, mostly during manual dischargin of spent catalyst from the reactor. Standard occupational safety measures, both technical and organisational, are in place for those situations. There are no reports regarding occupational health effects from linalool exposure. Consumers, on the other hand, are widely exposed to both natural and synthetic linalool in spices, herbs, fruits, fortified food and beverage products, cosmetics, soaps, perfumes as well as household cleaning and care products. In most of these cases, above 95% of applications, linalool is utilised for its odorant and fragrance properties, while probably less than 1% of synthetic linalool is used for its aroma and flavouring properties in food and beverages. While there are no data for inhalative exposure to vapourised linalool but there are two congruent recent estimates of linalool intake from formulated food and beverages in Europe and the USA, ranging between 21 and 72 µg/kg/d. Including linalool from natural food and spice sources, twice the upper range, *i.e.,* 140 µg/kg/d is assumed to constitute the maximal daily intake. Inhalative exposure to linalool can not be reasonably quantified, particularly for urban and indoors environments. In the short term, due to its odourant or fragrance function, inhalative exposure must needs be above the olfactory threshold of ~ 1 ppm, but this is predicted to fall rapidly due to atmospheric degradation.

Acute oral LD_{50} values for linalool from three sources regarded as dependable consistently range between 2,780 and 3,120 mg/kg bw in the rat and mouse. Acute dermal toxicity is in a comparable range, from 2,000 to approx. 8,000 mg/kg bw, which is in the same order of magnitude as two single subcutaneous and intramuscular data. Intraperitoneal LD_{50}s for rat and mouse are just over 300 mg/kg bw, which seems reasonable considering the oral range. There is only one, contested, inhalative mammalian LC_{50} corresponding to below 2,000 ppm, which contrasts with an avian, probably also inhalative, value above 5,600 ppm from the same source. From other inhalative studies, only qualitative effects are described, sedation as expected, but no deaths. No reports have been located regarding human intoxication due to linalool. Based on fiable studies, linalool is considered to be of low acute toxicity by both oral, dermal and inhalative route.

In subchronic studies the oral NOAEL was between 160 (equivalent to 117 mg/kg bw/d linalool) and 500 mg/kg bw/d. All effects at the lower end of this range are considered of low severity. The upper value of 500 mg/kg bw/d was also set as the maternal NOAEL in a reproductive study. In addition, a recent review of human exposure through food agreed with a relatively low toxicity and proposed a NOEL of 500 mg/kg bw/d for linalool. This is consistent with the current ADI for total terpenoid alcohols of 0–0.5 mg/kg bw, assuming an integrated safety factor of 1000.

In a reproductive study with essential oil of coriander, containing 72.9% of linalool, 22.3% other terpenoids and less than 5% unidentified ingredients, the maternal NOAEL was 500 mg/kg bw/d (equivalent to 365 mg/kg bw/d linalool). Higher doses resulted in changes to the index and length of gestation as well as in foetal and newborn toxicity, so that the NOAEL was 500 mg/kg bw/d for the offspring (equivalent to 365 mg/kg bw/d linalool). A NOEL for effects on fertility is set at 500 mg/kg bw/d (equivalent to 365 mg/kg bw/d linalool). This value was derived from a 28-day subchronic toxicity study. The NOELs and NOAELs of these studies can be regarded as possible evidence of some general toxic effect or mechanism that becomes active at repeat doses above 500 mg/kg bw/d.

Linalool was irritating to the skin in several tests with rabbits, moderately irritating to guinea pigs and mildly or not irritating to human subjects. Based on these data, mainly the three rabbit tests according to OECD protocol, linalool must be considered as irritating to the skin, although it seems to be only a mild skin irritant for man. Based on relatively few available results, linalool is at most a moderate eye irritant; in about two-thirds of test persons, linalool vapours produced eye irritation at the same concentration as nasal pungency (~ 320 ppm), while the other third remained unaffected. Apart from this pungency result, no data on respiratory tract irritation have been located. In conclusion, linalool is at worst a moderate skin irritant; in addition, it may produce restricted eye and nose irritation.

From several studies with a total of well over 2,000 subjects, the incidence of skin reactions to linalool in patch and maximisation tests with not pre-sensitized probands was consistently below 1%, while among subjects pre-sensitised to fragrance compounds the incidence was nearly 10%. In confirmation, linalool was not a sensitiser in guinea pig Draize tests. The weak allergenic potency is confirmed by data from a murine local lymph node assay. Based on these data, linalool is considered not to be a sensitiser.

Linalool was negative in seven out of eight bacterial mutagenicity tests, including a repeat of the one positive with the same strain. It also proved negative in an *in vitro* and an *in vivo* mammalian mutagenicity assay. It is concluded that the single positive bacterial test was a chance event and that linalool has no mutagenic properties.

Linalool was not carcinogenic in a mouse test with intraperitoneal administration over eight weeks and 16 weeks post-exposure. It did "elicit a weak tumour-promoting response" in a dermal co-

carcinogenicity test from 1960. In contrast, it was not tumour-promoting, but rather tumour-inhibiting or tumour-delaying, in a later oral feed co-carcinogenicity study.

In conclusion, linalool has a moderate to low acute, subchronic and reproductive toxicity towards mammals. It is a moderate irritant but has a low sensitising potential. Further, it is not mutagenic nor carcinogenic. While the entero-hepato-biliary recirculation in metabolism may prolong the load on the liver, linalool is still excreted relatively rapidly by pulmonary and urinary pathway and there is no tendency for bioaccumulation. The overall toxicity of linalool is low.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Linalool has been tested in several standard acute ecotoxicity studies, but also in a host of trials that specifically investigated its efficiency, i.e., toxic potential, against stored-food pests and parasites. Table 4 lists the results of these tests, beginning with the aquatic organisms.

Table 4: Ecotoxicity of Linalool.

Species	Results	Notes
Fish:		
Oncorhynchus mykiss, rainbow trout (freshwater)	NOEC < 3.5 mg/l LC_0 = 19.9 mg/l LC_{50} = 27.8 mg/l LC_{100} = 38.8 mg/l	OECD 203, 96-h acute test with emulsifier
O. mykiss	LC_{50} = 28.8 mg/l	
Lepomis macrochirus, bluegill (freshwater)	LC_{50} = 36.8 mg/l	
Leuciscus idus, golden orfe (freshwater)	NOEC = 22 mg/l LC_0 = 22 mg/l LC_{50} >22, <46 mg/l LC_{100} ≤ 46 mg/l	96 h, static; geometric mean LC_{50} = 31.8 mg/l
Crustaceans:		
Daphnia magna (freshwater)	NOEC = 25 mg/l EC_{50} = 59 mg/l EC_{100} > 75 mg/l	OECD 202, 48 h, static
D. magna	EC_0 = 20 mg/l EC_{50} = 60 mg/l EC_{100} = 100 mg/l	84/449/EEC, C.2, 24 h, static with emulsifier
D. magna	EC_0 = 8 mg/l EC_{50} = 20 mg/l EC_{100} = 80 mg/l	84/449/EEC, C.2, 48 h, static with emulsifier
"Aquatic invertebrates"	EC_{50} = 36.7 mg/l	no further information; EPA chemical fact sheet, 1985
Algae:		
Scenedesmus subspicatus (freshwater green algae)	EC_{10} = 38.4 mg/l EC_{50} = 88.3 mg/l	DIN 38412, 96 h, static with emulsifier
Chlorella pyrenoidosa (freshwater green algae)	effects data not convertible to aquatic concentrations	algae grown on agar; no effect from a paper disk dipped in 1 g linalool/l and placed on colony, but platewide lightening at 10 g/l; inhibition also through vapour phase at 10 g/l

Bacteria:			
Activated sludge bacteria	NOEC = NOEC =	100 mg/l 100 mg/l	OECD 209, 30 min OECD 209, 3 h
Activated sludge bacteria	EC_{10} ~ EC_{50} ~	110 mg/l 400 mg/l	OECD 209, 30 min
Activated sludge bacteria	EC_{20} = EC_{50} = EC_{80} =	0.05 mg/l 0.3 mg/l 0.7 mg/l	inhibition test, 24 h
Activated sludge bacteria	EC_{20} = EC_{50} > EC_{80} >	1 mg/l 1 mg/l 1 mg/l	inhibition test, 28 d
Pseudomonas putida	EC_{10} = EC_{50} = EC_{80} =	660 mg/l 1000 mg/l 1800 mg/l	DIN 38412, 30 min
Bacillus subtilis	MIC =	800 mg/l	MIC = Minimal Inhibitory Concentration
Brevibacterium ammoniagenes	MIC =	800 mg/l	
Enterobacter aerogenes	MIC >	800 mg/l	
Escherichia coli	MIC >	800 mg/l	
Propionibacterium acnes	MIC =	200 mg/l	
Pseudomonas aeruginosa	MIC >	800 mg/l	
Staphylococcus aureus	MIC >	800 mg/l	
Streptococcus mutans	MIC =	1600 mg/l	
“18 species of bacteria”	linalool was the most effective of 5 terpenes and inhibited 17 out of 18 species of bacteria		impossible to quantify and assess as no concentrations are given
Fungi, molds and yeasts:			
Penicillium chrysogenum	MIC =	800 mg/l	
Trichophyton mentagrophytes	MIC =	200 mg/l	
Candida utilis	MIC =	400 mg/l	
Pytirosporum ovale	MIC =	400 mg/l	
Saccharomyces cerevisiae	MIC =	800 mg/l	
“12 species of fungi”	linalool was the second most effective of 5 terpenes and inhibited 10 out of 12 species of fungi		impossible to quantify and assess as no concentrations are given

Terrestrial plants:		
Hordeum vulgare (barley)	germinating root length slightly enhanced (112% vs controls) at 10 mg linalool/l and very slightly reduced (96%) at 50 mg/l	no statistical significance given, test performed in aqueous solution
Lactuca sativa (lettuce)	NOEC = 100 mg/l; full germination inhibition and an undescribed effect on growth at 1000 mg/l	nonstandard germination and growth test, test performed in aqueous solution
Lepidum sativum (cress)	NOEC = 1000 mg/l	nonstandard germination and growth test, test performed in aqueous solution
Non-mammalian terrestrial animals:		
Colinus virginianus (bobwhite quail, birds)	LC_{50} > 5,620 ppm	probably inhalative, no further information; EPA chemical fact sheet, 1985
Bugs (Coleoptera), various species	$EC_{??}$ ~ 5–15 µl/l air effects through vapour or direct contact	many important stored-food pests are traditionally or experimentally controlled with natural products containing linalool or with linalool itself; the EC corresponds to ~ 2,500–7,500 ppm
Tribolium castaneum, grain weevil	LC_{50} = 25,000 ppm (conc. pipetted on paper	FAO contact method; linalool was shown to be an effective, reversible
	disc); paralysis, death through vapour or contact	inhibitor of acetylcholinesterase, explaining its neurotoxic activity
Fleas (Aphanipitera)	"kills adult fleas, eggs, larvae and pupa"	Flea Stop, a natural plant extract with a high concentration of linalool is useful for controlling pet fleas
Insects, fleas	"contact poison and may also have some fumigating action against fleas"	from a publication on alternatives in insect pest management

In freshwater, linalool is of moderate toxicity in standard acute ecotoxicity tests with fish, daphnia and algae, with all LC_{50}/EC_{50} values ranging between 20 and 90 mg/l. Some of these tests were performed using emulsifiers but the rationale for this it is not clear at all in view of the appreciable solubility of linalool. All four fish LC_{50}s group very closely between 27.8 and 36.8 mg/l. In daphnids the range of four data points from three tests is somewhat broader, from 20 to 60 mg/l. A static OECD 202 study under GLP without emulsifier resulted in a 48-hour EC_{50} of 59 mg/l and a NOEC of 25 mg/l. In a static test with emulsifier, the 24-hour EC_{50} was 60 mg/l but at 48 hours the EC_{50} had dropped to 20 mg/l, which, possibly, may indicate some influence from the emulsifier over the longer term, as no such effect was found in the GLP study, where even the NOEC was higher at 25 mg/l. The 1985 EPA Chemical Factsheet gives an EC_{50} of 36.7 mg/l for "aquatic invertebrates", which is taken to mean daphnids. An algal test with emulsifier over 96 hours (therefore possibly counting as a chronic study) resulted in an EC_{50} of 88.3 mg/l. A second algal test, performed on agar plates with linalool-dipped paper discs, does not permit to derive a comparable EC_{50} but only the conclusion that linalool may also have an effect through the vapour or gas phase.

Based on the acute ecotoxicity data, there is no indication for a specific, high toxicity to any of the systematic groups tested. Using the lowest EC_{50} located, an aquatic PNEC of 0.2 mg/l can be extrapolated with an assessment factor of 100. With the possible exception of the algal test, no chronic aquatic ecotoxicity results have been located; also, no marine data have been found.

A host of publications deals with toxicity to micro-organisms by linalool. A GLP OECD 209 test from 1991 showed a NOEC of 100 mg/l (both 30 min and 3 h), a non-GLP OECD 209 over 30 minutes resulted in a calculated EC_{10} of ~ 110 and EC_{50} of ~ 400 mg/l. This seems to be in stark contrast to the 24-hour result from a 1982 Sapromat inhibition test that gave an EC_{50} of 0.3 mg/l; however, there is a 28-day value of EC_{20} = 1 mg/l and both EC_{50} and EC_{80} > 1 mg/l. This is interpreted to describe the inhibition/toxicity control of a closed-bottle-like test with a test substance concentration of 1 mg/l and a correspondingly low concentration of activated sludge. Considering the result from a biodegradation test using soil extract as the inoculum, where at first no elimination was recorded over a lag phase of approximately 100 hours, after which rapid biodegradation set in, the very low 24-hour EC_{50} is assumed to reflect the initial lag phase where the bacteria had not yet adapted to the test substance. That linalool *per se* is not strongly toxic to micro-organisms is evidenced by a 30-minute DIN respiration inhibition test with *Pseudomonas putida,* with an EC_{50} of 1000 mg/l and by nonstandard minimal inhibition concentration (MIC) tests with eight common bacteria and five common fungi, molds and yeasts, where the MIC was in-between 200 mg/l (in 2/13 instances) and 1600 mg/l. In contrast, in a report on toxicity against micro-organisms, linalool was considered quite effective, inhibiting 17 out of 18 bacterial and 10 out of 12 fungal species tested. However, neither the concentrations used in these tests were stated nor any other details given, making these data impossible to assess quantitatively. Pending further information, 100 mg/l is regarded as a dependable NOEC for bacteria, the corresponding PNEC is 10 mg/l, using an assessment factor of 10.

4.2 Terrestrial Effects

Three germination tests with terrestrial plants, performed in aqueous solutions, were located. In the test with barley, germinating root length was measured: at 10 mg linalool/l, a slight elongation (112%) compared to controls was observed while there was a slight reduction (96%) at 50 mg/l, the highest concentration tested. As both deviations seem rather small, as the concentration range is limited and as no statistics are given, this test cannot be interpreted quantitatively. A germination and initial growth test with lettuce and cress spanned a concentration range up to 1000 mg/l. In lettuce, 1000 mg/l completely inhibited germination and had some undescribed effect on growth (presumably of plants pre-germinated in the absence of linalool, not stated) while the NOEC was 100 mg/l. For cress the NOEC for both germination and growth was 1000 mg/l. In a nonstandard phytotoxicity test, no effect of an unstated concentration of linalool, probably as an aerosol or vapour, on the closure of leaf stomata was found. In conclusion, linalool did not show any particular phytotoxic potential and the NOEC for germination and growth is 100 mg/l. These tests were performed in aqueous medium, therefore the derivation of a terrestrial plant PNEC is not possible.

Only one result was found for avian toxicity in the bobwhite quail, an LC_{50} > 5,620 ppm, which probably means that it was an inhalative test, but no further information is given in the source, the EPA chemical fact sheet (1985). Accepting this value as useful would characterise linalool as barely toxic to birds by inhalation.

Some experimental reports and several secondary sources confirm the efficacy of linalool respectively linalool-containing natural products, *e.g.,* dried leaves of the African basil *Ocimum canum* or the Australian clary sage *Salvia clarea,* in traditional stored-food and clothes storage insect pest control. Linalool, like other terpenes tested, was experimentally shown to be an effective reversible inhibitor of acetylcholinesterase. In the beetle *Tribolium confusum,* linalool showed repellent action and both contact and fumigant toxicity; it first paralysed and then killed unadapted beetles. In standardised FAO tests with blotting paper dipped into linalool solutions, both dried plant parts and essential oils containing linalool were shown to have insecticidal activity against major food pests of stored beans, grains, rice and flour, at a concentration of 5–15 µl pure linalool/l air (corresponding to ~ 2,500–7,500 ppm by volume). The FAO testing protocol is adapted to investi-

gate both contact and fumigant toxicity, but because of contact action the results do not translate simply into effective vapour concentrations nor are the latter measured, meaning that only a very approximate fumigant effective concentration against insects of ~ 2,500–7,500 ppm can be derived. However, compared with zimtaldehyde, which is described as a "rather strong insect toxicant", all of these effects were characterised as moderate. No proper PNEC for the gas phase can be derived because of insufficiently precise effective concentration data and because of the possibly influence of direct contact toxicity.

4.3 Other Environmental Effects

The toxicity of linalool to other environmentally relevant species has not been determined.

4.4 Initial Assessment for the Environment

A large body of physico-chemical, toxicological and environmentally relevant data exists for linalool, some of which are relatively old. While the quality of a single result often may be hard or even impossible to assess and while there are some contested outliers, the sheer volume and high congruence of the data result in a uniform picture all the same.

Approximately 12,000 tonnes of linalool *per annum* are estimated to be produced worldwide, both from natural sources or precursors and through total chemical synthesis. This amount is certainly dwarfed by natural linalool production by many different plants, mostly herbs and spices, citrus fruits, trees and others, from the tropics to boreal forests; the biogenic production from the latter forests alone is conservatively estimated at 93,000 t/a. Most linalool, both natural and man-made, will be released to the atmosphere, where it will be rapidly and extensively degraded by reaction with ozone or hydroxyl and nitrate radicals. Some linalool will be deposited on the soil and a certain fraction will be discharged into water. In both environmental compartments, specifically also in sewage works, linalool will be biodegraded to a wide extent in both aerobic and anaerobic conditions. Based on its physico-chemical properties, linalool is not expected to partition to sediment nor to bioaccumulate. There is one measured environmental concentration (MEC) of up to 0.11 µg/l from a river in a heavily industrialised region in Europe, one of 0.25 µg/l in undiluted effluent and one publication of ambient air concentrations in a boreal forest in Finland, where natural terpenes are emitted by trees during the vegetation period and where linalool reaches local summer peak MECs up to 120 ppt by volume. There are no MECs for seawater, soil or sediment.

In a series of acute aquatic ecotoxicity tests, linalool consistently showed moderate toxicity, with EC_{50} respectively LC_{50} values within the relatively narrow range of 20–90 mg/l. Some of these tests had been performed using an emulsifier, the reason for which is not clear considering the relatively good solubility. In particular, four fish results grouped very close between 27.8 and 36.8 mg/l, no matter whether the respective test was performed using emulsifier or not. In daphnia, a static OECD GLP study without emulsifier gave an EC_{50} of 59 mg/l, while a non-GLP study with emulsifier agreed with 60 mg/l at 24 hours but showed a subsequent drop to 20 mg/l at 48 hours, which is below the NOEC of the former study and suspected not to be a test-substance-related effect. In the only quantified algal study, the 96-hour EC_{50} was 88.3 mg/l. The lowest EC_{50} is 20 mg/l and the aquatic PNEC is extrapolated to 0.2 mg/l using an assessment factor of 100.

Linalool is of low toxicity to activated sludge bacteria, with the exception of one, contested, result from a non-standard activated sludge inhibition test. In all other, including OECD, tests, the NOEC was 100 mg/l or higher. This is confirmed by minimal inhibition concentration (MIC) tests with eight common bacteria and five common fungi, where in 2/13 cases the lowest MIC was 200 mg/l. Low toxicity is also inferred from biodegradation tests. Some published data on relatively high toxicity of linalool to 18 species of bacteria and 12 species of fungi cannot be assessed due to lack

of quantitative data. The NOEC of linalool for micro-organisms is set at 100 mg/l, the PNEC at 10 mg/l using an assessment factor of 10.

Similarly, for terrestrial plants, 100 mg/l was found as the NOEC for germination and growth in two instances while a third study only tested up to 50 mg/l, without evident toxicity.

The only avian study located, probably inhalative, is reported as LC_{50} > 5,620 ppm without any further data, which allows only the conclusion that linalool is barely toxic for birds.

Linalool is being used traditionally, mainly in the form of leaves with a relatively high content, as a fumigant against stored-food pests, the efficacy of which was proven in FAO and other tests, at a concentration of ~ 2,500–7,500 ppm. It was shown to work through inhibition of acetylcholinesterase, paralysing the insects and, at high concentrations, killing them. Linalool-containing products are also used for insect protection in clothes storage and flea control. While these data support insect toxicity through contact and fumigant action, this effect was characterised as moderate in comparison with a highly active insecticide.

In conclusion, linalool shows moderate toxicity to aquatic organisms and low toxicity to micro-organisms, terrestrial plants and birds. It paralyses insects at higher concentrations but it is characterised as a moderate insect toxicant at the same time. Overall, linalool has a low to moderate toxicity towards environmental species. Due to its ready degradability, abiotic in the atmosphere and biological in water and soil, the low tendency for bioaccumulation and the well developed metabolic pathways from bacteria to mammals, no concentrations that might cause toxicity are expected.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

I U C L I D

D a t a S e t

Existing Chemical	ID: 78-70-6
CAS No.	78-70-6
EINECS Name	linalool
EC No.	201-134-4
TSCA Name	1,6-Octadien-3-ol, 3,7-dimethyl-
Molecular Formula	C10H18O

Producer Related Part	
Company:	Hoffmann-La-Roche AG
Creation date:	29-MAY-2001

Substance Related Part	
Company:	Hoffmann-La-Roche AG
Creation date:	29-MAY-2001

Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 14, 26-28 March 2002

Printing date:	30-MAR-2004
Revision date:	
Date of last Update:	08-SEP-2003

Number of Pages:	150

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: sponsor country
Name: Switzerland
Contact Person: Dr. Georg Karlaganis Date: 02-FEB-2002
Street: Swiss Agency for the Environment, Forests and Landscape
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Homepage: http://www.umwelt-schweiz.ch/buwal/eng/index.html

29-JUL-2002

Type: lead organisation
Name: F.Hoffmann-La Roche AG
Contact Person: Dr. Louis Schnurrenberger Date: 29-MAY-2001
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29-JUL-2002

Type: cooperating company
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Phone: +49 621 6044712
Telefax: +49 621 6058043
Email: hubert.lendle@basf-ag.de

29-JUL-2002

1.0.2 Location of Production Site, Importer or Formulator

Type: manufacturer
Name of Plant: Teranol AG, Lalden
Street: PO Box 310
Town: 3930 Visp
Country: Switzerland
Phone: +41 27 9485733
Telefax: +41 27 9486184

01-FEB-2002

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

IUPAC Name: 1,6-Octadien-3-ol, 3,7-dimethyl-
Smiles Code: OC(C=C)(C)CCC=C(C)C
Mol. Formula: C10-H17-OH
Mol. Weight: 154.24

17-JUL-2001 (141)

1.1.1 General Substance Information

Test substance: Chemical characterisation:
Linalool is a monoterpene, specifically an hydroxy-substituted diene.
Reliability: (1) valid without restriction
22-JAN-2002 (61)

Purity type: typical for marketed substance
Substance type: organic
Physical status: liquid
Purity: = 97.9 - % w/w

Reliability: (2) valid with restrictions
24-JUL-2001 (145)

Purity type: other: minimum specification for marketed product
Substance type: organic
Physical status: liquid
Purity: >= 96 - % v/v
Colour: clear, colourless to pale yellow
Odour: lavender-like, bergamot-like

Reliability: (2) valid with restrictions
24-JUL-2001 (145)

Purity type: typical for marketed substance
Substance type: other: synthesised dl-Linalool
Physical status: liquid
Purity: >= 96 - % w/w
Colour: colourless
Odour: fresh, floral, slightly woody, herbal odour

Reliability: (4) not assignable
24-JUL-2001 (14) (141)

Purity type: measured for specific batch
Physical status: liquid
Colour: colourless
Odour: "matching control"

Remark: Batch description:
Result: Purity = 97.7% (area, GC)
Reliability: (2) valid with restrictions
24-JUL-2001 (146)

Method: Technical details on sample preparation through thin-layer chromatograhy (TLC) and analysis through capillary gas chromatography (CGC) and stable isotope ratio analysis (SIRA) coupled with isotope ration mass spectrometry (IRMS)

for enantioselective analysis of d- and l-linalool are described.
Remark: The aim of this work was to develop a method to determine if a given linalool sample was natural (R)-Linalool or mixed with synthetic material. However, as (R)-linalool is chirally instable in acidic media, eg fruit juices and other products, the method is only applicable to confirm such linalools as of natural origin that contain less than 15% (S)-linalool.
Result: Enantioselective analysis of d- and l-linalool
Test substance: (R)-linalool, (S)-linalool and (R,S)- resp. dl-linalool
Reliability: (4) not assignable
17-JUL-2001 (64)

1.1.2 Spectra

Type of spectra: GC

Result: Gas chromatogram, RIFM no. 70-66
Reliability: (4) not assignable
20-JUL-2001 (110)

Type of spectra: IR

Result: Infrared spectrum, RIFM no. 70-66.
Reliability: (4) not assignable
20-JUL-2001 (110)

Type of spectra: IR

Remark: Gas-phase IR spectrum
Owner: NIST Standard Reference Data Program
Origin: NIST Mass Spectrometry Data Center
Source reference: no. 114561 (NIST/EPA/NIH MS Database)
Instrument: HP-GC/MS/IRD
Reliability: (4) not assignable
04-DEC-2001 (148)

Type of spectra: mass spectrum

Remark: Owner: NIST Mass Spectrometry Data Center
Origin: G Brammer, University of Texas
Origin code: UOT
Instrument IE: 70 eV
EPA MS no: 43962
Reliability: (4) not assignable
04-DEC-2001 (148)

1.2 Synonyms and Tradenames

2,6-Dimethyl-2,7-octadiene-6-ol

30-JUL-2001 (141)

2,6-Dimethylocta-2,7-diene-6-ol

30-JUL-2001 (141)

3,7-Dimethyl-1,6-octadiene-3-ol

30-JUL-2001 (141)

Linalyl alcohol

30-JUL-2001 (141)

beta-Linalool

30-JUL-2001 (141)

p-Linalool

30-JUL-2001 (141)

allo-Ocimenol

30-JUL-2001 (141)

Linalol

30-JUL-2001 (141)

Linolool

30-JUL-2001 (141)

d-Linalool = Coriandrol

08-SEP-2003 (141)

l-Linalool = Licareol

08-SEP-2003 (141)

1.3 Impurities

Purity type: typical for marketed substance
CAS-No: 18479-51-1
EC-No: 242-359-8
EINECS-Name: 3,7-dimethyloct-6-en-3-ol
Mol. Formula: C10 H20 O
Contents: <= 1.9 - % v/v

Reliability: (2) valid with restrictions
23-JUL-2001 (145)

Purity type: typical for marketed substance
CAS-No: 29171-20-8
EC-No: 249-482-6
EINECS-Name: 3,7-dimethyloct-6-en-1-yn-3-ol
Mol. Formula: C10 H16 O
Contents: < .1 - % w/w

Reliability: (2) valid with restrictions
24-JUL-2001 (145)

Purity type: typical for marketed substance
CAS-No: 115-95-7
EC-No: 204-116-4

EINECS-Name: linalyl acetate
Mol. Formula: C12 H20 O2
Contents: < .5 - % w/w

Reliability: (4) not assignable
31-JUL-2001 (5)

Purity type: typical for marketed substance
Contents: < .2 - % w/w

Result: all other impurities (undefined)
Reliability: (2) valid with restrictions
31-JUL-2001 (145)

1.4 Additives

1.5 Total Quantity

Quantity: ca. 12000 tonnes produced in 2000

Remark: approx. 6600 t/a estimated to be produced through chemosynthetic route,
approx. 5400 t/a estimated to be produced through natural plant terpenes extraction
worldwide estimate
Reliability: (2) valid with restrictions
09-AUG-2001 (57)

1.6.1 Labelling

Labelling: provisionally by manufacturer/importer
Symbols: (Xi) irritating
R-Phrases: (38) Irritating to skin
S-Phrases: (24) Avoid contact with skin

Source: Directive 92/32/EEC on Classification, packaging and labelling of dangerous substances, 7th Amendment of directive 67/548/EEC.
Reliability: (2) valid with restrictions
30-JUL-2001 (141)

1.6.2 Classification

Classified: provisionally by manufacturer/importer
Class of danger: irritating
R-Phrases: (38) Irritating to skin
Specific limits: yes
Conc./Class. 1: >= 20 % Xi, R 38, S 24
Conc./Class. 2: < 20 % no classification

Source: Directive 1999/45/EC on Classification, packaging and labelling of dangerous preparations.
Reliability: (2) valid with restrictions
30-JUL-2001 (141)

1.6.3 Packaging

1.7 Use Pattern

Type: use
Category: Odour agents

Result: as an odour agent in soap, detergents, creams and lotions
22-JAN-2002 (110) (141)

Type: use
Category: Cleaning/washing agents and disinfectants

Result: Concentrations in soaps: usual 0.04%, maximal 0.3%
Concentrations in detergents: usual 0.004%, max. 0.03%
22-JAN-2002 (110) (141)

Type: use
Category: Cosmetics

Result: As an odoriferous substance and top note.
Concentration in creams/lotions: usual 0.02%, max. 0.1%
Concentration ion perfumes: usual 0.5%, max. 1.5%
22-JAN-2002 (110) (141)

Type: use
Category: other: Flavour ingredient in food industry

Result: As a fresh-fruity flavour ingredient and enhancer in prepared foods, including candies and chewing gums, and beverages at concentrations below 1 ppm to 60 ppm
Reliability: (2) valid with restrictions
22-JAN-2002 (20)

Type: use
Category: other: traditional/experimental insecticide for stored agricultural products

Result: At concentrations of 5-15 ul/l of air, corresponding to approx. 2,500-7,500 ppm, among other substances, essential oils of basil and lavender as well as pure linalool proved to be highly active as a fumigant against several stored-cereal pests.

Please see chapter 7.2, Effects on organisms to be controlled, for details.
Reliability: (4) not assignable
22-JAN-2002 (109) (131) (154)

Type: industrial
Category: Chemical industry: used in synthesis

Remark: mainly used in the synthesis of linalool esters and vitamin E compounds (dl-alpha-tocopherol, CAS 10191-41-0; dl-alpha-tocopheryl acetate, CAS 58-95-7); the latter use is not common
Reliability: (2) valid with restrictions
22-JAN-2002 (4) (141)

1.7.1 Detailed Use Pattern

Industry category: 3 Chemical industry: chemicals used in synthesis
Use category: 55/0 other
Extra details on use category: No extra details necessary
No extra details necessary
Emission scenario document: not available
Production: yes

Remark: synthesis of vitamin E compounds
Reliability: (2) valid with restrictions
04-JAN-2002 (4) (141)

Industry category: 3 Chemical industry: chemicals used in synthesis
Use category: 36 Odour agents
Extra details on use category: No extra details necessary
No extra details necessary
Emission scenario document: not available
Production: yes

Reliability: (2) valid with restrictions
04-JAN-2002 (141)

Industry category: 5 Personal / domestic use
Use category: 9 Cleaning/washing agents and additives
Extra details on use category: No extra details necessary
No extra details necessary
Emission scenario document: not available
Formulation: yes

Reliability: (2) valid with restrictions
04-JAN-2002 (141)

Industry category: 5 Personal / domestic use
Use category: 15 Cosmetics
Extra details on use category: No extra details necessary
No extra details necessary
Emission scenario document: not available
Formulation: yes

Reliability: (2) valid with restrictions
04-JAN-2002 (141)

Industry category: 5 Personal / domestic use
Use category: 26 Food/feedstuff additives
Extra details on use category: No extra details necessary
No extra details necessary
Emission scenario document: not available

Result:

Reported uses as a flavour enhancer	Concentration, ppm
Baked goods	18
Frozen dairy products	10
Meat products	46
Condiments, relishes	40
Soft candies	10
Gelatine puddings	10
Nonalcoholic beverages	7
Alcoholic beverages	0.4
Hard candy	15
Chewing gum	61

Reliability: (2) valid with restrictions
04-JAN-2002 (20)

Industry category: 5 Personal / domestic use
Use category: 55/0 other
Extra details on use category: No extra details necessary
No extra details necessary
Emission scenario document: not available

Result: Linalool is used as a flavour ingredient in the food industry, eg in imitation blueberry, lemon, lime, orange, grape and cola compositions; in apricot, pineapple, date, blackcurrant, plum, peach, cardamon and other fruit and spice complexes; in meat flavours; in cocoa and imitation chocolate.
Reliability: (2) valid with restrictions
04-JAN-2002 (31) (141)

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis
Type: Production

Result: Linalool can be either a) extracted from linalool-biosynthesising plants respectively distilled from their essential oils or b) part-synthesisied from natural pinene extracts or c) totally chemically synthesised from simple organic compounds.
a) Extraction of linalool is based on fractionation distillation of essential oils of mainly bois de rose, shiu (campher) or coriander.
b) Partial synthesis starts either from alpha- or beta-pinene (CAS 80-56-8 resp. 127-91-3). alpha-Pinene is hydrated selectively to cis-pinane (6876-13-7) and subsequently oxidised to cis/trans (c. 75%/25%) pinane hydroperoxide (28324-52-9), which is in turn reduced to pinanols (various CAS numbers) and the latter finally pyrolysed to the respective linalools.
c) Total chemical synthesis of linalool is by way of 2-methyl-2-hepten-6-one (110-93-0). It may start from addition of acetylene (74-86-2) to acetone (67-64-1) resulting in 3-methyl-1-butyn-3-ol (115-19-5), which is hydrated in the presence of a palladium catalyst to 3-methyl-1-buten-3-ol (115-18-4), which is reacted with either diketene or acetic acid ester to the acetoacetate and the latter thermally reacted to 2-methyl-2-hepten-6-one. Alternatively, 3-methyl-1-buten-3-ol is reacted with isopropenyl methyl ether (116-11-0) to 2-methyl-2-hepten-6-one. In a third synthetic pathway, isoprene hydrochloride is reacted with acetone in the presence of an alkaline condensating agent or in the presence of organic bases as catalysts to 2-methyl-2-hepten-6-one.
2-Methyl-2-hepten-6-one is then reacted with acetylene to dehydrolinalool (CAS 29171-20-8), which is finally partially hydrated using hydrogen gas on a catalyst of platinum on activated charcoal. Subsequently the product linalool is purified through vacuum distillation.
Reliability: (2) valid with restrictions
22-JAN-2002 (4) (145)

Orig. of Subst.: Natural origin
Type: other: Biosynthesis in higher plants

Method: Mevalonic acid radiolabelled in the C2-position (CAS 5489-96-3) was fed into twigs of the plant Cinammomum camphora var. linalooliferum for 1 day. Pure linalool was subsequently isolated from the twigs using steam-distillation and column chromatography. After subsequent derivatisation and degradation of the linalool molecules the degradation products were analysed as to radioactivity. From the identification of compounds and the distribution of radioactivity in the latter, the original constituting moieties of linalool could be determined.
Result: Natural linalool was shown to be biosynthesised through linking of equal parts of the isomeric derivatives of mevalonic acid (CAS 150-97-0), isopentenyl pyrophosphate (CAS 358-71-4) with the 3,3-dimethylallyl moiety of 3,3-dimethylallyl pyrophosphate (CAS 358-72-5), resulting in the intermediate geranyl pyrophosphate (CAS 763-10-0), which is subsequently transformed to linalool through cleavage of the pyrophosphate group and hydroxylation in the C3-position with concomitant shift of the double bond from the C2-C3 to the C1-C2 position.
Reliability: (4) not assignable
25-JUL-2001 (142)

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: other: VwVwS of May 17th, 1999
Labelled by: other: VwVwS of May 17th, 1999
Class of danger: 1 (weakly water polluting)

Result: officially classified in the Federal Republic of Germany as Water Hazard Class 1 (weakly hazardous to water) according to Verwaltungs-Vorschrift wassergefährdende Stoffe (VwVwS) of May 17, 1999 under registry number 1135.
Reliability: (2) valid with restrictions
07-AUG-2001 (68)

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: EINECS Number 201-134-4

Reliability: (1) valid without restriction

17-JUL-2001 (37)

Type: TSCA
Additional Info: TSCA Name: 1,6-Octadien-3-ol, 3,7-dimethyl-

Reliability: (1) valid without restriction
17-JUL-2001 (75)

Type: INCI
Additional Info: INCI Name: LINALOOL

Reliability: (2) valid with restrictions
17-JUL-2001 (28)

1.9.1 Degradation/Transformation Products

Type: degradation product in air
CAS-No: 409-02-9
EC-No: 206-990-2
EINECS-Name: methylheptenone
IUCLID Chapter: 3.8

Reliability: (2) valid with restrictions
17-JUL-2001 (135)

1.9.2 Components

1.10 Source of Exposure

Source of exposure: Human: exposure by production
Exposure to the: Substance

Result: Exposure is limited due to synthesis in quasi-closed systems, limited exposure can only happen during substance transfer for storage or transport, during manual removal of spent catalyst, during cleaning of systems or in case of accidents or spills.
Reliability: (2) valid with restrictions
22-JAN-2002 (141)

Source of exposure: Human: exposure of the consumer/bystander
Exposure to the: Substance

Result: Consumers will be exposed to linalool fumes through scented cosmetics, particularly perfumes, and household cleaning and care products as well as orally through formulated foods and beverages.
Reliability: (2) valid with restrictions
22-JAN-2002 (141)

Source of exposure: other: Human, exposure to natural sources
Exposure to the: Substance

Result: As hundreds of plants synthesise and contain linalool, particularly spices and fruits, regular exposure from natural sources must be assumed, depending on culinary tradition and availability.
Reliability: (2) valid with restrictions
22-JAN-2002 (141)

1.11 Additional Remarks

Memo: Natural occurrence: flowering plants

Result: Both the d-, l- and dl-forms of linalool have been described from over two hundred plants, mainly herbs and spices (mainly Lamiaceae, Lauraceae and Zingiberaceae) but also fruits (mainly Rutaceae and Rosaceae). The following list is not complete:

Latin name	Family	English name
Acacia farnesiana	Papilionaceae	cassie
Actaea sp.	Ranunculaceae	
Ailanthus glandulosa	Simaroubaceae	
Albizia julibrissin	Mimosaceae	
Allium schoenoprasum	Alliaceae	chives
Alpinia spp.	Zingiberaceae	galanga
Angraecum spp.	Orchidaceae	
Aniba rosaeodora	Lauraceae	bois de rose
Anthyllis vulneraria	Fabaceae	
Asarum canadense	Aristolochiaceae	Canadian snakeroot
Belliolum sp.	Winteraceae	
Betula pubescens	Betulaceae	birch
Betula pendula	Betulaceae	birch
Bifrenaria sp.	Orchidaceae	
Brassavola sp.	Orchidaceae	
Camellia sp.	Theaceae	camellia
Cananga odorata	Anonaceae	
ylang-ylang/cananga		
Catasetum spp.	Orchidaceae	
Cestrum		
Chaubardiella sp.	Orchidaceae	
Chimonanthus praecox	Calycanthaceae	
Cimicifuga spp.	Ranunculaceae	
Cinnammomum camphora	Lauraceae	tree camphor/ Mexican linaloe
Cinnamomum zeylanicum	Lauraceae	cinnamon
Citrus aurantium	Rutaceae	neroli bigarade
Citrus bergamia	Rutaceae	bergamot
Citrus limon	Rutaceae	lemon
Citrus sinensis	Rutaceae	orange
Cochleanthes sp.	Orchidaceae	
Cochlospermum sp.	Orchidaceae	
Convallaria majalis	Convallariaceae	
Coriandrum sativum	Apiaceae	coriander/cilantro
Cycnoches spp.	Orchidaceae	
Cymbidium sp.	Orchidaceae	
Cymbopogon spp.	Poaceae	lemongrass
Cypripedium calceolus	Orchidaceae	
Dendrobium superbum	Orchidaceae	
Dolichothele longimamma	Cactaceae	
Encephalarthos	Cycadaceae	
Erigeron canadensis	Asteraceae	erigeron
Freesia sp.	Iridaceae	
Fritillaria meleagris	Liliaceae	
Gardenia jasminoides	Rubiaceae	gardenia
Gongora spp.	Orchidaceae	
Helichrysum angustifolium	Asteraceae	immortelle
Hoya carnosa	Asclepiadaceae	
Humulus lupulus	Moraceae	hops
Hyacinthus sp.	Hyacinthaceae	

	Jasminum spp.	Oleaceae	jasmin
	Laurus nobilis	Lauraceae	laurel
	Lavandula spp.	Lamiaceae	lavender
	Licasia guaianensis	Lauraceae	Cajenne rosewood
	Ligustrum sp.	Oleaceae	
	Lilium candidum	Liliaceae	lily
	Lippia citriodora	Verbenaceae	lemon verbena
	Listera ovata	Orchidaceae	
	Lonicera spp.	Caprifoliaceae	honeysuckle
	Macrozamia moorei	Cycadaceae	
	Magnolia spp.	Magnoliaceae	
	Malus domestica	Rosaceae	apple
	Medicago sativa	Fabaceae	
	Musa spp.	Musaceae	banana
	Myristica fragrans	Myristicaceae	nutmeg/mace
	Narcissus tazetta	Amaryllidaceae	
	Nelumbo spp.	Nelumbonaceae	
	Neofinetia falcata	Orchidaceae	
	Nicotiana spp.	Solanaceae	
	Ocimum basilicum	Lamiaceae	(sweet) basil
	Ocotea caudata	Lauraceae	rosewood
	Ocotea parviflora	Lauraceae	Brazilian rosewood
	Oenothera odorata	Oenotheraceae	
	Ophrys spp.	Orchidaceae	
	Orchis spp.	Orchidaceae	
	Origanum maiorana (Maiorana hortensis)	Lamiaceae	(sweet) marjoram
	Origanum vulgare	Lamiaceae	oregano
	Osmanthus fragrans	Oleaceae	
	Paphinia grandiflora	Orchidaceae	
	Pelargonium spp.	Geraniaceae	geranium
	Pittosporum tobira	Pittosporaceae	
	Plantanthera spp.	Orchidaceae	
	Polycycnis gratiosa	Orchidaceae	
	Primula veris	Primulaceae	
	Prostanthera spp.	Lamiaceae	Australian mint
	Pyrus communis	Rosaceae	pear
	Pyrus pyrifolia	Rosaceae	Oriental pear
	Rebutia marsoneri	Cactaceae	
	Robinia pseudoacacia	Fabaceae	
	Rosa spp.	Rosaceae	rose
	Salix sp.	Salicaceae	willow
	Salvia officinalis	Lamiaceae	sage
	Salvia sclarea	Lamiaceae	clary sage
	Sambucus nigra	Sambucaceae	
	Sassafras albidum	Lauraceae	sassafras
	Saussurea lappa	Asteraceae	costus
	Selenicereus hamatus	Cactaceae	
	Stanhopea spp.	Orchidaceae	
	Stephanotis floribunda	Asclepiadaceae	
	Sulcorebutia kruegeri	Cactaceae	
	Syringa spp.	Oleaceae	lilac
	Thymus spp.	Lamiaceae	thyme
	Vitis vinifera particularly	Vit(id)aceae	grape, Muscat varietals
	Wistaria sinensis	Fabaceae	wisteria
	Zamia sp.	Cycadaceae	
	Zingiber officinale	Zingiberaceae	ginger
	Zygogynum spp.	Winteraceae	
Reliability:	(4) not assignable		
24-JUL-2002		(3) (16) (20) (25) (54) (87) (92) (101)	

Memo: Natural occurrence: mushrooms

Result: 82 species of fresh wild basidiomycete mushrooms collected in France in 1994 and 1995 were analysed for volatiles by GC-MS; 34/82 gave positive results for monoterpenes. Linalool was identified in the headspace of 6 and in the solvent extract of 7 species:

Species	Relative conc., % of total volatiles	
	headspace	solvent extraction
Agrocybe aegerita	ND	2
Boletus erythropus	ND	1
Clitocybe odora	0.5	2/1
Clitocybe nebularis	ND	1/1
Gomphidius glutinosus	ND	3/3
Hydnum repandum	0.5	ND
Lepista nuda	6	3
Lactarius salmonicolor	0.1	NA
Mycena rosea	5.2/<0.1	NA
Tricholoma saponaceum	NA	1
Tricholoma sulfureum	2	ND

ND = analysed but not determined; NA = not analysed.

Reliability: (4) not assignable
14-AUG-2001 (18)

Memo: Natural occurrence: wines

Result: Linalool is present in wines, mostly of the intensely flavoured Muscat varietals (various Muscat or Moscato and Gewürztraminer grapes). Total free monoterpene concentrations in Muscat wines, which are dominated by linalool, geraniol and nerol, may reach 6 mg/l. Linalool is present both as native linalool from the grape respectively the fresh grape juice and from splitting or during vinification of pyran or furan linalool oxides or glycosidase-mediated hydrolysis of the very abundant linalool glycoside esters.

Reliability: (4) not assignable
14-AUG-2001 (101)

1.12 Last Literature Search

Type of Search: Internal and External
Chapters covered: 3, 4, 5
Date of Search: 16-JUL-2001

17-JUL-2001

1.13 Reviews

Memo: BIBRA Toxicity Profile: Linalool (1995)

Reliability: (4) not assignable
27-JUL-2001 (17)

Memo: HSDB: Linalyl alcohol (online, July 2001)

Reliability: (4) not assignable
27-JUL-2001 (149)

Memo: RTECS: 1,6-Octadien-3-ol, 3,7-dimethyl-; RTECS accession no.

RG5775000 (online, April 2001)

Reliability: (4) not assignable
27-JUL-2001 (147)

Memo: Review: Toxicological aspects of linalool (1985)

Reliability: (4) not assignable
27-JUL-2001 (116)

Memo: Monographs on fragrance raw materials: Linalool (1979)

Reliability: (4) not assignable
27-JUL-2001 (110)

2.1 Melting Point

Value: < 20 degree C

Method: other
Year: 1991
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Source: The Flavor and Fragrance High Production Volume Consortia (2001): Robust Summaries for terpenoid tertiary alcohols and related esters. FFHPVC Terpene Consortium Registration Number 1101125.
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
31-JUL-2001 (123)

Value: = -57 degree C

Method: other: no data
Year: 1991
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: source for melting point given as "BASF internal data", no other details
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
31-JUL-2001 (5)

2.2 Boiling Point

Value: = 198 degree C

Method: other: not stated
Year: 1994
GLP: no data
Test substance: no data

Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
05-JUL-2001 (20)

Value: = 198 degree C

Method: other: not stated
Year: 1947
GLP: no

Test substance: d-Linalool
Reliability: (4) not assignable
05-JUL-2001 (139)

Value: = 199 degree C at 1013 hPa

Source: BASF AG Ludwigshafen
14-DEC-1993 (12)

2.3 Density

Type: density
Value: = .858 - .862 g/cm³ at 25 degree C

Method: other: not stated
Year: 1994
GLP: no data
Test substance: no data

Reliability: (4) not assignable
25-JUL-2001 (20)

Type: density
Value: = .8618 g/cm³ at 20 degree C

Method: other: determined with a pyknometer
Year: 1985
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
11-JUL-2001 (118)

Type: density
Value: = .868 g/cm³ at 20 degree C

Method: other: no data
GLP: no data
Test substance: no data

Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
25-JUL-2001 (12)

Type: relative density
Value: = .858 - .867 g/cm³ at 25 degree C

Method: other: no data
Year: 1999
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
01-FEB-2002 (14)

Type: density

Method: other: not stated
Year: 1997
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: real vapour density = 0.00173 g/cm3 at 20 °C
Reliability: (4) not assignable
13-JUL-2001 (44)

2.3.1 Granulometry

2.4 Vapour Pressure

Year: 1998
GLP: no data

Method: Aqueous solubility and vapour pressure measurement
To measure aqueous solubilities and vapour pressures on the monoterpenes, pure terpenes were equilibrated with water and air in 1-l Erlenmeyer flasks that were customised to prevent physical contact between the pure terpenes and water; terpenes were suspended over the water in glass cups attached to the flask stopper. 500 ml of pure water containing 0.005 M NaN3 to inhibit bacterial growth were placed in each flask. A septum port allowed collection of air samples. The flasks were gently shaken on a platform shaker to facilitate air-water exchange, through which the air and water phases eventually became saturated with the monoterpene tested.
Temperature conditions
The aqueous solubilities and vapour pressures were measured at room temperature (23.5 +/- 0.5 °C) and at a lower temperature (6 +/- 1 °C).
Sampling
Periodically the air phase was sampled through the septum port and a 2-ml volume extracted using a gas-tight syringe; flasks were then opened to collect 5-ml aliquots of the aqueous phase. These were extracted and analysed as described. Experiments were continued until the measured terpene concentration was constant for at least one week.
Sample extraction
Monoterpenes in both aqueous and gaseous samples were extracted in an iso-octane solution that already contained 200 uM bornyl acetate as an internal standard. In order to exclude the possibility of significant losses of internal standard during the extraction, the validity of adding bornyl acetate before extraction was confirmed in a separate test with pseudo-ectraction of pure water in three repeats. Similarly, the repoducibility of extraction was separately tested and confirmed.
Gas chromatography
A Hewlett-Packard 5890 gas chromatograph with a flame ionisation detector (GC-FID) was used for quantitative analysis of monoterpenes [including linalool]. The monterpenes were separated on a 30 m X 0.53 mm DB-5 megabore column (HP#19095J-023) using the following operating conditions: helium gas at a flow rate of 10 ml/min, nitrogen make-up gas, head pressure of 2 psi (13.8 kPa), spetum purge ON, detector temperature at 200 °C. Excellent resolution of the terpenes and the internal standard (bornyl acetate) was achieved using the following program: 100 °C for 14 min, 20°/min for 4 min and 180 °C for 5 min. [A typical gas chromatogram for a standard solution containing 200 uM of each monoterpene and bornyl acetate ist given in fig. 1 of the original publication.]
Standard solutions and calibration curves
Standard solutions containing approximately 200 uM of bornyl acetate as an internal standard and 6-1000 uM each of the eight terpenes [tested in this study] in iso-octane were prepared volumetrically from gravimetrically prepared 0.01 Mstock solutions of the solutes in iso-octane.Calibration

curves were constructed from the average quantitative analysis of multiple 1-ul injections of these standard solutions.The peak ratio method was used because that method is relatively insensitive to variations in the volume of injected samples and to evaporative losses of iso-octane solvent. Plots of peak area ratio versus concentration ratio (both terpene to internal standard) were highly linear. [Typical calibration results are given in table 2 of the original publication.]
Determination of vapour pressure
The vapour pressure was calculated from its gasphase concentration using the ideal gas equation.

Result: = 0.212 hPa at 23.5 °C
= 0.00751 hPa at 6 °C

Test substance: The test compounds [including linalool] were available commercially and they were used without further purification. Aldrich is listed as the source of linalool, the purity given as 97%.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

23-JUL-2001 (91)

Year: 1999

GLP: no data

Method: Saturated vapour pressure was measured over a range of temperatures using a static device that allows reliable measurements within a very large pressure range, from 0.005 hPa to 2000 hPa. The apparatus was described in an earlier paper of the same group [Sasse K, Jose J, Merlin JC (1988): Fluid Phase Equilibria 42: 287-304]; it consists "basically of a cell connected directly to a pressure gauge using high vacuum technology. The temperature is fixed and the vapour pressure is measured at equilibrium. The uncertanty of the measurements are: +/- 0.02 °C (temperature range -70 to 1900 °C), 0.2% for P >= 10 hPa and 1% for P < 10 hPa."
The test substance was introduced into the stainless steel cell at room temperature. Prior to vapour pressure determination, the sample was de-gassed under vacuum to eliminate the air dissolved and the volatile impurities that could be a cause of error. When de-gassing, the lower part of the ceel is heated and the coil is traversed by liquid NO2 so as to minimise losses of the compound during vapour venting. The de-gassed sample is cooled and the vapour pressure was determined at different temperatures from 223 to 468 K (-50 to 195 °C) and replicated at least twice.

Result: = 0.0249 hPa at 273.35 K (0.2 °C)
= 0.0654 hPa at 283.22 K (10.1 °C)
= 0.168 hPa at 293.16 K (20.0 °C)
= 0.27 hPa at 298 K (25 °C), interpolated vapour pressure
= 0.422 hPa at 303.14 K (30.0 °C)
= 0.9339 hPa at 313.1 K (40.0 °C)
= 2.0445 hPa at 323.08 K (50.0 °C)

Test substance: d-linalool from International Flavours and Fragrances (IFF, Longvic, France), as received from manufacturer, purity = 98%

Reliability: (2) valid with restrictions

23-JUL-2001 (41)

Value: = .273063 hPa at 20 degree C

Method: other (measured)

Year: 1997
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Result given as 273.063E-6 bar; 1 bar = 1000 hPa
Reliability: (4) not assignable
23-JUL-2001 (45)

Method: other (measured): not stated
Year: 1947
GLP: no

Result: = 1.33 hPa at 40 °C
= 13.3 hPa at 79.8 °C
= 133 hPa at 133.3 °C
Test substance: d-Linalool
Reliability: (4) not assignable
23-JUL-2001 (139)

Value: = .1 hPa at 20 degree C

Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
25-JUL-2001 (12)

Value: = 2 hPa at 50 degree C

Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
25-JUL-2001 (12)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = 2.97 at 23.5 degree C

Year: 1998
GLP: no data

Method: Octanol-water partition coefficient
Octanol-water partition coefficients were measured using the method of Karickhoff and Brown (1979) [Determination of cotanol/water distribution coefficients ...
EPA-600/4-79-032, US EPA, Athens, GA]: An octanol solution of a monoterpene was equilibrated with water by shaking gently for 20 min. Subsequently, the sample was centrifuged at 10,000 rpm for 10 min, then the phases were separated out of the centrifuge tube. The octanol phase was analysed by GC directly (see below). The aqueous phase was extracted in an iso-octane solution that already contained 200 uM bornyl acetate as an internal standard. In order to exclude the possibility of significant losses of internal standard during the extraction, the validity of adding bornyl acetate before extraction was confirmed in a separate test with pseudo-ectraction of pure water in three repeats. Similarly, the repoducibility of extraction was separately tested and confirmed.
Temperature conditions
At room temperature (23.5 +/- 0.5 °C).
Gas chromatography

A Hewlett-Packard 5890 gas chromatograph with a flame ionisation detector (GC-FID) was used for quantitative analysis of monoterpenes [including linalool]. The monterpenes were separated on a 30 m X 0.53 mm DB-5 megabore column (HP#19095J-023) using the following operating conditions: helium gas at a flow rate of 10 ml/min, nitrogen make-up gas, head pressure of 2 psi (13.8 kPa), spetum purge ON, detector temperature at 200 °C. Excellent resolution of the terpenes and the internal standard (bornyl acetate) was achieved using the following program: 100 °C for 14 min, 20°/min for 4 min and 180 °C for 5 min. [A typical gas chromatogram for a standard solution containing 200 uM of each monoterpene and bornyl acetate ist given in fig. 1 of the original publication.]
Standard solutions and calibration curves
Standard solutions containing approximately 200 uM of bornyl acetate as an internal standard and 6-1000 uM each of the eight terpenes [tested in this study] in iso-octane were prepared volumetrically from gravimetrically prepared 0.01 Mstock solutions of the solutes in iso-octane. Calibration curves were constructed from the average quantitative analysis of multiple 1-ul injections of these standard solutions.The peak ratio method was used because that method is relatively insensitive to variations in the volume of injected samples and to evaporative losses of iso-octane solvent. Plots of peak area ratio versus concentration ratio (both terpene to internal standard) were highly linear. [Typical calibration results are given in table 2 of the original publication.]

Result: The Kow (Pow) values were calculated as the ratio of molar concentrations of a monoterpene in octanol and water.

Test substance: The test compounds [including linalool] were available commercially and they were used without further purification. Aldrich is listed as the source of linalool, the purity given as 97%.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

12-JUL-2001 (91)

Partition Coeff.: octanol-water

log Pow: = 2.9

Method: other (measured): Determination of the partition coefficient (octanol/water) by reverse-phase thin-layer chromatography

Year: 1991

GLP: no

Method: Guideline
ECETOC Technical Report no. 9 (1983): Determination of the partition coefficient (octanol/water) by reverse-phase thin-layer chromatography. ECETOC, Brussels, 1983.
Principle
Reverse-phase thin-layer chromatography (TLC) is used on an octadecyl-modified stationary phase. Partitioning on the plate follows the order of hydrophobicity when a suitable mobile phase is used. From the relationships between the measured retention factors (Rf) and the known octanol/water partition coefficients of the respective reference substances the logPow of the test substance ma be interpolated.
Equipment
TLC tank and UV lamp for detection from CAMAG, Muttenz,

Switzerland.
Precoated chromatographic plates HPTLC RP-18 F 254 (article no. 13724, Merck, Darmstadt, Germany)
Mobile phase: acetonitrile:water 9:1 (v/v). Acetonitrile, article no. 690, Fluka AG, Buchs, Switzerland.
Spraying solution: sulfuric acid:ethanol 2:8 (v/v). Sulfuric acid, article no. 731, Merck; ethanol, article no. 2850, Fluka)
The spots are revealed by UV light or by spraying the plates with the above solution and heating to ca. 150 °C.

Result: logPow = 2.90 +/- 0.131, based on 4 different determinations with naphthalene and acetophenone in each case as reference substances. Single Rf values for all test runs are given.

Test substance: Linalool synthetic, Lot no. 175725, purity 97.6%, certificate of analysis dated 27/02/91
Reference substances:
Oxalic acid (purity >= 99.5%, logPow = -0.62, Fluka no. 495)
Acetophenone (purity >= 98%, logPow = +1.63, Merck no. 80028)
Maphthalene (purity >= 99%, logPow = +3.31, Merck no. 820846)

Reliability: (2) valid with restrictions
Reliability judged as 2 because the Givaudan lab was not GLP certified in 1991 and some details in the report are missing (temperature, time of TLC runs).

30-JUL-2001 (124)

Partition Coeff.: octanol-water
log Pow: = 2.84 at 25 degree C

Method: OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
GLP: no data

Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
type of partition coefficient, year, test substance and GLP conditions not stated

30-JUL-2001 (7)

Partition Coeff.: octanol-water
log Pow: = 3.1 at 25 degree C

Method: OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
GLP: no data

Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
type of partition coefficient, year, test substance and GLP conditions not stated

30-JUL-2001 (6)

Partition Coeff.: water - air
log Pow: at 25 degree C

Method: other (calculated)
Year: 2001
GLP: no

Remark: QSAR calculation
Result: Henry's Constant = 1.943E-05 atm/(mol/m3)

Reliability: (4) not assignable
30-JUL-2001 (136)

Partition Coeff.: water - air
log Pow: at 25 degree C

Method: other (measured): quotient of experimental vapour pressure and solubility
Year: 2001
GLP: no

Result: Henry's Constant = 1.945E-05 atm*m3/mol
Reliability: (4) not assignable
30-JUL-2001 (144)

Partition Coeff.: water - air
log Pow: at 25 degree C

Method: other (calculated)
Year: 2001
GLP: no

Remark: QSAR calculation
Result: Henry's Law Constant KH = 4.23E-05 atm*m3/mol
Reliability: (4) not assignable
30-JUL-2001 (144)

Partition Coeff.: soil-water

Method: other (calculated)
Year: 2001
GLP: no

Remark: QSAR calculation
Result: Organic-carbon/water partition coefficient Koc = 56.32
Reliability: (4) not assignable
30-JUL-2001 (144)

Year: 1998
GLP: no data

Method: logPdoc was estimateded using the logPow determined experimentally, based on a relationship respectively a formula published by Kile et al. [Kile DE, Chiou CT, Brinton TI (1989): Interactions of organic contaminants with fulvic and humic acid ... In Averett RC, Leenheer JA, McKnight DM, Thorn KA eds: Humic substances in the Suwannee River, Georgia. US Geological Survey, Denver, CO].
Result: The partition coefficient between water and dissolved organic carbon (logKdoc resp. logPdoc) was calculated to be 0.60.
Test substance: The test compounds [including linalool] were available commercially and they were used without further purification. Aldrich is listed as the source of linalool, the purity given as 97%.
Conclusion: Based on the low logPdoc, partitioning to the aqueous phase is likely.
Reliability: (4) not assignable
30-JUL-2001 (91)

Partition Coeff.: soil-water
log Pow: = 1.265

Method: other (calculated)
Year: 2001
GLP: no

Result: soil-water partition coefficient given as 18.4, which equals a log value of 1.265
Reliability: (4) not assignable
31-JUL-2001 (97)

Partition Coeff.: sediment-water
log Pow: = 1.564

Method: other (calculated)
Year: 2001
GLP: no

Result: sediment-water partition coefficient given as 36.7, which equals a log value of 1.564
Reliability: (4) not assignable
31-JUL-2001 (97)

Partition Coeff.: water - air
log Pow: = 3.03

Method: other (calculated)
Year: 2001
GLP: no

Result: air-water partition coefficient given as 9.25E-4, which translates to 1081, respectively to a log value of 3.03
Reliability: (4) not assignable
31-JUL-2001 (97)

Method: other (calculated)
Year: 2001
GLP: no

Result: fish-water partition coefficient = 46.7, which equals a log value of 1.669
Reliability: (4) not assignable
31-JUL-2001 (97)

Method: other (calculated)
Year: 2001
GLP: no

Result: suspended sediment-water partition coefficient = 36.7, which equals a log value of 1.565
Reliability: (4) not assignable
31-JUL-2001 (49)

Method: other (calculated)
Year: 2001
GLP: no

Result: organic carbon-water partition coefficient = 383, which equals a logKoc of 2.58
Reliability: (4) not assignable
31-JUL-2001 (49)

2.6.1 Solubility in different media

Value: = 1.45 g/l at 25 degree C
pH value: = 4.5
Conc.: 1.45 g/l at 25 degree C

Source: BASF AG Ludwigshafen
22-JAN-2002 (12)

Solubility in: Water
Value: = 1.589 g/l at 25 degree C

Method: other: not stated
Year: 1982
GLP: no data

Reliability: (4) not assignable
22-JAN-2002 (72)

Solubility in: Water
Value: = 5.862 g/l at 37 degree C

Method: other: not stated
Year: 1978
GLP: no
Test substance: no data

Reliability: (4) not assignable
22-JAN-2002 (43)

Solubility in: Water
Value: = 854 mg/l at 23.5 degree C

Year: 1998
GLP: no data

Method: Aqueous solubility and vapour pressure measurement
To measure aqueous solubilities and vapour pressures on the monoterpenes, pure terpenes were equilibrated with water and air in 1-l Erlenmeyer flasks that were customised to prevent physical contact between the pure terpenes and water; terpenes were suspended over the water in glass cups attached to the flask stopper. 500 ml of pure water containing 0.005 M NaN3 to inhibit bacterial growth were placed in each flask. A septum port allowed collection of air samples. The flasks were gently shaken on a platform shaker to facilitate air-water exchange, through which the air and water phases eventually became saturated with the monoterpene tested.
Temperature conditions
The aqueous solubilities and vapour pressures were measured at room temperature (23.5 +/- 0.5 °C) and at a lower temperature (6 +/- 1 °C).
Sampling
Periodically the air phase was sampled through the septum port and a 2-ml volume extracted using a gas-tight syringe; flasks were then opened to collect 5-ml aliquots of the aqueous phase. These were extracted and analysed as described. Experiments were continued until the measured terpene concentration was constant for at least one week.

Sample extraction
Monoterpenes in both aqueous and gaseous samples were extracted in an iso-octane solution that already contained 200 uM bornyl acetate as an internal standard. In order to exclude the possibility of significant losses of internal standard during the extraction, the validity of adding bornyl acetate before extraction was confirmed in a separate test with pseudo-ectraction of pure water in three repeats. Similarly, the repoducibility of extraction was separately tested and confirmed.
Gas chromatography
A Hewlett-Packard 5890 gas chromatograph with a flame ionisation detector (GC-FID) was used for quantitative analysis of monoterpenes [including linalool]. The monterpenes were separated on a 30 m X 0.53 mm DB-5 megabore column (HP#19095J-023) using the following operating conditions: helium gas at a flow rate of 10 ml/min, nitrogen make-up gas, head pressure of 2 psi (13.8 kPa), spetum purge ON, detector temperature at 200 °C. Excellent resolution of the terpenes and the internal standard (bornyl acetate) was achieved using the following program: 100 °C for 14 min, 20°/min for 4 min and 180 °C for 5 min. [A typical gas chromatogram for a standard solution containing 200 uM of each monoterpene and bornyl acetate ist given in fig. 1 of the original publication.]
Standard solutions and calibration curves
Standrad solutions containing approximately 200 uM of bornyl acetate as an internal standard and 6-1000 uM each of the eight terpenes [tested in this study] in iso-octane were prepared volumetrically from gravimetrically prepared 0.01 Mstock solutions of the solutes in iso-octane.Calibration curves were constructed from the average quantitative analysis of multiple 1-ul injections of these standard solutions.The peak ratio method was used because that method is relatively insensitive to variations in the volume of injected samples and to evaporative losses of iso-octane solvent. Plots of peak area ratio versus concentration ratio (both terpene to internal standard) were highly linear. [Typical calibration results are given in table 2 of the original publication.]

Result: = 854 +/- 3.4 mg/l at 23.5 °C
= 551 +/- 2.8 mg/l st 6 °C
In the original the solubility of linalool is given as M (mol/l), which was converted to mg/l using a molecular mass of 154.24. The standard deviation was was calculated from the averages of the last three measurements.

Test substance: The test compounds [including linalool] were available commercially and they were used without further purification. Aldrich is listed as the source of linalool, the purity given as 97%.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

22-JAN-2002 (91)

Solubility in: Water
Value: = 1.45 g/l

Method: other: not stated
Year: 1999
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: commonly accepted value, fopund in many reference works
Reliability: (4) not assignable
05-JUL-2001 (14)

Solubility in: Organic Solvents
Descr.: miscible

Method: other: not stated
Year: 1999
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
05-JUL-2001 (14)

2.6.2 Surface Tension

Test type: other
Concentration: other: "pure"

Method: other: determined with a stalagmometer
Year: 1985
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: = 20.969 mN/m,
based on the result given in the publication of 20.969 dyne/cm (1 dyne = 10E-2 mN).
Test condition: Temperature probably 20 °C (temperature given for other determinations)
Reliability: (4) not assignable
11-JUL-2001 (118)

Value: = 26.63 mN/m at 20 degree C

Method: other: not stated
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
17-JUL-2001 (44)

2.7 Flash Point

Value: = 55 degree C
Type: other: not stated

Method: other: not stated
Year: 2001
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
05-JUL-2001 (50)

Value: = 75 degree C
Type: closed cup

Method: other: DIN 51758
Year: 1999

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: DIN 51758 is a closed cup method with stirring
Reliability: (4) not assignable
05-JUL-2001 (14)

Value: = 78 degree C

Method: other: not stated
Year: 1994
GLP: no data
Test substance: no data

Reliability: (4) not assignable
05-JUL-2001 (20)

2.8 Auto Flammability

Value: = 260 degree C at 994 hPa

Method: other: DIN 51794
Year: 1994
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Dynamic thermal analysis in a high-pressure vessel TA 2000. Dynamic test from 25 °C to 360 °C, heating rate = 2.5 °C/min, 34.4 mg of test substance.
Test substance: synthetic linalool, purity = 97.5% (GC)
Reliability: (2) valid with restrictions
09-AUG-2001 (47)

Value: = 235 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
09-AUG-2001 (12)

2.9 Flammability

Method: other: DIN 51758
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: flash point = 79 °C
Reliability: (4) not assignable
30-JUL-2001 (5)

Method: other: no data
Year: 1997
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: flash point = 84 °C
30-JUL-2001 (44)

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: flash point = 75 °C
09-AUG-2001 (1)

2.10 Explosive Properties

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Explosion limits in air = 0.9-5.2% (v/v)
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
09-AUG-2001 (12)

2.11 Oxidizing Properties

Year: 2000
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: Substances
Approximately 100 component substances of essential oils were tested for antioxidant properties. Pure substances including linalool were purchased from listed sources.
Methods
Two test systems were used:
1) In a modified thiobarbituric acid reactive species assay, egg yolk homogenates in lipid-rich media were used as a substrate for oxygenation in the presence and absence of test substances and compared with aplha-tocopherol as a standard. Technical details are given in the paper.
2) The rate of conjugated diene formation from linoleic acid in the presence and absence of test substances was determined and compared with aplha-tocopherol as a standard. Technical details are given in the paper.
Determinations were made in quadruplicate and results are reported in the publication as means +/- standard deviation.
Remark: it is recognised that this category is normally used for inorganic substances.
Result: In a test for antioxidant properties, linalool proved to have pro-oxidant properties in one of the test systems [as just one of two substances among 100 tested, the other being (+/-)-cis-nerolidol] and no activity at all in the other.
Reliability: (2) valid with restrictions
31-JUL-2001 (122)

2.12 Dissociation Constant

Acid-base Const.: = 18.469

Method: other: calculated
Year: 2001
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: QSAR calculation
Reliability: (4) not assignable
30-JUL-2001 (136)

2.13 Viscosity

Test type: other: Oswald viscometer
Value: = 4.497 mPa s (dynamic) at 20 degree C

Method: other
Year: 1985
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
11-JUL-2001 (118)

Test type: other: not stated
Result: = 5.298 Pa*m/s (original: 5.30E-3 kg/(m*s))

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
09-AUG-2001 (44)

2.14 Additional Remarks

Memo: Abiotic degradation: gas phase reactions with OH radicals, NO3 radicals and O3

Method: Experiments were performed in various, 5800-l to 6700-l all-teflon chambers at 296+-2 K and 986 hPa (740 Torr) total pressure of purified air at approx. 5% relative humidity, with each chamber being equipped with two parallel banks of black lamps for irradiation. Chambers were equipped with teflon-coated fans, which were used only during introduction of the reactants into the chambers to ensure their rapid mixing.
Experiments were performed singly for OH radicals, NO3 radicals and O3. The radicals were generated on the spot and measures were taken (fully described in the paper) to prevent formation of any of the other radicals/reactants.
Linalool and selected products were quantified using various analytical techniques, depending on the chemical nature: GC-FID, GC-FTIR, GC-MS, atmospheric pressure ionisation MS (API-MS) and API tandem MS/MS.
Result: Reaction with O3
The follwing products were identified:
1) 4-hydroxy-4-methyl-5-hexenal or its cyclised form 2-ethenyl-2-methyl-5-hydroxytetrahydrofuran;
2) 5-ethenyldihydro-5-methyl-2(3H)-furanone;
3) acetone;
4) formaldehyde.
Rate constant = 4.3E-16 cm3/(molecule*second)
-
Reaction with the OH radical
Beside acetone the following products were identified:
1) 6-methyl-5-hepten-2-one;

2) 4-hydroxy-4-methyl-5-hexenal or its cyclised form 2-ethenyl-2-methyl-5-hydroxytetrahydrofuran;
3) acetone.
Rate constant = 1.59E-10 cm3/(molecule*second)
-
Reaction with the NO3 radical
Beside acetone the following products were identified:
1) 4-hydroxy-4-methyl-5-hexenal or its cyclised form 2-ethenyl-2-methyl-5-hydroxytetrahydrofuran;
2) acetone.
Rate constant = 1.12E-11 cm3/(molecule*second)

Reliability: (2) valid with restrictions
17-JUL-2001 (133)

Memo: Abiotic degradation: gas-phase reaction with ozone

Method: Mixtures of ozone and the test compounds were allowed to react in the presence of 400 ppm cyclohexane added to scavenge the hydroxyl radical, which may form as a reaction product and react with the compounds studied.
The experiments were carried out in the dark in 3.7- to 3.9-m3 FEP teflon chambers at ambient temperature (14-22 °C) and pressure = 1 atmosphere of purified, humid (RH = 55+/-10%) air. The reaction was followed under pseudo-first-order conditions. Ozone was monitored continuously by ultaviolet photometry with a precision of +/- 1-2 ppb. Control experiments involved measurements of the loss of ozone alone in purified, humid air and in the presence of cyclohexane. Comparison of ozone loss rates measured in the presence and absence of cyclohexane indicated that cyclohexane did not contain ozone-containing impurities. The baseline ozone loss rates were approximately two orders of magnitude lower than the pseudo-first-order loss rates of ozone in the experimental runs with ozone, cyclohexane and the unsaturated compounds.

Result: For the linalool reaction with ozone, based on three experimental runs with different concentrations of linalool and ozone at different temperatures the following pseudo-first-order constants (k) were determined:
1, 0.8 ppm linalool, 89 ppb ozone, T = 14 °C, k >= 0.00546/s
2, 3.0 ppm linalool, 299 ppb ozone, T = 15 °C, k >= 0.0158/s
3, 4.0 ppm linalool, 470 ppb ozone, T = 21 °C, k >= 0.0310/s
Based on these data, a second-order reaction rate constant of >=315+/-23 * 10E-18 cm3/(molecule*s) was determined.

Conclusion: "Using a typical ozone concentration of 50 ppb and the reaction rate constants [...], atmospheric half-lives of the unsaturated oxygenates against removal by reaction with ozone are <= 30 min for linalool [...]".

Reliability: (2) valid with restrictions
17-JUL-2001 (61)

Memo: Abiotic degradation: atmospheric reaction

Result: 6-Methyl-5-hepten-2-one (CAS 409-02-9) is a product of the OH-radical-initiated reaction of linalool
17-JUL-2001 (135)

Memo: Dangerous reactions: exothermic reaction in case of contact with acids

Remark: Gefaehrliche Reaktionen: Exotherme Reaktion mit Saeuren.
Source: BASF AG Ludwigshafen
22-JAN-2002 (12)

3.1.1 Photodegradation

Type: other

Result: no data located
23-JAN-2002

3.1.2 Stability in Water

Type: abiotic

Method: other: abiotic control of a, OECD 301 C biodegradability test
Year: 1991
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: In the sterile control of a ready biodegradability test, no indication of substance instability was noted over 28 days.
Reliability: (4) not assignable
30-JUL-2001 (123)

3.1.3 Stability in Soil

Type: other: outdoors semi-field test
Radiolabel: no
Year: 2000

Method: Experimental Setup
20 aluminium trays per substance were used: (4 different soils) X (2 different sewage sludges) X (spiked and unspiked) + 4 duplicates. Soils were taken from Georgetwon (DE), Newark (DE), Midwest (IL) and Southern (SC). Domestic, anaerobically digested sludges were taken from Georgetown (DE) and Wilmington (DE) STPs. For spiked mixtures, sludge (amount not stated) was spiked by rolling at 4 rpm for 30 min in glass jars (size not stated) pre-coated with test substance (amount not stated). For each tray, 1 l of sludge was mixed with 24 l of soil using a cement mixer. Each tray has a drain hole connected to a glass jar by teflon connector and tubing. Trays were exposed outdoors (exact location not stated).
Sampling
Leachate samples were collected after each rainstorm. Formaldehyde (3% v/v) was added to all samples and samples were stored at 5 °C until analysis. Soil corings (1 cm diameter, 15 cm depth) were taken at predetermined (not stated) times, the hole being plugged with a glass rod after sampling. Samples were stored at -20 °C until analysis.
Analysis
The analytical method is based on Simonich et al. [Envir Sci Technol 34: 959, 2000]. Liquid samples were extracted using JT baker Bond speed disks and eluted with dichloromethane. Soil samples were extracted with Accelerated Solvent Extraction (ASE) using dichloromehtane.
Dichlormomethane extracts were analysed using an Agilent 6890GC-5073MS gas chromatograph-mass spectrometer equipped with a J&W DB-1701 capillary column. 2-Methyl-naphthalene

(9.77 ng/ul) was used as an internal standard. Each fragrance material (test substance) was identified and quantified based on 2 or 3 compound-specific ions.
Remark: In a sewage treatment plant many undegraded fragrance materials will partition to sewage sludge and subsequently be applied to agricultural soil. An outdoors, long-term die-away experiment to study the fate of selected fragrance materials, including linalool, in sludge-amended soils due to leaching, volatilisation and degradation was therefore performed at the University of Delaware, Newark DE, USA.
Result: 13 of the spiked fragrance materials (including linalool; D Salvito, pers. comm.) were not detected in leachate or soils samples.
Test substance: "linalool", no further characterisation
Conclusion: The authors concluded the following from not detecting 13 fragrance materials, including linalool:
"Concentrations of all detected fragrance materials decreased over time in both soil and leachate. [...]
"This may be due to volatilisation losses and poor spiking efficiency during preparation or low recovery during extraction. [...]
"Leaching does not appear to be a significant fate process. The cumulative mass of fragrance materials leached in the first two months accounted for less than 5% of the initial mass for DPMI [1,2,3,5,6,7-Hexahydro-1,1,2,3,3-pentamethyl-4H-inden-4-one, CAS 33704-61-9] and less than 1% for all other fragrance materials."
Reliability: (4) not assignable
17-JUL-2001 (33)

3.2.1 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: surface water
Concentration: = .11 - µg/l

Method: Surface water from the Ruhr river in Germany was sampled and stripped for volatile organic carbons, then analysed using gas chromatography and mass spectrometry. Calibration was performed with reference compounds of the highest available commercial quality. Details of the procedure are given in the paper.
Reliability: (4) not assignable
13-AUG-2001 (83)

Type of measurement: background concentration
Medium: drinking water
Method: no data

Result: Linalool was detected in an unknown number of drinking water samples, concentrations not reported.
Reliability: (4) not assignable
13-AUG-2001 (134)

Type of measurement: background concentration
Medium: air

Result: Biogenic terpenoid emissions from forests in Finland were analysed and modelled over a vegetation period, from

April/May to October. Linalool is being emitted mostly by birch trees, mainly Betula pubescens but also B. pendula, which together are the dominant deciduous trees in the middle to northern boreal zones with a total of approx. 7.5% of all trees (just above 90% of all trees are evergreen pine and spruce, which are not reported to emit linalool). As predicted by the model and corroborated by analysis, total monoterpene ambient air concentrations ranged from approx. 500 ppt by volume (only graph given, no numerical data) in May to 1000-2000 pptv from June to the end of August and again declining to approx. 500 pptv in October; no data are given for the winter months proper. The linalool share of the total monoterpene emissions for the south, middle and north boreal zones ranges between 1.9, 1.5 and 0% in spring, 4.6, 6.4 and 6.1% in summer and 2.4, 3.1 and 2.8% in autumn. [The 0% in the north in spring is possibly due to leaves only just budding.] A rough average of 1-2% in spring, 5-6 % in summer and 2-3% in autumn of total monoterpene concentrations corresponds to approximately 5-10 pptv in spring, 50-120 pptv in summer and 10-15 pptv in autumn. Total monoterpene emission fluxes are given as approx. 5-10 ng/(m2 * s) in spring, 50-100 ng/(m2 * s) in summer and 5-30 ng/(m2 * s) in autumn, depending on latitude; again with the same linalool fractions this corresponds to linalool emissions of 0.05-0.2, 2.5-6 and 0.1-0.9 ng/(m2 * s).

Conclusion: The world's total boreal forests and other wooded land within the boreal zone cover 1.2 billion ha of which 920 million ha are closed forest (Stocks et al, 1998). Using the closed forest are of 9.2 * 10E12 m2 and an average of 12 hours emission during the day, the low linalool emission estimates from Lindfors et al (2000) based on measurements in Finnish boreal forests translate to daily emissions in spring, summer and autumn of approx. 20, 990 and 40 metric tonnes of linalool just by the global boreal forests. By adding these emissions (60 days in spring, 90 in summer and 60 in autumn) a total emission of approx. 93,000 t linalool/year by boreal forests is made likely. This very rough extrapolation is based on the low estimate for linalool emissions by Lindsfors et al (2000), but even with their own uncertainty factor of 70% there would still remain 28,000 t/year as a minimal global boreal forest emission of linalool.

Reliability: (4) not assignable

13-AUG-2001 (92) (137)

Type of measurement: other: detection in the headspace of household products
Medium: air

Method: Equal samples of all products were placed in a small porcelain cup with a defined surface area that was enclosed in a hermetically sealed glass container with inlet and outlet valves. A helium flow, corresponding to 6 volume changes per hour, was passed through the container and a Tenax absorption column fitted to the outlet valve. After a defined time the Tenax cartridges were thermally desorbed and volatile organic carbons were analysed by GC-MS with parallel FID and MS.

Result: Linalool was detected in the headspace of 4 water-based liquid waxes and of 1 water-based detergent, out of a total of 8 waxes and 2 detergents. No concentrations are given, but in the case of 3 water-containing waxes linalool had a

relative abundance in the headspace samples of 5, 26 and 29%, respectively.
Test substance: 10 household products used for cleaning or conservation of large surfaces, which may potentially lead to high emissions of volatile constituents, were analysed. In those 10 products, 3 were waxes that did not contain water while the 7 other products contained water as a main constituent (80-90%), 5 waxes and 2 detergents.
Reliability: (4) not assignable
13-AUG-2001 (88)

3.2.2 Field Studies

Type of measurement: other: environmental degradation by river bank and slow sand filtration
Media: river water, river bank sediment, gravel and slow sand filters

Method: Surface water from the Ruhr river in Germany as well as river bank filtrates and roughing gravel respectively slow sand filtrates were sampled from sampling wells and stripped for volatile organic carbons, then analysed using gas chromatography and mass spectrometry. Calibration was performed with reference compounds of the highest available commercial quality. Details of the procedure are given in the paper. The percentage of degradation of linalool was determined using the quantitative analyses.
Remark: In the Hengsen catchment area on the Ruhr river in Germany, river water is extensively used for water production by slow sand filtration. Upstream of a dam, Ruhr river water is diverted into a reservoir, from which it passes horizontally through the river bank, then through roughing gravel filters and an aeration step into slow sand filters and last into the groundwater aquifer. Due to the difference in elevation between the reservoir and the lower stretch of the river, some water flows through the river bank beside the water works toward the lower stretch.
Result: Elimination in the anoxic river bank: Hydrostatic flow through the anoxic river bank resulted a degradation for linalool of 98% compared with river water at a first sampling well "near to the bank" and of 99% approximately 50 m from the bank. Elimination in the aerobic slow sand filter system: Passage through the roughing gravel filters eliminated approx. 85% of the original linalool, subsequent aerobic slow sand filtration improved the overall degradation rate over 99%.
Conclusion: Up to 99% of relatively high concentrations of linalool in the Ruhr river in the heavily populated Ruhrgebiet are eliminated during passage through the natural, anoxic river bank. Water pretreatment through aerobic gravel and slow sand filtration prior to groundwater infiltration showed the same degree of degradation.
Reliability: (4) not assignable
09-AUG-2001 (83)

3.3.1 Transport between Environmental Compartments

Type: other: see chapter 3.3.2, Distribution

04-DEC-2001

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: other (calculation)
Year: 1998

Method: The conclusion is based on experimentally determined physicochemical properties (water solubility, vapour pressure, octanol/water partition coefficient) and a derived dissolved-organic-carbon/water partition coefficient for several monoterpenes including linalool.
Result: The physicochemical properties of the terpene alcohols [including linalool] used in this study indicate that the alcohols are likely to occur in the aqueous phase. Chemical and biological degradation of terpene alcohols in the aqueous phase are thus likely to be more important loss mechanisms than volatisation and sorption.
Reliability: (4) not assignable
31-JUL-2001 (91)

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level I
Year: 2001

Method: Physical properties input as follows:
data temperature = 20 °C
molecular mass = 154.25 g/mol
melting point = -57 °C
vapour pressure = 21.2 Pa
aqueous solubility = 1450 mg/l
Result:

Environmental compartment	Distribution, %
Air	20.0
Soil	35.8
Water	43.3
Sediment	0.796
Suspended sediment	0.025
Fish	0.002

Reliability: (4) not assignable
09-AUG-2001 (97)

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level III
Year: 2001

Method: Input of physical properties was as follows: molecular mass = 154.25, vapour pressure = 21.2 Pa, logKow = 2.79, water solubility = 1450 g/m3, melting point = -57 °C.
Remark: Emissions = 1000 kg/h each to air, water and soil.
Result:

Environmental compartment	Distribution, %
Air	0.097
Water	42.87
Soil	56.96
Sediment	0.072

Reliability: (4) not assignable
09-AUG-2001 (98)

Media: air - biota - sediment(s) - soil - water
Method: other (calculation): EPIWIN level III fugacity model
Year: 2001

Method: Input of physical properties was as follows: SMILES string,

vapour pressure = 13.3 mm Hg, logKow = 2.97, boiling point = 199 °C, melting point = -57 °C.

Remark: Emissions = 1000 kg/h each to air, water and soil.

Result:

Environmental compartment	Concentration, %
Air	0.0426
Water	30.5
Soil	69.1
Sediment	0.36

Reliability: (4) not assignable

31-JUL-2001 (144)

Media: other: room air - dust

Year: 1995

Method: A liquid mixture of bornyl acetate (10%), menthol (9%), camphor (11%), linalool (9%), camphene (15%), alpha-pinene (15%) and octane (14%) [percentages given as graph only, hence approximate values and total silghtly > 100%]¨was sprayed in an apartment. The distribution of the test substances between room air and house dust was then analytically determined.

Result: Linalool concentration recovered from room air was approximately [data given as graph only] twice as high as in house dust.

Conclusion: Among the different compounds used in the vaporising mixture, the more polar-hydrophilic compounds (nornyl acetate, menthol, camphor) tended to concentrate in the house dust whereas the non-polar onces concentrated in air (camphene, alpha-pinene, octane). With an approximate 2:1 air:dust distribution, linalool was intermediate regarding distribution.

31-JUL-2001 (42)

3.4 Mode of Degradation in Actual Use

Memo: Degradation during primary treatment of domestic wastewater

Method: Land application of domestic wastewater is considered an innovative alternate technology for water pollution control by the US Clean Water Act of 1977. At Fort Polk, Louisiana, the local sewage treatment plant (STP) did not produce acceptable secondary effluent despite upgrading. A very large, 32-ha rapid infiltration site was therefore constructed for tertiary treatment through land application of this secondary effluent. To test for the possibility of contaminating groundwater by this soil-based treatment, a transport and fate study was performed by Rice University. After primary treatment of the raw sewage to remove suspended solids and heavy metals, secondary effluent was drawn from the STP effluent and stored at 4 °C. In the laboratory it was then leached through soil columns. Both the secondary effluent and the leachate were analysed and quantified for trace organics using gas chromatography.

Result: In the secondary effluent (after removal of suspended solids and heavy metals), linalool was determined in two samples at 0.25 ug/l and 0.11 ug/l, respectively. The authors state that: "Readily biodegradable compounds such as linalool [...] were not consistently detected in the feed solution [for the leaching comlumns] and were not studied. These organics were probably degraded during storage of the feed solution at 4 °C."

Source: The original raw sewage was from the community at Fort Polk, Louisiana.
Reliability: (4) not assignable
17-JUL-2001 (69)

Memo: Degradation by river bank filtration and slow sand filtration prior to groundwater infiltration

Method: Surface water from the Ruhr river in Germany as well as river bank filtrates and roughing gravel respectively slow sand filtrates were sampled from sampling wells and stripped for volatile organic carbons, then analysed using gas chromatography and mass spectrometry. Calibration was performed with reference compounds of the highest available commercial quality. Details of the procedure are given in the paper.
The percentage of degradation of linalool was determined through the loss evidenced by quantitative analysis.
Remark: In the Hengsen catchment area on the Ruhr river in Germany, river water is extensively used for water production by slow sand filtration. Upstream of a dam, Ruhr river water is diverted into a reservoir, from which it passes horizontally through the river bank, then through roughing gravel filters and an aeration step into slow sand filters and last into the groundwater aquifer. Due to the difference in elevation between the reservoir and the lower stretch of the river, some water flows through the river bank beside the water works toward the lower stretch.
Result: Elimination in the anoxic river bank:
Hydrostatic flow through the anoxic river bank resulted a degradation for linalool of 98% compared with river water at a first sampling well "near to the bank" and of 99% approximately 50 m from the bank.
Elimination in the aerobic slow sand filter system:
Passage through the roughing gravel filters eliminated approx. 85% of the original linalool, subsequent aerobic slow sand filtration improved the overall degradation rate over 99%.
Conclusion: Up to 99% of relatively high concentrations of linalool in the Ruhr river in the heavily populated Ruhrgebiet are eliminated during passage through the natural, anoxic river bank. Water pretreatment through aerobic gravel and slow sand filtration prior to groundwater infiltration showed the same degree of degradation.
Reliability: (4) not assignable
17-JUL-2001 (83)

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 2 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: = 64.2 % after 28 day(s)
Result: readily biodegradable
Kinetic: 5 day(s) = 40.9 %
15 day(s) = 60.5 %
28 day(s) = 64.2 %
Control Subst.: Benzoic acid, sodium salt
Kinetic: 5 day(s) = 50.3 %
15 day(s) = 62.4 %

Deg. product:	not measured
Method:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year:	1991
GLP:	yes
Test substance:	as prescribed by 1.1 - 1.4
Method:	Activated sludge Activated sludge was collected from the mainly domestic sewage treatment plant of CH-4152 Reinach, Switzerland, on July 31st, 1991; the pH at collection was 7.8. Preparation of the sludge was carried out according to OECD Guideline 301D of May 1981. However, as a deviation from the Guideline, 0.5 ml/l inoculum were used instead of 1 drop/l. Procedure 250-ml BOD flasks with gas inlet were used as test vessels, the tes water was prepared according to the Guideline in a mixing tank. Temperature The test was performed at room temperature (20 +/- 1 °C). Duration 28 days. Substances tested Test substance: dl-Linalool from F. Hoffmann-La Roche Ltd, batch no. 08071, purity 97.8%, retest date June 30th 1992 (testing time was July 31st to Aug 28th, 1991). Reference substance: Sodium benzoate, source not stated. Blank: No test substance (2 vessels, sludge only). Test concentrations Test substance: A stock solution of 400 mg accurately weighed in 1 litre of water was prepared. From this stock solution, 15 ml were dissolved ad 3 l of test water prepared according to the Guideline, resulting in a final linalool concentration of 2 mg/l. Reference substance: 8.82 ml of a stock solution of 1000 mg/l was dissolved ad 3 l test water, resulting in a final sodium benzoate concentration of 2.94 mg/l. Sludge 0.5 ml sludge prepared according to the Guideline were added per litre of test water. Measurements Dissolved oxygen measurements were taken at the beginning, on days 5, 15 and 28. Oxygen concentration in mg/l was determined with an ORION Electrode Type 97-08 on an ORION Microprocessor Ionalizer 901. Calculations of biodegradation The degradation rate was calculated on the basis of the measured time-dependent oxygen consumption of blank, test solutions and reference substance in comparison with the theoretical oxygen demands for the test and reference substance concentrations, respectively. ThOD per mg was calculated on a stoichiometric basis.
Remark:	As the test substance was found to be volatile a Closed Bottle biodegradation test was performed.
Result:	The final biodegradation of Linalool in the Closed Bottle Test was 64.2% (BOD/ThOD). Due to only 3 DOC determinations at days 5, 15 and 28, no detailed biodegradation curve can be drawn and therefore the "10-day window" criterion cannot be confirmed nor refuted in the strict sense. However, ready biodegradability is still accpeted for linalool as, based on linear concatenation of the data points, both the test and reference substance cross the 10% degradation threshold within 1 day, and degradation of linalool was 10 percent

points below the reference substance on day 5 but slightly above the reference at day 28, which is interpreted a small adaptation or lag phase before linalool degradation gets going.
The test is judged to be valid because both test flasks showed parallel dissolved oxygen depletion, with the difference after 28 days < 0.5 mg O2/l (4.55 vs 4.08 mg O2/l); the DOC depletion in the two blank (sludge only) flasks was even closer with a final difference of 0.11 mg/l (8.17 vs 8.06 mg O2/l); and the degradation of the reference substance confirmed the activity of the sludge.

Reliability: (1) valid without restriction
OECD study under GLP, reliability 1.

Flag: Critical study for SIDS endpoint

29-JUL-2002 (58)

Type: aerobic
Inoculum: other bacteria: mixture of sludge from the communal WWTP of Geneva-Aïre, the combined industrial-municipal WWTP of Vernier-Ouest and soil sampled on the bank of the Rhone river in Geneva
Concentration: 100 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: = 80 % after 28 day(s)
Result: readily biodegradable
Kinetic:
4 day(s) = 2 %
6 day(s) = 44 %
8 day(s) = 58 %
10 day(s) = 65 %
14 day(s) = 75 %
Control Subst.: Aniline
Kinetic:
4 day(s) = 19 %
6 day(s) = 68 %

Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 1991
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: The biodegradability of linalool was determined by biochemical oxygen demand (BOD) over time in comparison to the theoretical oxygen demand (ThOD) based on the molecular formula of linalool, according to the guideline.
Equipment
Voith Sapromat automatic oxygen consumption measurement apparatus and sample incubator, from Laborapparate AG, CH-9105 Schönengrund, Switzerland.
Test temperature was 20 °C.
Test conditions
Test flasks 1 and 2: basal culture medium + 30 mg activated sludge/l + approx. 100 mg linalool/l (concentration to be analytically confirmed).
Positive control, flask 3: basal culture medium + 30 mg activated sludge/l + approx. 100 mg aniline/l (concentration to be analytically confirmed).
Baseline control, flask 4: basal culture medium + 30 mg activated sludge/l
Result: Linalool had an average BOD28 in test flasks 1 and 2 of 2.33 mg O2/mg linalool. In comparison with the ThOD of 2.90 mg O2/mg linalool, this corresponds to a biodegradation rate of 80%. The test was validated through the biodegradation rate

of the control substance, aniline, of 79%.
A graph of the average degradation of the 2 linalool flasks, the aniline control and the sterile control. No abiotic oxidative degradation was noted.

Flask	Test substance, mg/l	Respiration (BOD) mg O2/l, normalised to mg O2/mg	
Test 1	102 linalool	231	2.26
Test 2	98 linalool	233	2.39
Control	100 aniline	198	1.90
Blank	100 linalool, no sludge, sterile	0	

Test substance: Linalool synthetic, Lot no. 175725, purity 97.6%, certificate of analysis dated 27/02/91.
Reference substance: Aniline, purity >= 99.5% (Merck, Damrstadt, Germany, article no. 1261).

Reliability: (2) valid with restrictions
Reliability was judged to be 2 because the lab was not GLP certified in 1991 and some details in the test procedure and a table of all single BOD measurements are missing.

30-JUL-2001 (123)

Type: aerobic
Inoculum: other bacteria: BASF-Belebtschlamm
Concentration: 400 mg/l related to DOC (Dissolved Organic Carbon)
722 mg/l related to Test substance
Contact time: 13 day(s)
Degradation: >= 90 % after 3 day(s)
Kinetic: 3 hour(s) ca. 26 %
2 day(s) ca. 47 %
3 day(s) ca. 90 %
7 day(s) = 100 %
Control Subst.: other: no data
Deg. product: not measured

Method: other: IOS 9888, corresponding to the later OECD 302B
Year: 1977
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: An inherent biodegradability test was performed according to ISO guideline 9888, which closely corresponds to the later OECD 302B (Zahn-Wellens test). Briefly, 400 mg/l DOC (= 722 mg/l linalool was added to an inoculum of activated sludge from the BASF industrial wastewater treatment plant, rinsed and suspended at 1 g/l at a temperature of 20-25 °C. The test was run in duplicate. Samples were taken after 3 hours and subsequently once daily and analysed for DOC to determine the degradation kinetics.
Result: Biodegradation as measured by a decrease in DOC set in rapidly, attaining a full 26% within 3 hours, increasing to approximately 47% within 2 days, to 90% within 3 days and to 100% within 7 days. The test was run until day 13 when the average degradation had dropped very slightly to approximately 98%.
Source: BASF AG Ludwigshafen
Conclusion: Linalool is well inherently biodegradable.
Reliability: (2) valid with restrictions
Brief report from a professional industry emissions control laboratory, test performed according to international

guideline, reliability was judged as 2.
29-JUL-2002 (13)

Type: aerobic
Inoculum: other: extract from two forest soils, coniferous and hardwood, from Otto, NC, USA
Concentration: 40 mg/l related to Test substance
Degradation: >= 95 % after 160 hour(s)
Result: other: readily biodegradable after lag phase of ca. 100 h
Kinetic:
0 hour(s)	= 100 %
50 hour(s)	ca. 95 %
100 hour(s)	ca. 100 %
160 hour(s)	<= 5 %

Control Subst.: other: no positive control, only azide-amended sterile control showing no degradation

Method: Test systems and minimal medium
Test 1, mixed monoterpene alcohols and unacclimated inoculum:
2-l airtight glass flasks with glass-teflon valves and a septum-sealed port were used. Reactors were flushed with pure oxygen, then 1.4 l of oxygen-saturated minimal medium was added (minimal medium: 700 mg KH_2PO_4/l + 2000 mg K_2HPO_4/l + 150 mg NH_4Cl/l + 15 mg $CaCl_2*2H_2O$/l + 10 mg NaCl/l + 10 mg $FeCl_2*4H_2O$/l + 10 mg $MnCl_2*4H_2O$/l; pH 7.1; pure oxygen was bubbled through medium for at least 1 h). Continuous mixing was assured through magnetic stirrers at approx. 300 rpm.
Test 2, linalool and acclimated inoculum:
26-ml serum tubes were flushed with pure oxygen and sealed with teflon-lined septa. 10 ml of oxygen-saturated minimal medium and inoculum drawn from test 1 (above) were transferred to the serum tubes. The serum tubes were continuously rotated at approx. 1 rpm.
Test substances and sterile control
Test 1:
Undiluted terpene alcohols (linalool, arbanol, plinalol, alpha-terpineol) were added to the same flask through the port to achieve starting concentrations of ca. 40 mg linalool/l, ca. 30 mg plinol/l, ca. 23 mg arbanol/l and ca. 6 mg alpha-terpineol/l. [Note: data are given as graphs, not as tables showing exact values, hence approximate values are given here.] A sodium-azide-amended control (2.5g NaN_2H/l) was run in parallel.
Test 2:
Initial linalool concentration was ca. 36 mg/l [data given as graph only]. No control is mentioned.
Analytical methods
Samples were taken from both liquid and gas phases in duplicate at regular intervals and analysed for monotepenes and CO_2. Quantification of monoterpenes in liquid phase was achieved by liquid/liquid extraction and gas chromatography with bornyl acetate as an internal standard. Full details are given in the paper. Recovery varied between 89% to 103%, the detection limit for each monoterpene was 0.1 mg/l. Gas-phase hydrocarbon monoterpenes were determined using a headspace technique described in detail the paper, also with internal standard. Dissolved total carbon and dissolved inorganic carbon were measured using a carbon analyser; full details are given in the paper.
Result: Using unacclimated coniferous soil extract as the inoculum and a mixture of monoterpene alcohols as described in

methods, linalool showed a lag phase of 102 h and was thereafter readily biodegradable with a maximum degradation rate of >0.48 mg/(l*h) and measured concentrations in liquid and gas phase falling below the detection limit within approximately 60 h after lag phase, ie within a total of approximately 160 h.
In a second experiment using acclimated inoculum from the above test in a closed serum tube and ca. 36 mg linalool/l as the only substrate (full details in paper) the lag phase was shortened to approx. 24 h, then linalool concentrations dropped to below detection limit within 130 h; maximum degradation rate was 0.55 mg/(l*h), normalised degradation rate was 0.014/h. In parallel, microbial biomass as determined by absorbance (full details given in paper) increased.
Test condition: 23 °C, dark, magnetic stirrer
Reliability: (2) valid with restrictions
29-JUL-2002 (104)

Type: anaerobic
Inoculum: anaerobic microorganisms
Concentration: .5 mg/l related to Test substance
Contact time: 10 day(s)
Result: other: low anaerobic degradation without nitrate, high anaerobic biodegradation in the presence of nitrate, with the follwoing identified dergadation products:
106-24-1 203-377-1 geraniol
141-27-5 205-476-5 (E)-3,7-dimethylocta-2,6-dienal

Remark: Enrichment cultures for anaerobic micro-organisms were inoculated with activated sludge from a local wastewater plant (Lintel Osterholz-Scharmbeck, Germany) or with a water-mud mixture obtained from a ditch in a mixed forest near Bremen, Germany.
Result: "In the absence of nitrate the decrease in the amount of monoterpene was less than 8%. [...]
"In the case of linalool, the formation of geraniol and the formation of geranial, which is formed only in the presence of nitrate, suggest that linalool degradation is initiated by rearrangement to geraniol and then continues by oxidation on the pathway metioned above."
Reliability: (2) valid with restrictions
29-JUL-2002 (63) (70)

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: = 91 - 100 % after 28 day(s)
Result: readily biodegradable
Deg. product: not measured

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: Degradation was measured by three different parameters: biochemical oxygen demand (BOD), total organic carbon (TOC) and gas chromatography (GC)
Result: Biodegradation: average (flasks 1-2-3)
BOD: 90% (91%-91%-89%)
TOC: 99% (99%-99%-99%)

GC: 100% (100%-100%-100%)
BOD curve/graph is attached in the original on-line publication, including BOD of positive control (aniline) and blank (water + test substance)

Test condition: Concentration of test substance (TS): 100 mg/l
Concentration of activated sludge: 30 mg suspended solid/l
Volume of test solution: 300 ml
Number of parallel test flasks: 3 (TS + activated sludge)
Positive control: yes (aniline)
Blank/sterile control: yes (TS + water)
Cultivation temperature: 25 °C
Cultivation duration: 28 days

Conclusion: Full primary degradation as shown by GC analysis; more than 90%, i.e. ultimate degradation, as evidenced by TOC and BOD.

Reliability: (4) not assignable
reliability of these data is probably better than category 4, but no information on published test method nor on GLP is given

29-JUL-2002 (117)

Type: aerobic

Inoculum: other bacteria: Pseudomonas incognita

Result: other: biodegradable
1073-11-6 214-024-6
dihydro-5-methyl-5-vinylfuran-2(3H)-one
15249-35-1
28420-25-9 linalool-8-carboxylic acid
33746-68-8
5502-74-9 226-838-9
4-(2-hydroxy-2-propyl)cyclohexene-1-methanol
60047-17-8 262-038-6
2-(tetrahydro-5-methyl-5-vinyl-2-furyl)propan-2-ol
64142-78-5
98-55-5 202-680-6 p-menth-1-en-8-ol
??

Method: Pseudomonas incognita culture medium spiked with linalool (concentration not stated, probably as the sole organic carbon source) was processed (details not stated) to isolate and identify various metabolites.

Result: From the metabolites identified the existence of "at least two different pathways for the biodegradation of linalool" was derived.
Metabolic pathway 1:
Linalool; specific oxygenation of the C8 methyl group to 8-hydroxy-linalool, CAS 64142-78-5; further stepwise oxygenation in the presence of NAD-linked dehydrogenases to linalool-8-aldehyde, CAS 54664-89-0; then to linalool-8-carboxylic acid, CAS 28420-25-9.
Metabolic pathway 2:
Linalool; prototropic cyclisation to alpha-terpineol, CAS 98-55-5; progressive oxidation of the C10-methyl group to C10-hydroxymethyl alpha-terpineol, CAS 5502-74-9; then to oleoeuropeic acid, CAS 33746-68-8.
Probable metabolic pathway 3:
Linalool; (probably epoxidation of the 6,7 double bond to 6,7-epoxy-3,7-dimethyl-1-octen-3-ol, CAS 15249-35-1; possibly further oxidation leading to) cyclisation to linalool oxide, CAS 60047-17-8; formation of an unsaturated lactone, 5-ethenyldihydro-5-methyl-2(3H)-furanone, CAS 1073-11-6.

Conclusion: "Microbial degradation of geraniol, citronellol, linalool

and their corresponding acetates [...] are presented. Oxygenative and prototropic rearrangements are normally observed during the microbial metabolism of monoterpenes. Three types of oxygenationreactions are observed, namely, (a) allylic oxidation, (b) oxygenation on a double bond and (c) addition of water across the double bond. The studies indicate commonality in the reaction types or processes occurring during the metabolsim of various related monoterpenes and also establish the convergence of degradative pathways at a central catabolic intermediate."
Reliability: (4) not assignable
29-JUL-2002 (99)

Type: aerobic
Inoculum: Aspergillus niger (Fungi)

Method: In a doctoral thesis, the biotransformation of terpenes by fungi was studied as a way of producing microbial bioflavours. The thesis was only available as the abstract.
Result: "The biotransformation of (+/-)-linalool with submerged shaking cultures of Aspergillus niger ATCC9142 yielded a mixture of cis- and trans-furanoid linalool oxide and cis- and trans-pyranoid linalool oxide. Biotransformation of (R)-(-)-linalool with the same strain yielded almost pure trans-furanoid and trans-pyranoid linalool oxide (ee > 95). The biotransformation was also carried out with growing surface cultures."
Reliability: (4) not assignable
22-JAN-2002 (32)

3.6 BOD5, COD or BOD5/COD Ratio

Method: other: no data
GLP: no data

C O D

Method: other: DIN 38409 Teil 43
Year: 1982
GLP: no data
COD: = 2808 mg/g substance

R A T I O B O D 5 / C O D

BOD5/COD: = .55
Method: no details on BOD5 method available.
Result: BOD5 = 1531 mg/g, COD = 2808 mg/g, BOD5/COD = 55%
Source: BASF AG Ludwigshafen
Conclusion: Linalool is readily biodegradable.
Reliability: (4) not assignable
29-JUL-2002 (10)

3.7 Bioaccumulation

BCF: = 28

Method: other: QSAR estimate
Year: 2001
GLP: no

Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
17-JUL-2001 (144)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type:	static
Species:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period:	96 hour(s)
Unit:	mg/l Analytical monitoring: yes
NOEC:	< 3.5 - calculated
LC0:	= 19.9 - measured/nominal
LC50:	= 27.8 - calculated
LC100:	= 38.8 - measured/nominal
Limit Test:	no
Method:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year:	1991
GLP:	yes
Test substance:	as prescribed by 1.1 - 1.4

Method: This study was performed according to OECD Guideline 203, version of 1984.
Fish
Juvenile rainbow trout, in the report bearing the old name Salmo gairdneri, were acquired from commercial fish breeders P. Hohler, CH-4314 Zeiningen, Switzerland and acclimated for 34 days in the test lab. Based on 10 fish, the average length was 63 mm (57-72 mm), which is slightly out of the range stated by the Guideline, and the average weight was 2.12 g (1.51-2.75 g). 10 fish per concentration and control were used, fish were grouped 5 per test or control aquarium, resulting in a loading rate of 0.71 g fish/l test medium. Fish were adapted to the test aquaria for 24 h prior to exposure without feeding; they were not fed during the 96 h test period.
Aquaria and test conditions
Glass aquaria of 20 l volume (36x22x25 cm) were used and filled with 15 l of dechlorinated (activated carbon filtre) tap water of 180 mg CaCO3/l hardness; the water was aerated during the exposure. The temperature was kept at 14 +/- 0.5 °C during the test, there was a 16 h light/8 h dark lighting in the test room with fluorescent tubes.
Stock solution
5 g linalool was mixed with 5 g dimethylformamide.
Test concentrations
Nominal test concentrations were 100, 58, 32, 18 and 10 mg/l. They were made up by adding calculated amounts of stock solution to the test aquaria and mechanical mixing; on visual control, the test substance remained homogeneously distributed at all times and concentrations. Due to volatilisation of the test substance, concentrations dropped during the test. Analysis and mean measured concentrations as described further down were used for determining effects concentrations.
Controls were a blank (dechlorinated tap water) and a vehicle control containing 100 mg dimethylformamide/l.
Sampling
Composite samples, approx. 150 ml in duplicate, were drawn from each test concentration by mixing identical volumes of test solutions from the approximate centre of the test aquaria. These were taken immediately before exposure if the fish and after 96 h exposure and kept at -18 to -22 °C until

analysis.
Observations
Mortality was recorded after 14, 48, 72 and 96 h. At the same time behavioural symptoms of survivors were registered.
Measurements
Dissolved oxygen, pH and temperature were measured and registered at 0, 24, 48, 72 and 96 h.
Analysis
The content in water of linalool was determined by gas chromatography. For the sample solution, at least 2 samples of ideally 100 ml each were taken into a 250-ml separation funnel. The empty original sample bottle is rinsed with 10 ml n-hexane (all n-hexane to be of analytical grade); the funnel is extracted 3 times with 10 ml n-hexane; the collected organic phases are made up to 50.0 ml with n-hexane.
For the reference solution, at least 80 mg linalool are accurately weighed, then dissolved in and made up to 100.0 ml with n-hexane; from this stock solution at least two reference solutions are diluted to the range of test concentrations using n-hexane.
The GC apparatus and conditions were as follows:

Chromatograph:	HP 5890 Series II
Injector:	splitless, 100 °C
Injection volume:	5 ul (manual injection)
Oven program:	initial temperature 50 °C
	initial time 3 min
	temperature rise rate 32 °C/min
	final temperature 175 °C
	final time 1 min
Detector:	FID, 300 °C
	air: 400 ml/min
	H2: 30 ml/min
	He make-up: 30 ml/min
Integrator:	HP workstation
Column:	HP 5 (5% Ph-Me-Silicone, 10 m x 0.53 mm, 2.65 um film)
Mobile phase:	He, 30 ml/min
Retention time:	approx. 5 min
Analysis time:	approx. 8 min

Average concentration
Concentrations of samples from time 0 and 96 h were determined by GC and arithmetically averaged to give the average concentration.
Statistical analysis
LC50 values were calculated according to Berkson [(1953): JASA 48: 569-599] and also graphically determined on log-probit paper.

Result: All concentrations listed refer to average measured concentrations. The 96-h LC50 was calculated to be 27.8 mg/l (22.9-33.7 mg/l, 95% CL); the observed LC100 was 38.8 mg/l, the LC0 19.9 mg/l and the NOEC <3.5 mg/l. At 38.8 (nominal 100) mg/l, all fish were already dead at 24 h.
Behavioural observations resulted in the following symptoms: Swimming was affected at the 2 lowest concentrations (3.5 and 6.4 mg/l) from 72 h, at 10.3 mg/l from 48 h and at 19.9 mg/l from 24 h; loss of equilibrium was observed at 10.3 mg/l from 48 h and at 19.9 mg/l from 24 h; both respiratory function and pigmentation were affected at 19.9 mg/l from 24 h.

	Measured concentrations ranged between 33 and 46% of nominal at time 0 and between 26 and 32% at time 96 h, the average of both being between 32 and 39%.
Test substance:	Test substance: dl-Linalool from F. Hoffmann-La Roche Ltd, batch no. 08071, purity 97.8%, retest date June 30th 1992 (testing date was July 30th, 1991).
Reliability:	(2) valid with restrictions While the present test was performed according to an OECD Guideline and under GLP conditions, concentrations were not kept at 100 +/- 20% of nominal. Therefore the reliability is considered to be 2 rather than 1.
Flag:	Critical study for SIDS endpoint
02-OCT-2001	(152)

Type:	static
Species:	Leuciscus idus (Fish, fresh water)
Exposure period:	96 hour(s)
Unit:	mg/l Analytical monitoring: no
NOEC:	22 -
LC0:	22 -
LC50:	22 - 46
LC100:	<= 46 -
Limit Test:	no
Method:	other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische (= Determination of the effect of compounds in water on fish), DIN 38412 Teil 15
Year:	1989
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4
Method:	The acute fish toxicity of linalool was tested following DIN guideline 38412, part 15. Briefly, fish were exposed to linalool at different concentrations, a crude LC50 having been determined in a pretest, of 0 (controls) 10, 21.5, 46.4 and 100 mg linalool/l reconstituted freshwater (according to DIN 38412, part 11) at 21 °C for 96 hours. Test tanks were 10-l all-glass aquaria, slightly aerated in a room with a 16-hour-light/8-hour-dark cycle. The test substance was added directly to the prefilled tanks, without any emulsifier, before placing the fish in the tanks. Oxygen content, pH and temperature were measured every 24 hours. Fish were golden orfe, Leuciscus idus var., from Fischzucht Paul Eggers, Hohenwestedt, Germany, of an average length of 6.0 (5.5-7.1) cm and an average weight of 1.8 (1.2-2.8) g. They had been acquired about one month before the start of the test (details in report). Ten fish per concentration were placed in the tanks after adding the test substance; subsequently they were checked after 1, 4 24, 48, 72 and 96 hours.
Result:	At 0 (controls), 10.0 and 21.5 mg/l linalool there were no deaths throughout the whole test period; in contrast, at both 46.4 and 100.0 mg/l, all ten fish per tank were dead within the first hour.
Source:	BASF AG Ludwigshafen
Test substance:	Synthetic linalool from BASF, batch no. 88/601, of 97.7% purity.
Conclusion:	Linalool, tested without an emulsifier, was not acutel toxic to fish at concentrations up to 21.5 mg/l but killed all fish within one hour of exposure at concentrations of 46.6 mg/l and higher. Hence the LC50 is between 21.5 and 46.4 mg/l; the geometric-mean LC50 is 31.8 mg/l.

Reliability: (2) valid with restrictions
Not GLP, but detailed report from a professional industry ecotoxicity laboratory, reliability judged as 2.
29-JUL-2002 (9)

Type: other: not stated
Species: Oncorhynchus mykiss (Fish, fresh water)
Unit: mg/l Analytical monitoring: no data
LC50: = 28.8 -

Reliability: (4) not assignable
29-JUL-2002 (40)

Type: other: not stated
Species: Lepomis macrochirus (Fish, fresh water)
Unit: mg/l Analytical monitoring: no data
LC50: = 36.8 -

Reliability: (4) not assignable
29-JUL-2002 (40)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: = 25 - measured/nominal
EC0: = 25 - measured/nominal
EC50: = 59 - calculated
EC100: > 75 - measured/nominal
Limit Test: no

Method: other: OECD-Guideline No. 202, Part I, 1984 (nach GLP geprueft)
Year: 1991
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: This study was performed according to OECD Guideline 202, part I, version of 1984.
Daphnids
Daphnia magna from CIBA-GEIGY's own testing facility culture were used for the test. Cultures of daphnids were amintained in glass vessels containing approx. 2.5 l daphnid medium as per the Guideline at 21 +/- 1 °C. Water was renewed 3 times weekly. At each renewal the daphnids were fed with a suspension of green algae (Scenedesmus subspicatus) supplemented by a suspension of Tetramin extract in such quantities that the feed is consumed within 24 h.
24 h before test begin reproductive daphnia are separated from the young by sieving through a 0.8-mm sieve. Immediately before exposure this procedure is repeated and the young (0- to 24-h-old) are retained for the test. For each concentration and for the control 20 daphnids were used, in 4 replicates of 5 daphnids each. During the exposure the daphnids were not fed.
Vessels and test conditions
Glass beakers were filled with 100 ml daphnid medium that had been aerated for 24 h before the test and covered with

watch glasses during the test. The temperature was kept at 20 +/- 1 °C during the test, there was no lighting in the test room and no aeration of the vessels during the test.
Stock solution
250 mg linalool was dissolved in and made up with daphnid medium to 2000 ml.
Test concentrations
Nominal test concentrations were 100, 58, 32, 18 and 10 mg/l. They were made up by adding calculated amounts of stock solution to the test aquaria and mechanical mixing; on visual control, the test substance remained homogeneously distributed at all times and concentrations. Due to volatilisation of the test substance, concentrations dropped during the test. Analysis and mean measured concentrations as described further down were used for determining effects concentrations.
Controls were blanks (daphnid medium only).
Sampling
Composite samples, approx. 150 ml in duplicate, were drawn from each test concentration by mixing identical volumes of test solutions from the approximate centre of the test vessels. These were taken immediately before exposure of the daphnids and after 48 h exposure and kept at -18 to -22 °C until analysis. Observations Mortality was recorded after 14, 48, 72 and 96 h.
Observations
Immobilisations of daphnids were recorded at 24 and 48 h.
Measurements
Dissolved oxygen, pH and temperature were measured and registered at 0 and 48 h.
Analysis
The content in water of linalool was determined by gas chromatography. For the sample solution, at least 2 samples of ideally 100 ml each were taken into a 250-ml separation funnel. The empty original sample bottle is rinsed with 10 ml n-hexane (all n-hexane to be of analytical grade); the funnel is extracted 3 times with 10 ml n-hexane; the collected organic phases are made up to 50.0 ml with n-hexane.
For the reference solution, at least 80 mg linalool are accurately weighed, then dissolved in and made up to 100.0 ml with n-hexane; from this stock solution at least two reference solutions are diluted to the range of test concentrations using n-hexane.
The GC apparatus and conditions were as follows:

Chromatograph:	HP 5890 Series II
Injector:	splitless, 100 °C
Injection volume:	5 ul (manual injection)
Oven program:	initial temperature 50 °C
	initial time 3 min
	temperature rise rate 32 °C/min
	final temperature 175 °C
	final time 1 min
Detector:	FID, 300 °C
	air: 400 ml/min
	H2: 30 ml/min
	He make-up: 30 ml/min
Integrator:	HP workstation
Column:	HP 5 (5% Ph-Me-Silicone, 10 m x 0.53 mm, 2.65 um film)
Mobile phase:	He, 30 ml/min

	Retention time: approx. 5 min Analysis time: approx. 8 min Average concentration Concentrations of samples from time 0 and 48 h were determined by GC and arithmetically averaged to give the average concentration. Statistical analysis EC50 values were calculated according to the maximum likelihood probit model [McCullagh P, Nelder JA (1983): Generalised linear models. Chapman&Hall, London] and also graphically determined on log-probit paper.
Result:	All concentrations listed refer to average measured concentrations. The 48-h EC50 was calculated to be 59 mg/l (53-65 mg/l, 95% CL); the observed EC100 was above the maximum average concentration of 75 mg/l, the EC0 and NOEC were 25 mg/l. Immobilisation after 24 h was found in 17/20 daphnids (4, 4, 4 and 5 per group of 5) and after 48 h in 19/20 daphnids; no immobilisation was noted at lower test concentrations nor in the controls. Measured concentrations ranged between 85 and 99% of nominal at time 0 and between 51 and 72% at time 48 h, the average of both being between 70 and 81%.
Test substance:	Test substance: dl-Linalool from F. Hoffmann-La Roche Ltd, batch no. 08071, purity 97.8%, retest date June 30th 1992 (testing was performed between Sep 24th and Oct 10th, 1991).
Reliability:	(2) valid with restrictions While the present test was performed according to an OECD Guideline and under GLP conditions, concentrations were not kept at 100 +/- 20% of nominal. Therefore the reliability is considered to be 2 rather than 1.
Flag:	Critical study for SIDS endpoint
26-JUL-2001	(151)

Type:	static
Species:	Daphnia magna (Crustacea)
Exposure period:	48 hour(s)
Unit:	mg/l Analytical monitoring: no
EC0:	= 4 -
EC50:	= 20 -
EC100:	= 100 -
Limit Test:	no
Method:	Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year:	1988
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4
Method:	Linalool was tested for daphnid toxicity according to EC Guideline 84/449/EEC, C.2 which is equivalent with DIN 38412. Briefly, ten Daphnia magna each per concentration were exposed to linalool in aqueous emulsions using Tween 80 at one-tenth of the linalool concentration in reconstituted daphnia medium for 48 hours. Nominal linalool concentrations were 0 (water controls), 0 (emulsifier controls, Tween 80 concentration corresponding to that in highest test substance concentration), 2, 4, 8, 10, 20, 40, 80 and 100 mg/l. EC50 concentrations were dtermined using log-probit regression.
Result:	After 24 hours of daphnia to linalool in emulsions made with Tween80, the EC50 was 60 (32.28-111.4, 95% confidence interval) mg/l, which decreased after 48 hours to 20

(9.68-41.49) mg/l.
Source: BASF AG Ludwigshafen
Test substance: Linalool synthesised by BASF, lot no. 2204.88
Conclusion: Using Tween80 as an emulsifier, the 48-hour EC50 of linalool to daphnia was 20 mg/l.
Reliability: (2) valid with restrictions
Not GLP, but a well documented report from a professional ecotoxicology laboratory, following an accepted international guideline, relaibility was judged as 2.
29-JUL-2002 (11)

Type: other: not stated
Species: other: described as "aquatic invertebrates"
Unit: mg/l Analytical monitoring: no data
EC50: = 36.7 -

Reliability: (4) not assignable
29-JUL-2002 (40)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
EC10: = 38.4 -
EC50: = 88.3 -
Limit Test: no

Method: other: DIN 38412, part 9
Year: 1988
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: The test was performed according to Guideline Scenedesmus cell division inhibition test, DIN 38412, part 9, determination of the inhibitory effect of substances in water on green algae. Briefly, Linalool was emulsified using Tween80 (concentration one-tenth of the linalool concentration) and Scendesmus subspicatus algae were exposed to aqueous dilutions of this emulsified test substance for 96 hours in quadruplicate. The nominal test concentrations were 0 (water controls), 10, 32, 100, 320 and 1000 mg/l, based on a pretest. Cell densities were measured by chlorophyll fluorescence using impulse fluorometry in relative units. Based on cell densities over time, biomass and growth rates respectively the inhibition caused by the test substance were determined.
Result: After 96 hours exposure to linalool emuslified with Tween80, the algal growth inhibitions were as follows (nominal concentrations):
Biomass: EbC10 = 38.4 mg/l, EbC50 = 88.3 mg/l.
Growth rate: ErC0 = 32.0 mg/l, ErC10 = 54.3 mg/l, ErC50 = 156.7 mg/l.
Further, the test substance had no own fluorescence and had no negative influence on photosynthetic capability as measured by chlorophyll fluorescence.
Source: BASF AG Ludwigshafen
Conclusion: Using emulsified test substance, the EbC50 of linalool was 88.3 mg/l and the ErC50 was 156.7 mg/l.
Reliability: (2) valid with restrictions
Brief but detailed report from a professional ecotoxicology

laboratory, with full dat, according to an accepted guideline, reliability judged as 2.
Flag: Critical study for SIDS endpoint
29-JUL-2002 (11)

Species: Chlorella pyrenoidosa (Algae)
Endpoint: growth rate
Exposure period: 48 hour(s)
Unit: Analytical monitoring: no data
Limit Test: no

Method: other: plate growth inhibition assay
Year: 1992
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: Chlorella pyrenoidosa green algae were grown on agar plates in 100-mm-diameter Petri disks. Linalool (from Aldrich) was added to cultures by dipping 6-mm-paper disks in concentrations of 10, 1 and 0.1 mg linalool/ml ethanol, then 3 disks were placed on each of the agar plates. The plates were put under fluorescent light for further growth. After 48 h, zones of algal growth inhibition around the test substance disks were determined by lightening or total wipe-out of colour in the green chlorella lawns the net diameter of the inhibition zone was determined as an average of 3 disks per plate, run on 2 separate occasions.
Result: No inhibition was found with 1 mg linalool/l. At 10 mg/l a platewise lightening of algal lawn colour in comparison to controls is described. As similar lightening over the whole plate was also found if the paper test substance disks were placed on slightly larger teflon disks, the authors concluded that the inhibition was taking place through the vapour phase rather than through diffusion through the agar. As the lightening was not quantified it is not possible to give an EC50.
Reliability: (4) not assignable
22-JAN-2002 (71)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge, domestic
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring: yes
NOEC: = 100 -
EC50: > 100 -
EC20 : > 100 -
EC80 : > 100 -

Method: OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year: 1991
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Activated sludge
Activated sludge was collected from the mainly domestic sewage treatment plant of CH-4152 Reinach, Switzerland, on Sept 29th, 1991; the pH at collection was 7.3. Preparation of the sludge was carried out according to OECD Guideline

209 of April 1984. However, as a deviation from the Guideline, the sludge was separated from the aqueous layer only by settling instead of centrifugation.
Procedure
250-ml BOD flasks with gas inlet were used as test vessels, dechlorinated drinking water was used to make up the test solutions with the following dissolved nutrients: 16 g peptone, 11 g meat extract, 3.0 g urea, 0.7 g NaCl, 0.4 g (CaCl2 * 2 H2O), 0.2 g (MgSO4 * 7 H2O) and 2.8 g K2HPO4 per litre.
Temperature
The test was performed at room temperature (20 +/- 2 °C).
Duration
30 min and 3 hours.
Substances tested
Test substance: dl-Linalool as described under Test substance.
Reference substance: 3,5-dichlorophenol, source not stated.
Blank: None (2 vessels, sludge only).
Remark
The test substance was found to be volatile on pre-tests, with a reduction to 75% after 30 min with bubbling and to 42% after 3 h with bubbling compared to 100% without bubbling in both cases, measured by TOC. To compensate for this volatility, higher test substance concentrations were added to ensure concentrations above 100 mg/l at the end of the respective test.
Test concentrations
Test substance: 100.7, 32.22, 10.07, 3.22 and 1.01 mg/l.
Reference substance: 32, 10 and 3.2 mg/l.
The final sludge concentration in the test vessels was adjusted to 1.6 g dry weight per litre.
Measurements
Oxygen consumption per hour in mg/l was determined with an ORION Electrode Type 97-08 on an ORION Microprocessor Ionalizer 901 and plotted on a recorder.
GC Analysis
The content in water of linalool was determined by gas chromatography. For the sample solution, at least 2 samples of ideally 100 ml each were taken into a 250-ml separation funnel. The empty original sample bottle is rinsed with 10 ml n-hexane (all n-hexane to be of analytical grade); the funnel is extracted 3 times with 10 ml n-hexane; the collected organic phases are made up to 50.0 ml with n-hexane.
For the reference solution, at least 80 mg linalool are accurately weighed, then dissolved in and made up to 100.0 ml with n-hexane; from this stock solution at least two reference solutions are diluted to the range of test concentrations using n-hexane.
The GC apparatus and conditions were as follows:

Chromatograph:	HP 5890 Series II
Injector:	splitless, 100 °C
Injection volume:	5 ul (manual injection)
Oven program:	initial temperature 50 °C
	initial time 3 min
	temperature rise rate 32 °C/min
	final temperature 175 °C
	final time 1 min
Detector:	FID, 300 °C
	air: 400 ml/min
	H2: 30 ml/min

	He make-up: 30 ml/min
	Integrator: HP workstation
	Column: HP 5 (5% Ph-Me-Silicone, 10 m x 0.53 mm, 2.65 um film)
	Mobile phase: He, 30 ml/min
	Retention time: approx. 5 min
	Analysis time: approx. 8 min
	Inhibition calculations
	Inhibitions were calculated on the basis of the measured time-dependent oxygen consumption of blank, test solutions and reference substance.
Result:	Linalool did not inhibit during 30 min nor during 3h the oxygen consumption of activated sludge at any of the concentrations tested and analytically confirmed at the end of the test. The reference substance did inhibit oxygen consumption with a graphically determined EC 50 of 24 mg/l (30 min) respectively 19.9 mg/l (3 h).
Test substance:	Test substance: dl-Linalool from F. Hoffmann-La Roche Ltd, batch no. 08071, purity 97.8%, retest date June 30th 1992 (testing date was July 30th, 1991).
Reliability:	(1) valid without restriction
Flag:	Critical study for SIDS endpoint
30-JUL-2001	(59)

Type:	other: laboratory growth inhibition test
Species:	aerobic microorganisms
Exposure period:	2 day(s)
Unit:	mg/l Analytical monitoring:
MIC :	= 200 - 1600 measured/nominal
Year:	1995
GLP:	no data
Test substance:	other TS: "from previous studies"
Method:	Microorganisms
	All microorganisms tested were pruchased from the American Type Culture Collection (ATCC) at Rockville MD, USA. The species with their ATCC numbers are listed under Results.
	Culture
	Culture media for bacteria, modls and yeasts are described in ht epaper.
	Antimicrobial assay
	Unless otherwise specified, the highest concentration tested was 800 mg/l (in the original: 800 ug/ml) due to limited solubility of test substences in the aqueous media. The broth dilution method was adopted, with the test compounds being first dissolved in dimethylformamide, then serial 1:2 dilutions in DMF prepared and last 30 ul of the dilutions being added to sterile media in order to achieve consistent 1% DMF concentrations that did not affect the growth of any on the microorganisms. Test flasks were then inoculated and cultured at 30 or 37 °C for 2 days in general resp. 3 days for P. ovale, 5 days for molds. The microorganisms were cultured stationary, with the exception of molds which were shaken. After the test, the growth was determined by turbidity (optical density at 660 nm) except for P. ovale and the molds which were assessed visually. The minimal inhibitory concentration (MIC) was the lowest concentration of a test compound that completely prevented growth.
Result:	Microorganism ATCC no. Linalool MIC, mg/l
	Bacteria:

	Bacillus subtilis	9372	800
	Brevibacterium ammoniagenes	6872	800
	Enterobacter aerogenes	13048	>800
	Escherichia coli	9637	>800
	Propionibacterium acnes	11827	200
	Pseudomonas aeruginosa	10145	>800
	Staphylococcus aureus	12598	>800
	Streptococcus mutans	25175	1600
	Molds:		
	Penicillium chrysogenum	10106	800
	Trichophyton mentagrophytes	18748	200
	Yeasts:		
	Candida utilis	9226	400
	Pytirosporum ovale	14521	400
	Saccharomyces cerevisiae	7754	800

Conclusion: Linalool was relatively nontoxic to defined species of bacteria, molds and yeasts
Reliability: (2) valid with restrictions

04-DEC-2001 (89)

Type: aquatic
Species: activated sludge, domestic
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring: yes
EC10: ca. 110 - calculated
EC50: ca. 400 - calculated
EC50 : > 100 - measured/nominal

Method: OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year: 1989
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: According to the guideline, 2 blank controls (sludge plus nutrients); 3 times 2 linalool concentrations (96, 304, 912 mg/l) plus sludge plus nutrient; and 1 inhibitory/negative control (sludge plus nutrient plus 272 mg 2,5-dichlorophenol/l) were tested in parallel.

Result:

Vessel	Linalool, mg/l	Respiration rate	Inhibition, %
Control1	0	1.053	-
Control2	0	1.111	-
Substance1	96	1.081	7
Substance2	96	1.081	7
Substance3	304	0.727	37
Substance4	304	0.741	36
Substance5	912	0.260	78
Substance6	912	0.267	77
Inhibition	(272 dichlorophenol)	0.367	68

Reliability: (4) not assignable
Reliability is probably better than 4 but available test report is incomplete.
04-DEC-2001 (22)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring:
EC10: = 660 -
EC50: = 1000 -
EC90 : = 1800 -

Method: Pseudomonas-Atmungs-Hemmtest, DIN 38412 Teil 27, in Vorber., Bestimmung der Hemmwirkung von Abwasser auf die Sauerstoffzehrung von Pseudomonas putida (= Pseudomonas repsiration inhibition test, DIN 38412, part 27, in preparation; determination of the inhibitory effect of sewage on the oxygen consumption of Pseudomonas putida)
Remark: Geprueft mit Tween 80 als Loesungsvermittler. (= tested using Tween 80 as an emulsifier)
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
22-JAN-2002 (11)

Type: aquatic
Species: other bacteria: BASF-Belebtschlamm (= activated sludge from the BASF industrial STP)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = .3 -
EC20 : = .05 -
EC80 : = .7 -

Method: other: Hemmtest im Sapromaten (= inhibition test in the Sapromat apparatus)
Year: 1982

Remark: No further details are available from the study report.
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
08-SEP-2003 (10)

Type: aquatic
Species: other bacteria: BASF-Belebtschlamm (= activated sludge from the BASF industrial STP)
Exposure period: 28 day(s)
Unit: mg/l Analytical monitoring:
EC50: > 1 -
EC20 : = 1 -
EC80 : > 1 -

Method: other: Hemmtest im Sapromaten (= inhibition test in the Sapromat apparatus)
Year: 1982

Remark: No further details are available from the study report.
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
08-SEP-2003 (10)

Type: other: laboratory screening of antibacterial and antifungal activity

Year: 1997
GLP: no data

Remark: Seen only as the abstract.
Result: Five aromatic constituents of essential oils (cineole, citral, geraniol, linalool and menthol) were tested for antimicrobial activity against 18 bacteria (including Gram-positive cocci and rods and Gram-negative rods) and 12 fungi (3 yeast-like and 9 filamentous). In terms of antibacterial activity linalool was the most effective and

inhibited 17 bacteria [...]. Against fungi, the citral and geranial oils were the most effective (inhibiting all 12 fungi), followed by linalool (inhibiting 10 fungi) [...].
Test substance: Linalool, constituent of essential oil; no other data in abstract.
Reliability: (4) not assignable
22-JAN-2002 (115)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Species: other terrestrial plant: Hordeum vulgare (barley)
Endpoint: other: root growth of germinating barley
Expos. period: 3 day(s)
Unit: mg/l
NOEC: >= 50 - measured/nominal

Method: other
Year: 1982
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: All plants were grown in 9-cm-diameter Petri dishes on two filter papers (Whatman 1) with 5 ml of water (controls) or test solution. [Barley grains were probably pre-soaked in water for 3 days, based on cross-reading with a parallel test and transferred to the experimental Petri dishes.] The dishes were incubated in the dark at 25 +/- 2 °C for 3 days. Root length was measured as the endpoint. All treatments consisted of 5 replicate Petri dishes.
Result: Germinating barley root lengths

Linalool concentration, mg/l	Relative root length, %
0 (control)	100
1	106
10	112
50	96

Test substance: Linalool was obtained from Sigma, London; all isoprenoid alcohols used in this study, including linalool, are stated to have a minimum purity of 90%.
Test solutions (emulsions) were prepared by dissolving the test substance in a small quantity of acetone, adding water containing a few drops of teepol and shaking vigorously prior to making up to volume with water.
Conclusion: At 10 mg/l there was a slight stimulatory effect on root growth. As no statistical analysis is provided in the paper, the slight decrease at 50 mg/l cannot be characterised as to significance.
Reliability: (4) not assignable

09-AUG-2001 (153)

Species: other terrestrial plant: Lactuca sativa (lettuce) and Lepidum sativum (cress)
Endpoint: other: germination and initial growth
Expos. period: 3 day(s)
Unit: mg/l
NOEC: >= 100 - measured/nominal

Method: other
Year: 1982
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: All plants were grown in 9-cm-diameter Petri dishes on two filter papers (Whatman 1) with 5 ml of water (controls) or

test solution. 100 seeds (lettuce or cress) were spread on one Petri dish.The dishes were incubated in the dark at 25 +/- 2 °C for 3 days. Germination and growth [probably size, not stated] were measured as the endpoints. All treatments consisted of 3 replicate Petri dishes.
Result: Treatment with 1 g linalool/l resulted in full inhibition of germination and "an effect" (unspecified) on the growth of lettuce, but in no adverse effect on germination or growth of cress.
In the discussion, the authors write that "although it prevented lettuce germination at 1 g/l, lower concentrations [100 mg/l, table 3 in paper] were without effect even on growth and no effect was observed on the growth of cress."
Test substance: Linalool was obtained from Sigma, London; all isoprenoid alcohols used in this study, including linalool, are stated to have a minimum purity of 90%. Test solutions (emulsions) were prepared by dissolving the test substance in a small quantity of acetone, adding water containing a few drops of teepol and shaking vigorously prior to making up to volume with water.
Conclusion: No adverse effect was observed on germination and initial growth of lettuce and cress at or above 100 mg linalool/l.
Reliability: (4) not assignable
22-JAN-2002 (153)

Species: other terrestrial plant: species not stated
Endpoint: other: stomatal aperture/closure

Method: other: not stated
Year: 1976
GLP: no data
Test substance: no data

Remark: Citation of data from Fenton R, Mansfield TA, Wellburn AR (1976): Effects of isoprenoid alcohols on oxygen exchange of isolated chloroplasts in relation to their possible physiological effects on stomata. J Exp Bot 27: 1206-1214.
Result: No effect of linalool [at unspecified concentration] on stomatal closure.
Reliability: (4) not assignable
09-AUG-2001 (153)

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

Species: Colinnus virginianus (avian)
Endpoint: mortality
Unit: ppm
LC50: > 5620 -

Method: other: not stated
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: correct species name for the Virginia quail is Colinus virginianus
Reliability: (4) not assignable
15-AUG-2001 (40)

Species: other not soil dwelling arthropod: various stored-food pests of worldwide importance
Endpoint: mortality

Test substance: other TS

Result: Many important stored-food pests, eg rice, grain and bean weevils, are traditionally or experimentally controlled with success using products containing linalool or linalool itself. Linalool is active both as a fumigant and as a contact toxicant. See also chapter 7.2, Effects on Organisms to be controlled.
Test substance: both dried plants and essential oils containing linalool and pure linalool
Reliability: (4) not assignable
22-JAN-2002 (109) (131) (154)

Species: other: Tribolium castaneum (Coleoptera; grain weevil)
Endpoint: mortality
Expos. period: 5 hour(s)
Unit: ppm
LC50: = 25000 - measured/nominal

Year: 1988
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: FAO contact method: 0.5-ml-aliquots of serial dilutions using 2% ethanol as an solution aid were pipetted onto 5.5-cm-diameter filter papers and the ethanol was lallowed to evaporate for approx. 1 min. Then, batches of 20 beetles each were transferred onto the papers, confined in Petri plates sealed on top, and placed in an incubator at 28 °C. Mortality was determined after 5 hours by the inability of single insects to satnd up or walk after being toppled by a gentle push with a forceps. Tests were performed in duplicate and also with duplicate controls (ethanol in water only). LC50 concentrations were determined graphically using log-probit paper.
Result: Linalool proved to be an insecticide with an LC50 of 2.5 * 10E+4 ppm (concentration of the test solution pipetted onto paper disc). In a comparison with gossypol, citral, bornyl acetate and cineole, the relative potency of linalool was a medium-strength insecticide, its LC50 being between citral and bornyl acetate.
From the test it was evident that beetles became paralysed prior to death.
Test substance: Linalool, purity 99%, from Aldrich, England.
Reliability: (2) valid with restrictions
22-JAN-2002 (126)

Species: other: fleas, species not stated (Aphaniptera: Ctenocephalides spp.)
Endpoint: mortality

Result: "Linalool (Flea Stop) with a citrus scent kills adult fleas, eggs, larvae and pupa for dogs, cats, puppies and kittens."
Test substance: Test substance was a natural plant extract containing an unspecified, but high, concentration of linalool.
Conclusion: Natural linalool-containing product is useful to kill fleas

on pets.
Reliability: (4) not assignable
22-JAN-2002 (96)

Species: other: insects (no further definition)
Endpoint: mortality

Result: "Botanicals are naturally occurring insecticides derived from plant sources. [...]
Pure chemicals isolated from plants. These are purified insecticidal compounds that are isolated and refined by a series of extractions, distillations or other processes and are formulated into concentrates. Included in this category are [...] linalool.
The modes of action of [...] linalool in insects are not fully understood. Little has been published regarding the mode of action of linalool in insects.
[...] linalool are contact poisons and may also have some fumigating action against fleas."
Reliability: (4) not assignable
20-AUG-2001 (155)

4.7 Biological Effects Monitoring

Memo: Experimental toxicity against bacteria and fungi

Result: Five aromatic constituents of essential oils (cineole, citral, geraniol, linalool and menthol) were tested for antimicrobial activity against 18 bacteria (including Gram-positive cocci and rods and Gram-negative rods) and 12 fungi (3 yeast-like and 9 filamentous). In terms of antibacterial activity linalool was the most effective and inhibted 17 bacteria [...]. Against fungi, the citral and geranil oils were the most effective (inhibiting all 12 fungi), followed by linalool (inhibiting 10 fungi) [...].
Reliability: (4) not assignable
31-JUL-2001 (115)

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

Memo: "The optically active forms (d- and l-) and the optically inactive form [dl-] occur naturally in more than 200 oils from herbs, leaves, flowers and wood."

Reliability: (4) not assignable
04-DEC-2001 (20)

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo:	In vivo
Type:	Absorption
Species:	rat
Route of administration:	other: gavage and intraperitoneal
Exposure time:	72 hour(s)
Year:	1974
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4

Method: An unspecified number of male, 12-week-old Wistar rats were administered by stomach tube 500 mg 14C-labelled linalool (14C in positions 1 and 2; 10 uCi) per kg body weight as a 25% solution in propylene glycol. The animals were individually housed in special cages that allowed for passing of expired air through traps containing ethanol-ethanolamine (2:1, v/v). Urine, faeces and air trap samples were collected at intervals over the 72-hour experimental period. After 72 h, the animals were killed and residual radioactivity was counted in the following tissues after digestion in hyamin: brain, lung, liver, heart, spleen, gastro-intestinal tract, kidney, skin and skeletal muscle.
To investigate biliary excretion and enterohepatic re-circulation, in the first experiment 2 male 12-week-old rats had a cannula inserted into the common bile duct under urethane anaesthesia and and 20 mg of radiolabelled linalool as above (1 uCi) was administered intraperitoneally as a 10% (w/v) solution in propylene glycol; the bile was collected at intervals over a period of 6 h in one animal and over 11 h in the other. In a second experiment, two male rats as above were anaesthetised and bile ducts cannulated as follows: a cannula from the bile duct of animal 1 was inserted into the duodenal end of the bile duct of animal 2; another cannula was inserted into the hepatic end of the bile duct of animal 2 and its bile duct ligated between the two cannulae. Thus, bile from the animal 1 was introduced into the duodenum of animal 2, while at the same time bile from animal 2 could be collected. Then, animal one was dosed i.p. as above; the presence of radioactivity in the bile of animal 2 would then show re-absorption through enterohepatic re-circulation.

Result: From the gavage experiments, linalool appeared to be rapidly absorbed from the intestinal tract as extensive and rapid urinary excretion of radioactivity occurred with no delay between dosing and appearance in urine.
Faecal excretion of radioactivity was delayed; as this is not explicable in terms of time for gastro-intestinal transit, hepato-biliary-intestinal recirculation was made likely.

Conclusion: Linalool is rapidly absorbed after oral uptake.

Enterohepatic re-circulation with biliary excretion of polar conjugates and hydrolysis in the gut may cause repeated absorption, which might have the effect of prolonging the metabolic load on the liver over a relatively short period.

Reliability: (2) valid with restrictions
19-JUL-2001 (114)

In Vitro/in vivo: In vitro
Type: Absorption
Species: pig
Route of administration: other: penetration through excised buccal mucosa

Year: 2000
GLP: no data

Method: Using Franz cells, the in vitro penetration of the essential oil of Salvia desoleana, containing linalool amongst other terpenes, and the same essential oil in microemulsions, in a gel and in microemulsion-gels was tested; components and compositions of the formulations are detailed.
Buccal mucosa from freshly slaughtered young male pigs (30-50 kg bw) was removed, kept in ice-cold buffer for transport to the laboratory, carefully freed from connective tissue and mounted in Franz diffusion cells with a diffusion area of 0.64 square cm. The cells were kept at 37 °C. A 2:3 ethanol:water solution was placed in the receptor compartment and stirred constantly in order to solubilise the essential oil components. 1 ml of test solution was placed in the donor compartment. Aliquot samples were removed from the receptor compartment at defined intervals (0.5, 1, 2, 4 8, 12, 24 h) for analysis, which was performed using GC-FID for identification and quantification of the single components using an internal standard (details given). Tests were performed in triplicate.
Result: Overall permeation of essential oils of Salvia desoleana containing approx. 14.5% linalool is nearly linear over 24 h. No details as to the penetration of linalool from the essential oil are given. However, in formulations linalool was found to cross the membrane from microemulsions-gels, but not from only the microemulsions nor from only the gel. In the micromulsions-gel the permeability coefficient decreases with an increase of the essential oil concentration.
Test substance: Essential oil of Salvia desoleana Atzei & Picci (Labiatae), prepared fresh through distillation of leaves in a Clevenger-type apparatus; boiling range for distillation was 80-100 °C at 1 atm. Terpene components listed as permeant were as follows:

Linalool	14.46% w/w
beta-Pinene	1.99% w/w
Cineole	10.20% w/w
alpha-Terpineol	0.18% w/w
Linalyl acetate	26.76% w/w
alpha-Terpinyl acetate	17.00% w/w

Conclusion: Linalool may permeate porcine (and by extension also human) buccal mucosa in function of its concentration and of formulation.
Reliability: (4) not assignable
27-JUL-2001 (23)

In Vitro/in vivo: In vivo
Type: Metabolism
Species: rat
Exposure time: 72 hour(s)

Year: 1974
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method:	An unspecified number of male, 12-week-old Wistar rats were administered by stomach tube 500 mg 14C-labelled linalool (14C in positions 1 and 2; 10 uCi) per kg body weight as a 25% solution in propylene glycol. The animals were individually housed in special cages that allowed for passing of expired air through traps containing ethanol-ethanolamine (2:1, v/v). Urine, faeces and air trap samples were collected at intervals over the 72-hour experimental period. After 72 h, the animals were killed and residual radioactivity was counted in the following tissues after digestion in hyamin: brain, lung, liver, heart, spleen, gastro-intestinal tract, kidney, skin and skeletal muscle. To investigate biliary excretion and enterohepatic re-circulation, in the first experiment 2 male 12-week-old rats had a cannula inserted into the common bile duct under urethane anaesthesia and and 20 mg of radiolabelled linalool as above (1 uCi) was administered intraperitoneally as a 10% (w/v) solution in propylene glycol; the bile was collected at intervals over a period of 6 h in one animal and over 11 h in the other. In a second experiment, two male rats as above were anaesthetised and bile ducts cannulated as follows: a cannula from the bile duct of animal 1 was inserted into the duodenal end of the bile duct of animal 2; another cannula was inserted into the hepatic end of the bile duct of animal 2 and its bile duct ligated between the two cannulae. Thus, bile from the animal 1 was introduced into the duodenum of animal 2, while at the same time bile from animal 2 could be collected. Then, animal one was dosed i.p. as above; the presence of radioactivity in the bile of animal 2 would then show enterohepatic re-circulation.
Result:	From the gavage experiments, linalool appeared to be rapidly absorbed and metabolised as extensive and rapid urinary excretion of radioactivity occurred over the first 36 hours, with no delay between dosing and appearance in urine. After several hours, substantial amounts of radioactivity appeared in the expired air, principally as 14C-carbon dioxide and not as linalool or other volatile metabolites; ultimately 23% of the total excreted radioactivity was found in the expired air. The appearance of 14C-carbon dioxide and the delay in its pulmonary excretion suggest that linalool enters pathways of intermediary metabolism. Faecal excretion of radioactivity was delayed and found mostly between 36 and 48 hours after dosing. As this is not explicable in terms of time for gastro-intestinal transit, hepato-biliary-intestinal re-circulation was made likely. Approx. 15% of total excretion was by faecal route. From the experiments with cannulated bile ducts and intraperitoneal dosing, substantial biliary excretion was confirmed with more than 25% of the i.p. dose appearing in bile in 6-10 hours, principally within the first 4 hours after dosing. The radioactivity present in the bile was exclusively in the form of polar conjugates, no free linalool was detectable. The conjugates were partially hydrolysed by beta-glucuronidase and to a greater extent by a mixture of beta-glucuronidase and sulfatase. Moreover, the experiments with linked bile ducts suggests that enterohepatic re-circulation after hydrolysation and re-absorption in the gut constitutes an important metabolic loop that may prolong the load on the liver on one hand.
Conclusion:	This study suggests that large doses of linalool may be metabolised in the rat by conjugation and excretion in urine

and bile, while a substantial proportion may enter intermediary metabolism up to formation of carbon dioxide that is excreted by pulmonary route. Enterohepatic re-circulation might have the effect of prolonging the metabolic load on the liver over a relatively short period.
Reliability: (2) valid with restrictions
27-JUL-2001 (114)

In Vitro/in vivo:	In vivo
Type:	Metabolism
Species:	mouse
Route of administration:	inhalation
Exposure time:	90 minute(s)

Year:	1991
GLP:	no data

Method: The change in motor activity of young and adult mice due to inhalation of essential oil of lavender and its main constituents, linalool and linalyl acetate, was studied. Mixed (m/f) groups of 4 mice, either young (6-8 weeks) or adult (6 months), were exposed two airtight experimental cages with controlled air exchange; one cage was for the experimental group, the other for parallel, untreated controls. Control groups of mice had previously shown highest motor activity levels between 10 am and 2 pm. Tests were started at 12 noon, when the two groups of 4 mice were transferred to the airtight cages and left to adapt (without any treatment but with food available) for 1 hour. At 1 pm, 1.5 ml for the younger mice, respectively 3 ml for the adult mice due to weaker response in motor activity, of the respective fragrance compound was injected through a seal into a small horizontal glass tube with a slit of 3 mm width and 5 cm length fixed within the experimental cage. Test substance then evaporated and diffused through the slit into the cage. Air was sampled from the cages using NIOSH activated charcoal tubes to subsequently determine the air concentrations of test compounds. Blood samples were collected from the mice and mixed with heparin for storage prior to analysis for test compounds. GC-FID and GC-MS were used for analysis, an internal stadard (tiglinic acid benzyl ester) used for quantification [full details are given].
Result: After 90 min of inhalative exposure to linalool, the concentration of linalool in blood samples was 7-9 ng/ml serum. After 90 min of inhalative exposure to linalyl acetate, the concentration of linalyl acetate was 1-2 ng/ml while that of linalool was 4-5 ng/ml.
Test substance: Essential oil of Lavender, "Mont Blanc" quality, containing 37.3% linalool and 41.6% linalyl acetate, from Dragoco, Vienna, Austria.
Pure linalool and linalyl acetate, from Dragoco, Vienna, Austria.
Conclusion: Linalyl acetate is metabolised to linalool through ester hydrolysis by esterases.
Reliability: (4) not assignable
27-JUL-2001 (19) (81)

In Vitro/in vivo:	In vivo
Type:	Metabolism
Species:	rat

Route of administration: gavage
Exposure time: 20 day(s)

Year: 1984
GLP: no data

Method: Animals
A number (not stated) of male IISc strain rats of 160-200 g bw were used for the study.
Administration
For the induction study 600 mg linalool/kg bw was administered once daily for 6 days by gastric tube as a suspension in 1% methyl cellulose solution. Control rats were only given the vehicle.
For the identification of metabolites 800 mg linalool/kg bw was administered once daily for 20 days (probably also by gastric tube as a suspension in 1% methyl cellulose solution). After dosing, control and experimental rats were housed singly in metabolism cages with feed and water ad libitum. Urine was collected in bottles maintained at 0-4 °C.
Preparation of microsomes and enzyme assays
Microsomes were prepared according to a cited method and the enzyme assays are described in detail.
Extraction of urinary metabolites
Urine samples from 20 days were adjusted to pH 3-4 with 1 M HCl and extracted 3 times with distilled ether. The aqueous portion containing conjugated metabolites was then subjected to acid hydrolysis (pH 3-4, refluxed for 6 h)and extracted with ether. Neutral and acidic fractions of ether extracts were separated by extracting with 5% NaHCO3.
Analysis
TLC was carried out on silica gel plates, GC on a Chemito 380 with FID, HPLC on a Waters ALC/GPC 244 and NMR spectra on either Varian T-60 or Bruker 270 MHz spectrometer. Technical details are given in each case.

Result: 8-Hydroxy-linalool (CAS 64142-78-5) and 8-carboxy-linalool (CAS 26187-81-5) were identified in the urine, showing selective oxidation of the C8-methyl in linalool.
The 8-hydroxylase present in both lung and liver microsomes was shown to be mediated by a cytochrome P-450 (CYP450) system. After 3 days of dosing, liver and lung microsomal CYP450 was increased; on the other hand, both NADH- and NADPH-cytochrome c reductase activities were not significantly changed during the 6 days of treatment.

Test substance: Linalool from Hindustan Lever, Bombay, was purified by column chromatography on silica gel using ethyl acetate-hexane (1:9, v/v) as eluent and finally distilled under reduced pressure. Final purity was >99.5% as confirmed by GLC.

Reliability: (4) not assignable
20-AUG-2001 (24)

In Vitro/in vivo: In vivo
Type: Metabolism

Remark: comment in the discussion of a paper on sedative effects due to inhalation, without further references

Result: "A similar metabolic pathway is also known for linalool, which is metabolised as a primary alcohol to the water

soluble glucuronide and eliminated by urine."
Reliability: (4) not assignable
30-JUL-2001 (19)

In Vitro/in vivo:	In vivo
Type:	Excretion
Species:	rat
Exposure time:	72 hour(s)

Year:	1974
GLP:	no

Test substance: as prescribed by 1.1 - 1.4

Method: An unspecified number of male, 12-week-old Wistar rats were administered by stomach tube 500 mg 14C-labelled linalool (C14 in positions 1 and 2; 10 uCi) per kg body weight as a 25% solution in propylene glycol. The animals were individually housed in special cages that allowed for passing of expired air through traps containing ethanol-ethanolamine (2:1, v/v). Urine, faeces and air trap samples were collected at intervals over the 72-hour experimental period. After 72 h, the animals were killed and residual radioactivity was counted in the following tissues after digestion in hyamin: brain, lung, liver, heart, spleen, gastro-intestinal tract, kidney, skin and skeletal muscle. To investigate biliary excretion and enterohepatic re-circulation, in the first experiment 2 male 12-week-old rats had a cannula inserted into the common bile duct under urethane anaesthesia and and 20 mg of radiolabelled linalool as above (1 uCi) was administered intraperitoneally as a 10% (w/v) solution in propylene glycol; the bile was collected at intervals over a period of 6 h in one animal and over 11 h in the other. In a second experiment, two male rats as above were anaesthetised and bile ducts cannulated as follows: a cannula from the bile duct of animal 1 was inserted into the duodenal end of the bile duct of animal 2; another cannula was inserted into the hepatic end of the bile duct of animal 2 and its bile duct ligated between the two cannulae. Thus, bile from the animal 1 was introduced into the duodenum of animal 2, while at the same time bile from animal 2 could be collected. Then, animal one was dosed i.p. as above; the presence of radioactivity in the bile of animal 2 would then show enterohepatic re-circulation.

Result: From the gavage experiments, linalool appeared to be rapidly excreted. Urinary excretion of radioactivity occurred over the first 36 hours, with no delay between dosing and appearance in urine; by 72 hours, approx. 60% of the total excreted dose was found in urine.
After several hours, substantial amounts of radioactivity appeared in the expired air, principally as C14-carbon dioxide and not as linalool or other volatile metabolites; ultimately 23% of the total excreted radioactivity was found in the expired air.
Faecal excretion of radioactivity was delayed and found mostly between 36 and 48 hours after dosing. As this is not explicable in terms of time for gastro-intestinal transit, hepato-biliary excretion was made likely. Approx. 15% of total excretion was by faecal route.
From the graph of total excretion and excretion by urinary, faecal and pulmonary route, measured as C14, a half-life for

linalool of approx. 18 hours can be derived.
From the experiments with cannulated bile ducts and intraperitoneal dosing, substantial biliary excretion was confirmed with more than 25% of the i.p. dose appearing in bile in 6-10 hours, principally within the first 4 hours after dosing.

Conclusion: This study suggests that large doses of linalool may be metabolised in the rat by conjugation and excretion in urine and bile, while a substantial proportion may enter intermediary metabolism up to formation of carbon dioxide that is excreted by pulomnary route. The rapid excretion of linalool and its metabolites suggests no long-term hazard from tissue accumulation on chronic concentrations normally encountered in foods. However, enterohepatic re-circulation might have the effect of prolonging the metabolic load on the liver over a relatively short period.

Reliability: (2) valid with restrictions
27-JUL-2001 (114)

In Vitro/in vivo: In vitro
Type: Toxicokinetics

Year: 1988
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: Inhibition of acetylcholinesterase by terpenoids including linalool was assessed by an invitro assay first described by Ellmann et al (1961: A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol 7: 88-95). Briefly, 1 ml of serial dilutions of linalool in 0.1 M phosphate buffer, pH 8, was incubated with 40 ul acetycthiocholine iodide, 20 ul 5,5'-dithio-bis-2-nitrobenzoic acid as a colour reagent and 100 ul electric eel acetycholinesterase. Hydrolysis of the substrate at 25 °C was measured in a Pye Unicam SP8-100 spectrophotometer at 412 nm. Duplicate test and control assays were corrected by blanks for nonenzymatic hydrolysis.

Result: Linalool, like the other terpenes tested, proved to be an effective, reversible inhibitor of acetylcholinesterase. Specifically, it paralysed and killed nonadapted insects (Tribolium castaneum, grain weevil) and inhibited electric eel acetylcholinesterase. Based on tests with two different concentrations of the substrate acetylthiocholine iodide, the inhibition constant (Ki) of linalool was 5.5 mM.

Test substance: Linalool, purity 99%, from Aldrich, England.
Conclusion: Linalool is an effective acetylcholinesterase inhibitor.
Reliability: (2) valid with restrictions
20-AUG-2001 (126)

In Vitro/in vivo: In vivo
Type: Absorption

Result: Linalool applied to mouse skin was not resorbed within two hours.
Source: BASF AG Ludwigshafen

Reliability: (4) not assignable
20-AUG-2001 (103)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Osborne-Mendel
Sex: male/female
No. of Animals: 10
Vehicle: other: no vehicle
Doses: no data
Value: = 2790 mg/kg bw

Year: 1964
GLP: no

Method: Groups of 10 young adult Osborne-Mendel rats evenly divided by sex were fasted for approx. 18 hours prior to treatment, Animals had access to water at all times and the food was replaced in cages as soon as the animals received their respective doses.
All doses of linalool were given undiluted by intubation (gavage). Dose range is not stated.
All animals were maintained under close observation for toxic signs and time of death. Such observation was continued until animals appeared normal and showed weight gain. The usual observation period was 2 weeks.
LD50s were computed by the method of Litchfield & Wilcoxon (1949).
Result: LD50 in the rat was 2790 mg/kg, with 95% confidence limits of 2440-3180 mg/kg. The slope of the dose-response curve was 1.3 (1.2-1.4, 95% CL).
Clinical observations are described as "ataxia soon after treatment".
Death occurred within 4-18 hours after treatment.
Test substance: Linalool, "commercially available material"
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
30-JUL-2001 (80)

Type: LD50
Species: mouse
Strain: no data
Sex: no data
Vehicle: no data
Value: = 3120 mg/kg bw

Method: other
Year: 1977
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The following effect doses (mg/kg bw) are described:

Dose type	after 24 h	after 10 days
LD10	2000	2000
LD50	3120 +/- 500	3120 +/- 500
LD90	4900	4900

Reliability: (4) not assignable
26-JUL-2001 (21)

Type: LD50
Species: rat
Strain: no data
Sex: male
Value: = 4.9 mg/kg bw

Method: other: not stated
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (3) invalid
all other acute oral toxicity data are in the range of a few grams per kg body weight, the LC50 given here in the range of mg/kg bw is assumed to be a typing error and should probably read 4.9 g/kg bw; therefore the source is regarded as invalid regarding acute oral toxicity data
17-JUL-2001 (40)

Type: LD50
Species: rat
Strain: no data
Sex: female
Value: = 4.13 mg/kg bw

Method: other: not stated
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (3) invalid
all other acute oral toxicity data are in the range of a few grams per kg body weight, the LC50 given here in the range of mg/kg bw is assumed to be a typing error and should probably read 4.13 g/kg bw; therefore the source is regarded as invalid regarding acute oral toxicity data
17-JUL-2001 (40)

Type: LD50
Species: mouse
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 3000 mg/kg bw

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: "effects = behavioural (somnolence, ataxia); lungs, thorax or repsiration (dyspnoea)"
Reliability: (4) not assignable
24-JUL-2001 (150)

5.1.2 Acute Inhalation Toxicity

Type: other: sedative effects after inhalation
Species: mouse
Strain: Swiss

Sex:	male/female
Exposure time:	90 minute(s)
Year:	1991
GLP:	no data
Method:	The change in motor activity of young and adult mice due to inhalation of essential oil of lavender and its main constituents, linalool and linalyl acetate, was studied. Activity was measured with light barriers at 2 cm above the cage floor; activity of the mice interrupted this light barrier and triggered impulses that were recorded and used for statistical evaluation. Mixed (m/f) groups of 4 mice, either young (6-8 weeks) or adult (6 months), were exposed two airtight experimental cages with controlled air exchange; one cage was for the experimental group, the other for parallel, untreated controls. Control groups of mice had previously shown highest motor activity levels between 10 am and 2 pm. Further groups of mice were injected 0.5 ml per animal of 1 mg caffeine/ml phosphate-buffered saline i.p. before the test to increase normal, baseline motor activity. Tests were started at 12 noon, when the two groups of 4 mice were transferred to the airtight cages and left to adapt (without any treatment but with food available) for 1 hour. At 1 pm, 1.5 ml for the younger mice, respectively 3 ml for the adult mice due to weaker response in motor activity, of the respective fragrance compound was injected through a seal into a small horizontal glass tube with a slit of 3 mm width and 5 cm length fixed within the experimental cage. Test substance then evaporated and diffused through the slit into the cage. Air was sampled from the cages using NIOSH activated charcoal tubes to subsequently determine the air concentrations of test compounds. Blood samples were collected from the mice and mixed with heparin for storage prior to analysis for test compounds. GC-FID and GC-MS were used for analysis [full details are given].
Result:	Motor activity after inhalation: For linalool, young mice showed a progressive relative decrease of motor activity, compared with untreated controls from 100% at time 0, to 32% at 30 min, 8% at 60 min and 0% at 90 min exposure. Adult mice showed a decrease to 96% at 30 min, 85% at 60 min and 71% at 90 min. For essential oil of lavender, containing 37.3% linalool and 41.6% linalyl acetate, young mice showed a progressive decrease to 22% at 30 min and 0% at both 60 and 90 min. Adult mice showed a decrease to 71% at 30 min, 57% at 60 min and 42% at 90 min. In further experiments, the motor activity due to i.p. caffeine injection was increased to 160% compared with non-caffeine-treated controls; after 60 min inhalation the activity was reduced by test compounds to 105% for lavender oil and 126% for linalool. Plasma levels after inhalation: Due to inhalation of linalool, plasma levels rose from 0 at time 0 to ca. 0.9 ng/ml plasma at 30 min, to ca. 2.6 ng/ml plasma at 60 min and to ca. 2.8 ng/ml plasma at 90 min (data only given as a graph). A direct correlation was found between plasma concentration and inhalation time. Subsequent to inhalation of lavender oil, three linalool signals (m/z) were differentiated in a plasma GC-MS spectrum.

Test substance: Essential oil of Lavender, "Mont Blanc" quality, containing 37.3% linalool and 41.6% linalyl acetate, from Dragoco, Vienna, Austria.
Pure linalool and linalyl acetate, from Dragoco, Vienna, Austria.
Conclusion: Essential oil of lavender, containing approx. 40% each of linalool and linalyl acetate, as well as the pure terpenoids were shown to have a sedative effect on motor activity after inhalative absorption. The effect was progressive with exposure time; in the case of pure linalool, also the plasma concentration was shown to rise in parallel with exposure time.
Differences in the effectiveness of the three test compounds are explained by the authors by the synergistic effect of other components of lavender oil, eg 1,8-cineole, on one hand. On the other hand, the lesser effectiveness of linalool and linalyl acetate in comparison with may also be due to hydrolysis of linalyl acetate due to esterases and to glucuronidation and subsequent urinary excretion of linalool.
The effectiveness of all three test compounds was greater in young animals than in adults; this is explained by the authors by the higher amount of fat in older animals, which will absorb more of the lipophilic terpenoids and thereby reduce the effective plasma concentration.
In the test with caffeine-induced hyperactive animals, the decrease in motor activity was significantly higher if the animal inhaled the test substances 1 hour after caffeine injection compared with directly afterwards, showing the combined effect of both test substance plus metabolisation of the caffeine.
Reliability: (2) valid with restrictions
22-JAN-2002 (19)

Type: LC50
Species: other: not stated
Value: < 2.95 mg/l

Method: other: not stated
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: other toxicity data from this source are considered doubtful
Reliability: (4) not assignable
22-JAN-2002 (40)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 5610 mg/kg bw

Method: other: no data
Year: 1986
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Due to the very brief reference lacking detail, result could not be validated.
Source: RTECS
Reliability: (4) not assignable
08-SEP-2003 (100)

Type: LD50
Species: rabbit
Strain: other: albino
Value: = 2000 mg/kg bw

Method: other: not stated
Test substance: as prescribed by 1.1 - 1.4

Remark: Due to the very brief reference lacking detail, result could not be validated.
other toxicity data from this source are doubtful
Reliability: (4) not assignable
08-SEP-2003 (40)

Type: LD50
Species: other: not stated
Value: ca. 3578 - 8374 mg/kg bw

Method: other: not stated
GLP: no data
Test substance: other TS: linalool derived from plant sources

Remark: Due to the very brief reference lacking detail, result could not be validated.
Reliability: (4) not assignable
08-SEP-2003 (155)

Type: LD50
Species: rabbit
Value: > 5000 mg/kg bw

Method: other: no data
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Due to the very brief reference lacking detail, result could not be validated.
Original source not available
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
08-SEP-2003 (90)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Route of admin.: i.p.
Value: = 307 mg/kg bw

Method: no data

```
  Year:           1973
   GLP:           no
Test substance:   as prescribed by 1.1 - 1.4

Remark:           "effects = behavioural (somnolence, change in motor
                  activity, ataxia)"
Reliability:      (4)  not assignable
24-JUL-2001                                                        (76)

Type:             LD50
Species:          mouse
Strain:           no data
Sex:              no data
Vehicle:          no data
Doses:            no data
Route of admin.:  i.p.
Value:            = 340 mg/kg bw

Method:           other: no data
  Year:           1973
   GLP:           no
Test substance:   as prescribed by 1.1 - 1.4

Remark:           "effect = behavioural (somnolence, chancge in motor
                  activity, ataxia)"
Reliability:      (4)  not assignable
24-JUL-2001                                                        (76)

Type:             LD50
Species:          mouse
Strain:           no data
Sex:              no data
Vehicle:          no data
Doses:            no data
Route of admin.:  s.c.
Value:            = 1470 mg/kg bw

Method:           other: no data
  Year:           1952
   GLP:           no
Test substance:   as prescribed by 1.1 - 1.4

Remark:           "effect = peripheral nerve and sensation (spastic paralysis

                  with or without sensory change)"
Reliability:      (4)  not assignable
24-JUL-2001                                                       (128)

Type:             LD50
Species:          mouse
Strain:           no data
Sex:              no data
Vehicle:          no data
Doses:            no data
Route of admin.:  i.m.
Value:            = 8000 mg/kg bw

Method:           other: no data
  Year:           1962
   GLP:           no
Test substance:   as prescribed by 1.1 - 1.4
```

Reliability: (4) not assignable
24-JUL-2001 (82)

Type: other
Species: cat
Route of admin.: other: see remark

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Cats dipped in 1% solution, no toxic effects
Source: BASF AG Ludwigshafen
05-JAN-1994 (65)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: no data
Exposure Time: no data
EC classificat.: irritating

Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: Authors of relevant literature publications as well as companies known to possess such data were contacted whether they would make available individual rabbit skin test data, the in vivo test method and the specifications of the chemicals used. Data received were included in the reference chemical databank if they met stringent quality criteria [details given in the original paper].
Result: Linalool (1), 97.1% purity, 3 animals, PII = 3.33
Linalool (2), 97.1% purity, 4 animals, PII = 3.42
Linalool (3), 97.1% purity, 4 animals, PII = 2.08
PII = Primary Skin Irritation Index
Conclusion: with consistent Primary Skin Irritation Indices > 2 the test substance is considered to be irritating to the skin, following the criteria of the European Union [EC Directive 92/32/EEC, appendix VI, chapter 3.2.6.1].
Reliability: (4) not assignable
30-JUL-2001 (2)

Species: other: rabbit, guinea pig, minipig, man

Year: 1979
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Coding of test substances
All test substances were coded prior to experiments by an independent collaborator, coding was only resolved after evaluation of reactions.
Species/probands
Rabbits: albino angora strain of 2.3-3.0 kg bw (avg 2.6 kg); 6 animals per group.
Guinea pigs: Hartley strain males of 0.35-0.5 kg bw; 6

animals per group.
Minipigs: Pitman-Moore Improved strain, 1 month old; 6 animals altogether.
Probands: 50 adult male volunteers without a history of allergic reactions.
Application
Rabbits: 6 test areas of 3x3 cm were clipped on the dorsum; after 24 h, 0.1 g of 3 test substances and 1 control was directly applied from a glass tuberculin syringe to 4 areas while the two central areas remained untreated, the test compunds were immediately spread over the whole area; application areas for the same compound were rotated among the 6 rabbits. The areas were not covered, rabbits were prevented from licking by a large collar. First readings of reaction were taken after 24 h using a score card (details given in paper), then the test compunds were applied again, probably on the same area (not stated), and second readings and applications were made after another 48 h, totalling 72 h. Aminals were then totally clipped on the dorsum, infused with 40 mg Evans Blue/kg bw, after 1 h killed and skinned. The dilating rate of blood vessels, the bluing rate as a function of increased capillary permeability and the bleeding rate on test sites were evaluated under transmitting light using a score card.
Guinea pigs and rats: 2 test areas of 3x3 cm were clipped on the dorsum; after 24 h, 0.1 g of 1 test substances was directly applied from a glass tuberculin syringe to 1 area while the other area remained untreated. The period of testing, the frequency of application and the evaluation method of skin reactions were the same as in the rabbit test.
Minipigs: The animal was immobilised in a special restrainer, the hair on the whole back was removed with a clipper and the dorsal skin washed with warm water. After 24 h, 0.05 g of the tests compunds were placed under a 15-mm-diameter patch; patches were secured with adhesive tape, then the entire trunk of the animals were wrapped with rubberised cloth for the 48-hour exposure period. Then cloth and patches were removed and skin reactions were evaluated using the same score card as above. Test animal skins from all three species were additionally examined histopathologically, after fixation and histological preparation, as 5-um sections stained with haematoxylin-eosin.
Probands: 0.05 g of the tests compunds were placed under a 15-mm-diameter patch; patches were the placed on the back of probands and secured with adhesive tape for 48 h, subsequently removed and the sites cleaned of remaining material with dry gauze. After another 30 min, the test sites were evaluated using a patch test score card (details given in paper); if necessary, additional readings at 72, 96 or 120 h after application were also taken.

Result: Linalool produced a broad variation of effects in four mammal species in this comparative study, from severely irritating to not irritating:

Species	Concentration	Scoring
rabbit	100% (undiluted)	severely irritating
guinea pig	100% (undiluted)	moderately irritating
minipig	100% (undiluted)	negative (not irritating)
man	32% in acetone	mildly irritating

Test substance: Synthetic linalool, technical grade, purity > 95%.
Control substance: Hexadecane, reagent grade.

Reliability: (4) not assignable
Reliability of this study may be better than 4, possibly 2, but no details on the single animals/probands and reactions are given.
30-JUL-2001 (105)

Species: rabbit
Concentration: 500 mg
Exposure: no data
Exposure Time: 24 hour(s)
Vehicle: no data

Method: other: no data
Year: 1976
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Effects described as "mild"
Reliability: (4) not assignable
17-JUL-2001 (52)

Species: rabbit
Concentration: 100 mg
Exposure: no data
Exposure Time: 24 hour(s)
Vehicle: no data

Method: other: no data
Year: 1979
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: Effects described as "severe"
Reliability: (4) not assignable
17-JUL-2001 (27)

Species: rabbit
Result: irritating

Method: other: occlusive, 24 hours, intact and abraded skin
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: original source not available
Source: BASF AG Ludwigshafen
05-JAN-1994 (51)

Species: rabbit
Result: not irritating

Method: other: occlusive, 24 hours, intact and abraded skin
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: original source not avaible
Source: BASF AG Ludwigshafen
05-JAN-1994 (90)

Species: guinea pig
Concentration: 100 mg
Exposure: no data
Exposure Time: 24 hour(s)

```
Vehicle:          no data

Method:           other: no data
  Year:           1979
   GLP:           no
Test substance:   as prescribed by 1.1 - 1.4

Result:           Effects described as "moderate"
Reliability:      (4)  not assignable
17-JUL-2001                                                          (27)


Species:          human
Concentration:    48 mg
Exposure:         no data
Exposure Time:    48 hour(s)
Vehicle:          no data

Method:           other: no data
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Result:           Effects = "mild". No further details given
Reliability:      (4)  not assignable
18-JUL-2001                                                          (27)

Species:          human
Result:           not irritating

Method:           other: occlusive, 48 hours ("patch-test")
   GLP:           no
Test substance:   as prescribed by 1.1 - 1.4

Remark:           Probands
Source:           BASF AG  Ludwigshafen
Test substance:   20% solution in petrolatum
Reliability:      (4)  not assignable
27-JUL-2001                                                          (85)

Species:          human
Result:           not irritating

Method:           other: occlusive, no exposure time given
   GLP:           no
Test substance:   as prescribed by 1.1 - 1.4

Remark:           Probands
                  different ways of application
Source:           BASF AG  Ludwigshafen
Test substance:   20% in vaseline or ointment, 2% and 0.4%  in ethanol or a
                  cream base respectively.
05-JAN-1994                                                          (53)

Species:          human
Result:           not irritating

Method:           other: occlusive, 48 hours
   GLP:           no
Test substance:   as prescribed by 1.1 - 1.4

Remark:           Probands
Source:           BASF AG  Ludwigshafen
```

Test substance: 8% solution in petrolatum
05-JAN-1994 (86)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Comment: not rinsed
No. of Animals: 3
Vehicle: none
Result: not irritating

Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year: 1988
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: An eye irritation test was performed according to guideline OECD 405. Briefly, three rabbits (White Vienna, from Savo GmbH, Kisslegg, Germany; 2 males of average weight 2.68 kg and one female of 2.40 kg) were marked by ear tattoo and kept singly in stainless-steel cages at full climate control (20-24 °C, 30-70% RH, 12-hour light/dark cycle) with feed ad libitum and approximately 250 ml tap water per day. Acclimatisation was at least 8 days before the study under the same conditions. The animaly were dosed by single application of 0.1 ml of undiluted test substance to the conjunctival sac of the right eye, the substance was not washed out. The animals were observed according to a detailed catalogueat 1 hour and at 1, 2, 3, 8 and 15 days after application. The untreated eye served as the negative control.

Result: Detailed ratings for all three animals are listed in the report. Briefly, after 1 hour, all three animals showed well defined chemosis and conjunctival redness plus clearly to distinctly increased eye discharge; additionally, 1/3 showed contracted pupil. After 1 day, all animals showed slight corneal opacity with at least one-quarter of the cornea involved, well defined to severe conjunctival redness, slight to no chemosis and slightly increased discharge; this pattern remained for another day (day 2); on both days 1 and 2, 2/3 animals showed contracted pupils and one of the loss of corneal tissue. On day 3 slight corneal opacity was distributed over at least half of the cornea, the iris showed circumcorneal injection and there was still well-defined to severe redness, but chemosis and discharge were only remarkable in 1/3 animals; all three animals showed contracted pupils, loss of corneal tissue and 1/2 had small retractions in the eyelid. On day 8, with the exception of slight corneal opacity in one male all animals were free of quantified symptoms, one male showed small eyelid retractions, marginal vascularisation of the cornea, loss of hair at margins of eyelids and loss of corneal tissue. On day 15, there were no qunatified reactions in any animal, but one male still showed small retractions of the eyelid and loss of hair at the margins of the eyelid.

Source: BASF AG Ludwigshafen

Conclusion: While there are clear signs of ocular reactions to undiluted linalool, these are transient and resolve within some days.

Linalool has a low potential of eye irritation.
Reliability: (2) valid with restrictions
Short but detailed report form a professional industry toxicology laboratory, test according to international guideline but not under GLP, reliability judged as 2.
Flag: Critical study for SIDS endpoint
29-JUL-2002 (8)

Species: rabbit
Dose: .1 ml
Comment: no data
Vehicle: no data

Method: other: no data
Year: 1968
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Effects are described as "moderate"
Reliability: (4) not assignable
29-JUL-2002 (150)

Species: human
Vehicle: other: mineral oil

Year: 1998
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: Six terpene test compounds commonly found indoors including linalool were dissolved in mineral oil serial dilutions of 1/3 each, ie, 100%, 33%, 11%, 3.7% etc, all percentages as % v/v. Stimuli were presented to the test subjects from "squeeze bottles". Quantification of the vapour-phase concentration was achieved via direct gas chromatography with flame ionisation detector (GC/FID) of the headspace, using the saturated vapour concentration at room temperature (approx. 23 °C) of each compound as a reference.
In order to detect odour thresholds, nasal pungency, nasal localisation and eye irritation, 4 anosmic subjects (2 m, 2 f, age range 23-53 years) and 4 normosmic subjects (2 m, 2 f, age range 37-58) participated. Anosmics provided nasal pungency thresholds and normosmics provided odour thresholds. All subjects provided nasal localisation and eye irritation thresholds. Each type of threshold was measured 8 times (hals with each nostril or eye) per subject-stimulus combination. Typically, each subject participated in a total of 10-14 sessions held on different days. Each sessions lasted between 1 and 3 hours. Stimuli were presented via a forced-choice procedure (against the blank mineral oil) with ascending concentrations over trials. Five correct choices in a row consituted the criterion for threshold.
Result: Linalool produced eye irritation at concentrations of ca. 320 ppm (no precise data given, only graph with log ppm) for both normosmics and anosmics. However, in 38% of instances for both groups, linalool failed to produce an eye irritation threshold.
Eye irritation thresholds did not significantly differ between normosmics and anosmics. Moreover, the threshold for nasal pungency was very close to the eye irritation, on the graph the three data points fall together.
Reliability: (4) not assignable

22-JAN-2002 (26)

5.3 Sensitization

Type: Patch-Test
Species: human
Result: sensitizing

Method: other: no data except patch test
Year: 1983
GLP: no data

Method: Subsequent to a diagnosis of cosmetic allergy in a 52-year-old man, patch tests were performed as detailed in the paper.
Result: Positive reactions were noted to Peru balsam, ICDRG perfume mix, a hair lotion and an after-shave used by the subject. Testing with the single ingredients of the after-shave yielded allergic reactions to linalool and hydroxycitronellal.
In the discussion the authors note that in a patch test series with 792 patients using 10% linalool in petrolatum, Fregert & Hjorth [Contact Dermatitis Newsletter (1969): 5: 85] only a 0.5% incidence of positives was found.
Reliability: (4) not assignable
31-JUL-2001 (31)

Type: Patch-Test
Species: human
Vehicle: petrolatum

Year: 1987
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: In a Dutch multicentre study into the causative allergens in cosmetic products, from March 1986 to July 1987, 119 patients suffering from suspected or confirmed cosmetic-related contact dermatitis were challenged using van der Bend patch test chambers fixed to the skin with acrylate tape for applying suspected potential allergens during two days. After removal, skin reactions were graded after 20 min and again 1-2 days later. A diagnosis of cosmetic allergy was confirmed by one or more of the following criteria:
1) A positive patch test to a cosmetic product (92/119).
2) Negative patch tests with cosmetics, but positive use tests with one or more suspected cosmetic ingredients (5/119).
3) Negative patch tests with cosmetics, but positive repeated open application tests (7/119).
4) Stopping the use of cosmetic products that were negative on patch testing but known to contain one or more allergens in the European standard series or in in additional test series to which the patiens reacted, resulted in a cure or marked improvement of dermatitis (15/119).
Result: One (1) out of 119 patients with cosmetic-related contact dermatitis proved allergic to linalool subsequent to patch-test challenge with 10% linalool in petrolatum. In the series of 119 patients, 39 proved allergic to fragrances including the one with linalool allergy.

Reliability: (4) not assignable
31-JUL-2001 (30)

Type: Patch-Test
Species: human

Year: 1987
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: The records of all patients patch-tested because of suspected contact dermatitis in a private practice in a medium-sized town in the Netherlands during the period 1981-1986 were reviewed and screened for contact allergy to cosmetics.All were tested with the European Standard Series (ICDRG) [of known allergens] and, when appropriate, with a supplementary series, eg an occupational series or the patients' own products.
The ingredients of the cosmetics were obtained from the manufacturers and diluted to the proper test concentration and vehicle. When no data on the proper test concentration were available, patch tests were performed at an empirically determined concentration, utilising controls to exclude irritancy. Most cosmetics products were tested undiluted, shampoos and shaving soaps were diluted to 2% in water, hair colours to 5% in water.
The patch test materials used were Silver Patch testers and in 1986 Van der Bend Patch Test Chambers, fixed on Leukosilk and covered with Fixomull acrylate tape [sources given for all materials].
Patch test procedures were carried out according to ICDRG recommendations. The diagnosis of cosmetic allergy was based on a positive patch test to a product and sometimes on a positive usage test and/or a repeated opan allication test (ROAT). In all cases dermatitis was or had been present at the site of application of the cosmetic product. On cessation of the use of cosmetics the eruption either cleared >(when the dermatitis was caused exclusively by the cosmetic product) or markedly improved (when the cosmetic had been applied to already eczematous skin). These clinical features were additional criteria for the diagnosis of cosmetic allergy.
Result: 76 patients out of 1781 patch-tested were determined to have cosmetic allergy. In 3 instances, linalool was identified to be the causative allergen with certainty or high probability. Linalool was present in one case each as an ingredient of dry shampoo, hair lotion and after shave.
Conclusion: The author concludes that fragrances and fragrance chemicals were responsible for the majoritty of reactions (45.1%). In most cases (23 out of 37 fragrances) the individual fragrance components were not determined, but when they were, the most frequent causes were hydroxycitronellal (6/37) and linalool (3/37).
Reliability: (4) not assignable
31-JUL-2001 (29)

Type: Draize Test
Species: guinea pig
Concentration 1st: Induction .05 % intracutaneous
2nd: Challenge 10 % open epicutaneous
No. of Animals: 4
Vehicle: other: "suitable solvent"

Result: not sensitizing
Classification: not sensitizing

Method: other: Draize JH (1959): Dermal toxicity. Ass. Food and Drug Officials of the U.S., page 46-59
Year: 1978
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
30-JUL-2001 (132)

Type: other: comparison of Local Lymph Node Assay with Human Potency Class from literature
Species: human

Year: 2001
GLP: no
Test substance: no data

Method: Allergenic potency classifications from undescribed tests in literature and from Local Lymph Node Assays are compared in a short overview paper.
Result: Human potency class for linalool is described as "extremely weak", Local Lymph Node Assay potency class for linalool is described as "weak".
Reliability: (4) not assignable
31-JUL-2001 (15)

Type: Patch-Test
Species: human

Method: other: no data
GLP: no
Test substance: other TS: Peru-Balsam and linalool

Remark: Equivocal; 1/16 Patients sensitized to Peru-Balsam cross-reacted to Linalool. 2/253 Controls reacted positive as well to a 10% solution of Linalool.
Original reference not seen
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
22-JAN-2002 (66)

Type: no data
Species: other: no data, probably man

Method: other: no data
Year: 1985
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: "not a sensitiser"
Reliability: (4) not assignable
17-JUL-2001 (40)

Type: other
Species: human

Method: other: no data
GLP: no

Test substance: as prescribed by 1.1 - 1.4

Remark: Original reference not seen
Results of seven cases cross reacting to certain acyclic terpenes are presented. For the lack of information about test methods and evalution of results, the sensitizing potential of Linalool can not be estimated.
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
22-JAN-2002 (93)

Type: other: maximization test
Species: human
Result: not sensitizing

Method: other: according to Kligman, A.M.: J. Invest. Derm. 47, 369
Year: 1966
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Negative results in 25 of 25 persons tested.
Original reference not seen
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
22-JAN-2002 (60)

Type: other: maximization test
Species: human
Result: not sensitizing

Method: other: no data
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Original reference not seen.
Source: BASF AG Ludwigshafen
Test substance: 20% solution in petrolatum
Reliability: (4) not assignable
22-JAN-2002 (85)

Type: other: maximization test
Species: human
Result: not sensitizing

Method: other: no data
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Probands
Source: BASF AG Ludwigshafen
Test substance: 8% solution in petrolatum
Reliability: (4) not assignable
22-JAN-2002 (86)

Type: other: no data
Species: other: no data, presumably human
Result: sensitizing

Method: other: no data
GLP: no data

Test substance: other TS: oil of linaloe containing linalool

Remark: Equivocal. The authors mention that the oils of Linaloe are suspected to cause dermal sensitization. 2-Linalool is considered to be the causative ingredient, because of structure relationship to citronellol, which is said to cause sensitization. Sharp D.W.: Toxicology 9, 261-271, (1978) cites Klarmann E.G.: Ann.Allergy 16, 425-434, (1985) "causing contact sensitization".
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
22-JAN-2002 (84)

5.4 Repeated Dose Toxicity

Type: Chronic
Species: rat Sex: male
Strain: Wistar
Route of administration: gavage
Exposure period: 64 days
Frequency of treatment: once daily
Post exposure period: none
Doses: 500 mg/kg bw/d
Control Group: yes, concurrent vehicle
NOAEL: = 500 mg/kg bw

Year: 1974
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Linalool was administered to (an unstated number, but initially at least 24) 4-week-old male Wistar rats by intragastric intubation at a dose of 500 mg/kg body weight per day as a 25% (w/v) solution in propylene glycol. Control rats were given a similar volume of propylene glycol. At intervals of 0, 3, 7, 14, 30 and 64 days after first dose, 4 animals from each of the test and control groups were killed by cervial dislocation, the livers rapidly excised, freed from adhering connective tissue and weighed. Liver homogenates and microsomal fraction were then prepared according to published literature.
Result: There were no deaths over the 64-day period, nor was there any significant effect on body weight gain. Both the absolute and relative liver weights remained unaffected up to the 30th day of exposure, but by the 64th day there was a slight but significant ($P < 0.05$) increase in these parameters.
From liver homogenates and microsomal fractions the following biochemical changes were derived: The microsomal protein concentration was unaffected up to day 14, but was increased by 20% ($P < 0.02$) and remained at this elevated level to the 64th day. Cytochrome p-450 and cytochrome b5 showed a biphasic response, both being depressed on day 7 ($P < 0.02$ in each case), but subsequently increased by 50% ($P < 0.01$) by day 30; CYP450 remained at this elevated level while CYb5 had further increased to 70% ($P < 0.002$) by day 64. 4-Methylumbelliferone glucuronyl transferase increased on chronic exposure to linalool to 17% ($P < 0.02$) on day 3, with a further dramatic rise to 150% ($P < 0.001$) by day 64. Alcohol (ethanol) dehydrogenase showed a biphasic response, being initially depressed by 33% ($P < 0.002$) on day 3, then

increased by36% (P < 0.001) on day 7; normal values were regained by day 14 and thereafter there was no significant difference between test animals an controls.

Conclusion: No outward effect was noted at a daily dose of 500 mg/kg body weight, the observed effects were only detected through biochemical analysis of metabolising liver enzymes. The results show that, with the exception of alcohol dehydrogenase, prolonged exposure to linalool was required before significant effects were observed. The biphasic effect on alcohol dehydrogenase, in contrast to the steady increase in 4-methylumbelliferone glucuronyl transferase and the delayed induction of CYP450 and CYb5, may indicate that initially linalool is not readily metabolised and inhibits alcohol dehydrogenase. Subsequently, when the activities of drug-metabolsing enzymes (especiall 4-methylumbelliferone glucuronyl transferase) were increased, hepatic concentrations of free linalool may have fallen sufficiently to enable the adaptive increase in alcohol dehydrogenase to be observed. Still later in the study, 4-methylumbelliferone glucuronyl transferase was able to meet the whole of the increased metabolic demand and no effects on alcohol dehydrogenase were observed any longer. In corroboration of the importance of glucuronidation, it had been observed in an earlier study that linalool is excreted largely in urine and bile in the form of conjugates with glucuronic acid. Based on this reasoning, the observed effects of linalool are interpreted to represent a physiological adaptation to exposure and not toxicity in a strict sense. Therefore, a daily dose of 500 mg/kg body weight is seen as a NOAEL.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

03-DEC-2001 (113)

Type: Sub-chronic
Species: rat Sex: male/female
Strain: other: Crl:CD/BR
Route of administration: gavage
Exposure period: 28 days
Frequency of treatment: once daily
Post exposure period: 1 d
Doses: 160, 400 and 1000 mg/kg/d in 1% methyl cellulose
Control Group: yes, concurrent vehicle
NOAEL: = 160 mg/kg bw
LOAEL: = 400 mg/kg bw

Year: 1990
GLP: yes
Test substance: other TS

Method: Animals and keeping
Four-week-old Sprague-Dawley rats, Crl:CD/BR strain, were acclimated in single cages with Purina Certified Rodent Chow 5002 and tap water available ad libitum for two weeks. Both feed and water analyses were obtained and kept on record. Temperature in the animal rooms was kept at 72+/-6 °F (approx. 22+/-3 °C), relative humidity at 50+/-20% and a 12/12-h light-dark cycle was maintained.
After 14 days, rats were examined by a staff vet and randomised using a weight homogenisation computer program to 3 treatment and 1 control groups of 10 males and 10 females each.

Test article formulation and administration
B10 containing 72.9% linalool was administered in 1% methyl cellulose in distilled water. Test mixtures were prepared fresh weekly with an amount of B10 being added according to the animals' weight (recorded weekly) and a target administration volume of 10 ml/kg. Concentration was confirmed by analysis performed on all mixtures by the sponsor of the study. Appropriate volumes were administered by gavage to the rats once daily.
Treatment period
The animals were observed twice daily for moribundity and mortality. Approximately 1 hour after dosing, daily cageside observations for obvious toxic effects were recorded. Individual body weights and feed consumption were recorded weekly, when also a physical examination and clinical observation were performed. Treatment groups were dosed until the day before killing and necropsy, control animals received vehicle only.
Clinical and haematological data and necropsy
Before the test, 10 animals per sex were taken at random from the pool of healthy animals not selected for the study, to serve as a baseline group for clinical chemistray and haematology. They were fasted overnight. Under ketamine anaesthesia, blood samples for haematology and clinical chemistry were collected by venipuncture of the orbital sinus. After the last dosage the surviving test animals, both treatment and control groups, were also fasted overnight and blood samples taken as above. The following haematological and clinical-chemistry parameters were determined.
Haematology: leukocyte count, erythrocyte count, haemoglobin, haematocrit, platelet count, leukociate differential count, cell morphology and, for the control and high-dosage groups at week 5 (after test) only, the myeloid/erythroid ratio.
Clinical chemistry: Na, K, Ca, Cl, total CO2, total protein, albumin, total bilirubin, blood urea nitrogen, creatinine, glucose, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase and alkaline phosphatase.
Gross necropsy
All surviving animals, after 28 days of treatment and after venipuncture as above, were weighed and killed by exsanguination under sdium pentobarbital anaesthesia. All animals were dissected by trained personnel following standardised procedures. Necropsy included detailed examination of external surfaces, orifices, cranial cavioty, carcass, nasal cavity and paranasal sinuses, cervical tissues and organs, external surface of brain and spinal cord, thoracic, abdominal and pelvic cavities and viscera. The following organs were dissected, freed from fat and connective tissue and weighed: brain, spleen, liver, heart, kidneys, testes with epididymides, thyroid with parathyroids, adrenals glands, ovaries, pituitary. The same organs or tissues plus the following from each animal were fixed in 10% neutral formalin: femoral bone marrow, lung, any laesion, oesophagus, stomach, duodenum, jejunum, ileum, colon, caecum, rectum, pancreas, urinary bladder and mesenteric lymph nodes. Histopatholopgy was performed after paraffin-embedding, microtoming and staining with haematoxylin and eosin.
Statistical analysis

	Mean body weight changes, total food consumption, quantitative clinical pathology data, absolute organ weight and organ-to-body-weight rations of the control group were compared statistically by ANOVA with the data from the same sex in the treatment groups according to a detailed flow chart for homogenisation of variances.
Result:	Mortality and clinical observations One high-dose female was found dead on day 2 and was replaced by another female that was dosed for the full time of the test. One high-dose male was found dead on day 9; on necropsy the findings were inconclusive as to the cause of death but a handling accident appeared to be a probable cause. There were no further deaths in both control and treatment groups. There were no significant differences between the control and treatment groups for mean body weight changes and food consumption. No treatment-related findings were noted in the clinical haematology data. there were minor changes in clinical chemistry data, with elevated total protein and albumin in the midlle- and high-dose males and in the high-dose females, elevated calcium in the high-dose males and decreased glucose in the middle- and high-dose males. Pathology Most notable gross pathology changes were noted in the middle- and high-dose males and females, with mainly thickened liver lobes, pale areas noted in kidneys and thickened stomach mucosa. Treatment-related increases in liver weight were noted for male and female middle- and high-dose animals. Increase in absolute kidney weight was noted in the high-dose males and females and in relative kidney weight in the middle-dose males and all high-dose animals. A certain increase in liver weights in the low-dose males and females was not statistically significant. Histopathologically, all treated female groups showed hepatocellular cytoplasmic vacuolisation while the high-dose males had an increase in degenerative laesions in the renal cortex.Middle-and high-dose females also had laesions in the nonglandular part of the stomach, with some erosion, subacute inflammation and acanthosis.
Source:	B10: essential oil of coriander containing 72.9% of natural linalool. Additional constituents were identified as 3.9% alpha-pinene (CAS 80-56-8), 0.6% camphene (79-92-5), 0.9% myrcene (123-35-3), 4.0% p-cymene (99-87-6), 2.7% limonene (138-86-3), 3.6% gamma-terpinene (99-85-4), 4.6% camphor (76-22-2), 0.8% alpha-terpineol (98-55-5) and 1.2% geranyl acetate (105-87-3). The total of ingredients identified by gas chromatography is 95.5% (area-%), the reaminder being minor peaks in the chromatogram.
Test substance:	B10: essential oil of coriander containing 72.9% of natural linalool. Additional constituents were identified as 3.9% alpha-pinene (CAS 80-56-8), 0.6% camphene (79-92-5), 0.9% myrcene (123-35-3), 4.0% p-cymene (99-87-6), 2.7% limonene (138-86-3), 3.6% gamma-terpinene (99-85-4), 4.6% camphor (76-22-2), 0.8% alpha-terpineol (98-55-5) and 1.2% geranyl acetate (105-87-3). The total of ingredients identified by gas chromatography is 95.5% (area-%), the reaminder being minor peaks in the chromatogram.
Conclusion:	No treatment-related effects on survival, clinical observations, body weight or food consumption were observed in any of the treatment groups. There were some treatment-related increases in total serum protein and albumin, with a concomitant increase in calcium; the

pathogenesis of these increases is unknown. Liver and kidneys were the organs affected both macroscopically and histopathologically, with dose-related increase in expression of those findings. Based on these findings, treatment-related effects were found in all groups except the low-dose males. However, the severity of the incidences was low. Due to the study layout, any potential reversibility of the effects could not be tested.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
08-SEP-2003 (130)

Type: Sub-chronic
Species: rat Sex: male/female
Strain: no data
Route of administration: oral feed
Exposure period: 12 weeks
Frequency of treatment: no data
Post exposure period: no data
Doses: 50 mg/kg bw/d
Control Group: no data specified
LOAEL: = 50 mg/kg bw

Method: other: no data
Year: 1967
GLP: no
Test substance: other TS

Result: "in male rats slight retardation of growth at 50 mg/kg bw/d" [probably no effect on females at this dose level], "without effect on food efficiency"
Source: FAO Nutrition Meetings Report Series No. 44A WHO/Food Add./68.33. online at Inchem: http://www.inchem.org/documents/jecfa/jecmono/v44aje23.htm
Test substance: "mixed alcohols"
Reliability: (4) not assignable
03-DEC-2001 (111)

Type: Sub-acute
Species: mouse Sex: no data
Strain: other: A strain
Route of administration: i.p.
Exposure period: 2 weeks
Frequency of treatment: 3 times per week
Post exposure period: up to 2 months
Control Group: yes, concurrent vehicle
NOAEL: = 125 mg/kg bw

Year: 1973
GLP: no

Method: Animals:
A/He mice were bought from the Institute for Cancer Research, Philadelphia, of from the US National Cancer Insitute. The 6- to 8-week old animals weighed an average of 18-20 g. They were randomly distributed among experimental and control groups. Groups of 5 were housed in plastic boxes. Commercial grade sawdust chips were used for bedding. Purina laboratory chow and water were available ad libitum. Hygienic conditions were maintained by twice-weekly changes of the animal cages and water bottles and weekly

disinfection of animal quarters. The water bottles were routinely sterilised.
Chemicals:
All chemicals were stored in the dark and prepared for injection in separate rooms at a distance from the animals.
Administration:
In a preliminary toxicology test, the maximally tolerated single dose (MTD) for each test substance was determined by injecting intraperitoneally serial two-fold dilutions of chemicals into groups of 5 mice. The MTD was defined as that maximum single dose that all 5 mice tolerated after receiving 6 i.p. injections over a 2-week period. For evidence of delayed toxicity, animals receiving 6 doses of the MTD were held for another 1-2 months before experimental groups were initiated.

Result: the maximally tolerated single dose (MTD) for linalool was determined to be 125 mg/kg bw.

Test substance: as prescribed by 1.1 - 1.4: Linalool, Lot no. 1777162, from Givaudan. Test substance was stored at 4 °C.

Reliability: (4) not assignable

03-DEC-2001 (138)

Type: Sub-acute
Species: mouse Sex: female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 5 days
Frequency of treatment: once daily
Post exposure period: not stated
Doses: no data on single doses as this was a dose-finding test for another study
Control Group: yes, concurrent vehicle
LOAEL: = 375 mg/kg bw

Method: other
Year: 1993
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: In a sub-acute dose-finding 5-day repeated dose toxicity test for an immunotoxicity study, minimal toxic effects, described as body weight changes or clinical signs, were observed at a dose of 375 mg/kg bw/d

Reliability: (4) not assignable

03-DEC-2001 (55)

Type: Sub-acute
Species: rat Sex: male
Strain: Wistar
Route of administration: gavage
Exposure period: 5 days
Frequency of treatment: once daily
Post exposure period: 1 day
Doses: 1500 mg/kg/d
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: The test-substance caused induction of the peroxisomal

enzymes (palmitoyl CoA oxidation, bifunctional enzymes) but not of cytochrome P-450IVA1. Absolute and relative liver weights were statistically significant increased in treated animals; microsomal protein content was decreased.
Source: BASF AG Ludwigshafen
Reliability: (4) not assignable
03-DEC-2001 (121)

5.5 Genetic Toxicity 'in Vitro'

Type: Bacillus subtilis recombination assay
System of testing: Bacillus subtilis M 45 (rec-), H 17 (rec +)
Concentration: up to 10 ul/disk
Metabolic activation: no data
Result: positive

Method: other: according to Hirano, K. et al.: Mutation Research 97, 339-347
Year: 1982
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Source: BASF AG Ludwigshafen
04-DEC-2001 (157)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100
Concentration: 0.05 - 100 ul
Metabolic activation: with
Result: negative

Method: other: according to Ames, B.N. et al.: Mutation Research 31, 347-364
Year: 1975
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: S-9
Source: BASF AG Ludwigshafen

05-JAN-1994 (119)

Type: Escherichia coli reverse mutation assay
System of testing: Escherichia coli WP 2 uvr A (trp-)
Concentration: 0.125 - 1.0 mg/plate
Metabolic activation: no data
Result: negative

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Source: BASF AG Ludwigshafen
05-JAN-1994 (157)

Type: Ames test
System of testing: Salmonella typhimurium TA100
Concentration: no data
Metabolic activation: with and without
Result: negative

Method: other: according to Ames, B.N. et al.: Mutation Reserach 31, 347
Year: 1975
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: S-9
Source: BASF AG Ludwigshafen
05-JAN-1994 (36)

Type: Bacillus subtilis recombination assay
System of testing: Bacillus Subtilis H 17 (rec+), M 45 (rec-)
Concentration: up to 17 ug/disk
Metabolic activation: no data
Result: negative

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Source: BASF AG Ludwigshafen
05-JAN-1994 (108)

Type: Ames test
System of testing: Salmonella typhimurium TA92,TA94,TA100,TA1535,TA1537
Concentration: 0.0625, 0.125, 0.25 mg/ml
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: S-9
Result taken from schedule
The above remark from the BASF IUCLID is unclear.
Source: BASF AG Ludwigshafen
Flag: Critical study for SIDS endpoint
23-JAN-2002 (73)

Type: Cytogenetic assay
System of testing: Chinese hamster fibroblast cell line
Concentration: 0.0625, 0.125, 0.25 mg/ml
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: S-9
Source: BASF AG Ludwigshafen
05-JAN-1994 (73) (74)

Type: Ames test
System of testing: Salmonella thyphimurium TA98,TA100,TA1535,TA1537,TA1538
Concentration: 0.01 - 3 ul/2 ml
Metabolic activation: with and without
Result: negative

Method: other: according to Rannung, U. et al.: Chem.-biol. Interact. 12, 251
Year: 1976
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: S-9
Source: BASF AG Ludwigshafen
Flag: Critical study for SIDS endpoint
04-DEC-2001 (34) (35) (94) (95)

Type: other: NBP-test (see remark)
Result: negative

Method: other: according to Preussmann, R. et al.: Arzneimittel-Forsch. - Drug Res. 19, 1059
Year: 1969
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Testsystem: Test for alkylating activities (NBP-Test)
Source: BASF AG Ludwigshafen
05-JAN-1994 (34) (35) (95)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: other: Swiss CD-1 mice (SPF)
Route of admin.: gavage
Exposure period: 24 and 48 hours
Doses: two treatment groups of 1500 mg/kg bw; one treatment group of 1000mg/kg bw; one treatment group of 500 mg/kg bw; one vehicle-control group and one positive-control group receiving 50 mg cyclophosphamide/kg bw
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 2001
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Animals
young adult (6 to 8 weeks old) Swiss CD-1 mice (SPF) were acquired from Charles River Labs, Sulzfeld, Germany. Females were confirmed nulliparous and non-pregnant. On arrival at the test facility all animals were examined to ensure good state of health. Identification of single animals was by unique number on tail. Animals were randomised to treatment respectively control groups, group size in all cases was 5 males and 5 females per sampling time in each group.
Husbandry
Mice were housed in an air-conditioned room with approx. 15 air changes per hour and a controlled environment with a temperature of 21 +/- 3 °C and a relative humidity of 30-70%. The room had a light-dark cycle of 12 and 12 hours. Animals were housed 5 per sex per cage in labelled polycarbonate cages containing purified sawdust bedding material (SAWI, Jelu-Werk, Rosenberg, Germany). Paper bedding was procided as nest material (BMI Helmond, The

Netherlands). Mice had free access to standard pelleted diet (Altromin, code VRF1, Lage Germany) and also free access to tap water. The acclimatisation period under laboratory conditions before start of treatment was at least 5 days.
Dose range finding study
Two dose groups, 2 M and 2 F respectively 3 M and 3 F, received single doses of linalool by gavage in order to determine a non-lethal dose for the main test. Survival and physical condition were followed for 4 days. Based on this pretest a maximal treatment dose of 1500 mg linalool/kg bw was selected.
Test procedure
5 M and 5 F mice were used in each group, there were 6 groups all in all. All mice received one single dose by gavage as per the following scheme:

Treatment	Dose (mg/kg bw)	Sampling time (h)	Group
Vehicle (maize oil)	-	24	A
Linalool	1500	24	B
Linalool	1500	48	C
Linalool	1000	24	D
Linalool	500	24	E
Cyclophosphamide	50	48	F

At sampling time, mice were killed by cervical dislocation, both femurs were removed by dissection and the ends shortened until the marrow canal became visible. The marrow was then flushed with 2 ml of foetal claf serum, the marrow cell suspension collected and centrifuged at 1000 rpm for 5 minutes. The supernatant was removed by pipette, the cell sedmient resuspended in 1 drop of foetal calf serum, taken up in a pipette and placed on a mciroscope glass slide, spread using the blood sample spreading technique, air-dried, fixed for 5 min in 100% methanol and autmatically stained in an "Ames" HEMA-tek slide Stainer (Miles, Bayer Nederland BV, The Netherlands). Slides were then embedded in MicroMount and covered with a glass coverslip. Two slides per animal were prepared and marked with both the animal and the NOTOX test number.
Analysis
All slides were randomly coded and the original identification markers covered with an adhesive label prior to sreening and scoring. Screening for regions of suitable technical quality was done at a magnification of X100, scoring in that region at X1000. Scoring was performed by counting the number of micronucleated polychromatic erythrocytes in a total of 2000 polychromatic erythrocytes. The ratio of polychromatic to normochromatic erythrocytes was determined at the same time by counting and differentiating the first 1000 erythrocytes. Micronuclei were only counted in polychromatic erythrocytes. Averages and standard deviations were calculated.

Result: Based on the results of the range-findng test, doses from 500 to 1500 mg/kg bw were selected for the micronucleus test.
Mean bodyweights of test animals, males compred with males and females with females, were not statistically different in the 6 groups.
All test data validate the test procedure.
Both for the number of micronucleated polychromatic erythrocytes per 2000 polychromatic erythrocytes and for the ratio of polychromatic to normochromatic erythrocytes, both for the male and female test groups, only the cyclophosphamide control groups showed statistically

significant, massive differences. There was no significant difference between any of the vehicle control and linalool dosages groups.
Test substance: Linalool, from F.Hoffmann-La Roche Ltd, manufactured at Teranol Ltd, Batch no. UU01052889, corresponding to specifications, purity 97.7% (GC, area-%), expiry date 10 May 2002.
For treatment linalool was dissolved in maize oil(OPG, Utrecht, The Netherlands); stock solutions were protected from light and dosed within 4 hours after preparation.
Conclusion: Linalool was not mutagenic in the micronucleus test.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
02-OCT-2001 (102)

5.7 Carcinogenicity

Species: mouse Sex: male/female
Strain: other: A/He mouse
Route of administration: i.p.
Exposure period: 8 weeks
Frequency of treatment: 3 times weekly
Post exposure period: 16 weeks
Doses: total dose = 3 g/kg bw for the high-dose group and 0.60 g/kg bw for the low-dose group
Result: negative
Control Group: other: yes, four concurrent control groups, one untreated negative control (50 m/50 f), one vehicle negative control (80 m/80 f) and two urethan-treated positive controls with different dose levels (10 mg: 20 m/20 f; 20 mg: 20 m/20 f)

Year: 1973
GLP: no

Method: Animals:
Male and female A/He mice were bought from the Institute for Cancer Research, Philadelphia, of from the US National Cancer Insitute. The 6- to 8-week old animals weighed an average of 18-20 g. They were randomly distributed among experimental and control groups. Groups of 5 were housed in plastic boxes. Commercial grade sawdust chips were used for bedding. Purina laboratory chow and water were available ad libitum. Hygienic conditions were maintained by twice-weekly changes of the animal cages and water bottles and weekly disinfection of animal quarters. The water bottles were routinely sterilised.
For tests with linalool, 4 groups of 15 animals each were used, one group each of 15 males and 15 females for the high and for the low dose.
Chemicals:
All chemicals were stored in the dark and prepared for injection in separate rooms at a distance from the animals.
Administration:
In a preliminary toxicology test, the maximally tolerated single dose (MTD) for each test substance was determined by injecting intraperitoneally serial two-fold dilutions of chemicals into groups of 5 mice. The MTD was defined as that maximum single dose that all 5 mice tolerated after receiving 6 i.p. injections over a 2-week period. For evidence of delayed toxicity, animals receiving 6 doses of

the MTD were held for another 1-2 months before experimental groups were initiated. For linalool the MTD was determined to be 125 mg/kg bw.
For the main carcinogenicity test series with food additives, including linalool, 2 dose levels were used, the MTD and a 1:5 dilution of the MTD. All injections of linalool were administered as 0.1 ml/dose of solutions in tricaprylin, with the dose adjusted to the body weight of the mice. Each chemical was injected i.p. 3 times per week for 8 weeks, totalling 24 doses.
Duration:
The experiments were terminated 24 weeks after the first injection.
Examination and statistics:
Treated and control animals were killed by cervical dislocation and dissected. The lungs were removed and fixed in Tellyesniczky's fluid. 3-4 days after fixation, the milky white nodules on the lung were counted and some were taken for histological examination. The lungs were also examined for the rpesence of other abormalities, eg inflammatory reactions and adenomatosis. Liver, kidney, spleen, thymus, intestine and salivary and endocrine glands were examined at autopsy for the presence of abnormalities. Suspicious tissues were examined as to type and catalogued with respect to incidence. Tumour incidences in treated and appropriate vehicle control animals were compared by the standard chi-square test to determine whether a compound was positive, ie producing significantly more tumours.

Result: In the linalool treatment groups of 15 animals each the following incidences of pulmonary tumours was found:
1) total dose 3 g/kg bw, males, 9 survivors, 2 with 1 tumour;
2) total dose 3 g/kg bw, females, 11 surv., 3 with 1 tumour;
3) total dose 0.6 g/kg bw, males, 11 surv., 1 with 1 tumour;
4) total dose 0.6 g/kg bw, females, 9 surv., 1 with 1 tumour.
These incidences were not statistically different from vehicle controls, P > 0.05

Test substance: as prescribed by 1.1 - 1.4: Linalool, Lot no. 1777162, from Givaudan. Test substance was stored at 4 °C.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

20-JUL-2001 (138)

Species: mouse Sex: no data
Strain: other: "101 strain (inbred)" and "stock albino (random bred)"
Route of administration: dermal
Exposure period: 33 weeks
Frequency of treatment: once weekly
Post exposure period: no data
Doses: no data
Result: ambiguous
Control Group: yes

Year: 1960
GLP: no

Method: Skin tumour promotion by essential oils:
"Experiments were started when the mice were approx. 8 weeks of age. In the case of test groups, treatment began with a

single application of 3,4-benzopyrene, 9,10-dimethyl-1,2-benzanthracene or urethane to the whole of the dorsal skin after removal of the hair by electric clippers. These substances were applied to the skin in acetone solution, the dose being sufficient to initiate skin tumour formation but, generally speaking, inadequate for complete carcinogenesis [...]. No further treatment was given for a period of three weeks, after which the test substance was applied once weekly, either in undiluted form or diluted with acetone. Control groups received either the initial treatment alone or treatment with the test substance following an initial application of acetone only."

Result: Bergamot oil, test substance 1, was less irritant than the other citrus oils in the preliminary skin tests and proved inactive as a tumour-promoting agent. In another test, linalool as a 20% solution in acetone elicited a weak tumour-promoting response.

Test substance: Test substance 1: Essential oil of bergamot, "60-70% of [which] consists of alcohols and esters. [...] Linalool is one of the principal alcohols in bergamot."
Test substance 2: Linalool in a 20% solution in acetone.

Reliability: (4) not assignable
23-JAN-2002 (120)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: 20 weeks
Doses: 1% w/w in powdered Wayne Lab Blox chow
Control Group: yes, concurrent no treatment

Year: 1989
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: 6-week-old female rats were randomised to experimental (n = 50 rats) and control groups (n = 51 rats) and fed experimental (1% test substance, linalool) and control diets for two weeks. Then, mammary tumours were induced with 7,12-dimethylbenz[a]anthracene (DMBA) in the 55-day-old experimental and control rats with a single gastric intubation of 65 mg DMBA/kg bw in 0.5 ml sesame oil. Rats were further fed control or experimental diets; the latter were extensively mixed with test compound, prepared bi-weekly and stored in sealed containers at -20 °C. Chow was replaced in the feed cups 3 times per week. Starting 5 weeks post-intubation with DMBA, the rats were weighed and palpated for mammary tumours at weekly intervals. All tumours were fixed and processed for histopathology. More than 95% of the tumours were mammary carcinomas.
The effectiveness of the various monoterpenoids, including linalool, was evaluated on the basis of the time to appearance of the first tumour (tumour latency). Comparison of latencies between treated and control groups was made by one-sided log-rank test. Total tumour numbers per treatment group were also registered and compared on the basisa of a chi-square test adjusted for total number of days at risk.

Result: The linalool treatment group had a median tumour latency of 84 days compared to 56 days for controls; at P = 0.08 this difference was not statistically significant. The linalool treatment group had 96 tumours overall (1.9 per animal) while the control group had 119 tumours (2.3 per animal); at

P > 0.1, this difference was not statistically significant.
Conclusion: The linalool group had both a lower incidence of mammary tumours and a longer median latency, however, both effects were not statistically significant.
Reliability: (2) valid with restrictions
04-DEC-2001 (125)

5.8.1 Toxicity to Fertility

Type: One generation study
Species: rat
Sex: female
Strain: other: Crl:CD(SD)BR rat
Route of administration: gavage
Exposure Period: up to 39 days, depending on time to conception
Frequency of treatment: once daily
Premating Exposure Period
female: 7 days
Duration of test: up to 46 days (7 days acclimatisation without treatment, 7 days pretreatment, up to 7 days mating period, approx. 21 days of gestation, all animals killed at 4 to 5 days post-delivery)
No. of generation studies: 1
Doses: 0 (vehicle control), 250, 500 and 1000 mg/kg bw/d
Control Group: yes, concurrent vehicle
NOAEL Parental: = 500 mg/kg bw
NOAEL F1 Offspring: = 500 mg/kg bw
NOEL parental : < 250 mg/kg bw
Result: statistically non-significant decrease in gestation index at 500 mg/kg bw/d; significant decrease in gestation index and viability of foetuses at 1000 mg/kg bw/d

Method: other: US Food and Drug Administration (1966): Guidelines for reproduction studies for safety evaluation of drugs for human use.
Year: 1989
GLP: yes
Test substance: other TS

Method: Treatment and control groups
Groups of 10 virgin female rats were administered by gavage 250, 500 or 1000 mg/kg bw/d in 1% methylcellulose, respectively only the vehicle (1% methylcellulose) in the controls. The females were mated with untreated males.
Endpoints
Clinical signs, body weight and food consumption were recorded throughout the study. Mating performance, fertility, duration of gestation and parturition, maternal behaviour, litter size, dystocia, number of implantation sites and gross lesions at necropsy were examined. F1 offspring were examined for viability, sex ration, external morphology and body weight at birth and on day 4 postpartum.
Statistics
Analysis of variance followed by Dunnett's test.
Result: Parental data
250 mg/kg bw/d: increased body weight and food consumption.
500 mg/kg bw/d: non-significant decreases in body weight, food consumption, gestation index and length of gestation.
1000 mg/kg bw/d: significant decreases in body weight, food

consumption, gestation index and length of gestation.
F1 offspring data
1000 mg/kg bw/d: significant decrease in litter size and increase in number of pups dying in the first 4 days postpartum.

Source: The Flavor and Fragrance High Production Volume Consortia (2001): Contact: Tim Adams, Ph.D., Technical Contact Person of FFHPVC, The Roberts Group, 1620 I Street N W, Suite 925, Washington, D.C. 20006

Test substance: B10: essential oil of coriander containing 72.9% of natural linalool. Additional constituents were identified as 3.9% alpha-pinene (CAS 80-56-8), 0.6% camphene (79-92-5), 0.9% myrcene (123-35-3), 4.0% p-cymene (99-87-6), 2.7% limonene (138-86-3), 3.6% gamma-terpinene (99-85-4), 4.6% camphor (76-22-2), 0.8% alpha-terpineol (98-55-5) and 1.2% geranyl acetate (105-87-3). The total of ingredients identified by gas chromatography is 95.5% (area-%), the remainder being minor peaks in the chromatogram.

Conclusion: Reproductive toxicity
No adverse effects regarding mating, fertility (as measured by the number of rats pregnant) or duration of gestation or parturition occurred in any treatment group including the high-dose at 1000 mg/kg/d.
However, clear adverse effects on reproductive performance and pup development occurred at 1000 mg/kg/d, that also resulted in significant maternal clinical signs, significant inhibition of average maternal weight gain before mating and significant increases in maternal weight gain and feed consumption during gestation.
In the absence of significant toxicity to the dams, B10 did not affect the reproductive performance or the developmental parameters of pups. The effects observed on reproduction and development are not, therefore, uniquely reprotoxic or developmentally toxic effects but general toxic effects.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
06-FEB-2002 (67)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
Strain: other: Crl:CD(SD)BR rat
Route of administration: gavage
Exposure period: up to 39 days, depending on time to conception
Frequency of treatment: once daily
Duration of test: up to 46 days (7 days acclimatisation without treatment, 7 days pretreatment, up to 7 days mating period, approx. 21 days of gestation, all animals killed at 4 to 5 days post-delivery)
Doses: 250, 500 and 1000 mg/kg bw/d in maize/corn oil
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 500 mg/kg bw
NOAEL Fetotoxicity : = 500 mg/kg bw
other: NOAEL Developmental toxicity : = 500 mg/kg bw
other: NOAEL gross Teratogenicity : = 1000 mg/kg bw

Method: other: US Food and Drug Administration (1966): Guidelines for reproduction studies for safety evaluation of drugs for human

use.
Year: 1989
GLP: yes
Test substance: other TS

Result: Toxicity to dams
No female rats from any dosage group died during the study. Dosages of B10 resulted in excess salivation, with statistically significant numbers for the middle- and high-dosage groups ($p < 0.05$, resp. $p < 0.01$) in comparison with vehicle controls. A significant ($p < 0.01$) number of rats given the high dosage (1000 mg/kg/d) also showed urine-stained abdominal fur during the premating period. One or two of this group showed ataxia and/or decreased motor activity during premating and gestation. No other clinical or necropsy observations were considered effects of the test article. Body weight gain and feed consumption were significantly ($p < 0.01$) decreased in the 1000-mg/kg/d group, but only during the premating period.
During gestation, in contrast, remarkable increases in weight gain and feed consumption occurred for every treatment group in comparison with controls. Significant ($p < 0.05$ to $p < 0.01$) increases in body weight gain occurred in the low- and high-dosage groups. Significant ($p < 0.05$ to $p < 0.01$) increases in both absolute (g/d) and relative (g/kg/d) weight gain occurred in all treatment groups. These effects remained present but decreased in magnitude during the initial lactation period up to termination of the test.
Reproductive performance
Dosages up to 1000 mg/kg/d did not adversely affect the reproductive performance of the females. There were no dose-dependent or statistically significant differences in duration of cohabitation, incidence of pregnancy or implantation averages among the four groups ($p > 0.05$). All pregnant dams delivered at least one live pup.
Foetal/pup toxicity
Negative effects were only noted in the maternal high-dose group, with foetal deaths in utero, a concomitant decrease in live litter size and a significant increase in pup morbidity and mortality during the first four or five days postpartum. However, even at the highest dose administered to dams, there were no effects on length of gestation, pup sex ratio, pup body weight or gross morphology. While at 1000 mg/kg bw/d there was significant foetal and pup mortality, there were no gross signs of teratogenicity in the pups. Specifically, the original report mentions that "No anatomical malformations or variations were revealed by external examination or necropsy of the pups in this study". Based on this evidence, 500 mg/kg bw/d was the NOEL for the offspring.
Source: The Flavor and Fragrance High Production Volume Consortia (2001): Contact: Tim Adams, Ph.D., Technical Contact Person of FFHPVC, The Roberts Group, 1620 I Street N W, Suite 925, Washington, D.C. 20006
Test substance: B10: essential oil of coriander containing 72.9% of natural linalool. Additional constituents were identified as 3.9% alpha-pinene (CAS 80-56-8), 0.6% camphene (79-92-5), 0.9% myrcene (123-35-3), 4.0% p-cymene (99-87-6), 2.7% limonene (138-86-3), 3.6% gamma-terpinene (99-85-4), 4.6% camphor (76-22-2), 0.8% alpha-terpineol (98-55-5) and 1.2% geranyl acetate (105-87-3). The total of ingredients identified by gas chromatography is 95.5% (area-%), the remainder being

minor peaks in the chromatogram.

Conclusion: Maternal toxicity
The maternal NOEL for B10 was below 250 mg/kg/d, based on clinical signs, such as salivation and altered body weight gains and feed consumption. These changes were not considered to be evidence for strong toxicity, hence the NOAEL was higher at 500 mg/kg/d.
Offspring toxicity
The NOEL for B10 was 500 mg/kg/d administered to dams. The highest-dosage (1000 mg/kg/d) group had reduced delivered litter sizes, indicating in utero deaths, and siginifcant incidences of pup mortality in the first four days postpartum.
Reproductive toxicity
No adverse effects regarding mating, fertility or duration of gestation or parturition occurred in any treatment group including the high-dose at 1000 mg/kg/d. Clear adverse effects on reproductive performance and pup development occurred at 1000 mg/kg/d, that also resulted in significant maternal clinical signs, significant inhibition of average maternal weight gain before mating and significant increases in maternal weight gain and feed consumption during gestation.
In the absence of significant toxicity to the dams, B10 did not affect the reproductive performance or the developmental parameters of pups. The effects observed on reproduction and development are not, therefore, uniquely reprotoxic or developmentally toxic effects but general toxic effects.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
08-SEP-2003 (67)

5.8.3 Toxicity to Reproduction, Other Studies

Type: other: dissection and histopathology data from 28-day subchronic study
In Vitro/in vivo: In vivo
Species: rat
Strain: other: Crl:CD/BR Sex: male/female
Route of administration: gavage
Exposure period: 28 days
Frequency of treatment: once daily
Duration of test: 28 days
Doses: 0 (vehicle only), 160, 400 and 1000 mg/kg bw/d
Control Group: yes, concurrent vehicle

Year: 1990
GLP: yes
Test substance: other TS

Result: In the dams, all dosages caused excess salivation, which was significant in the middle- (500 mg/kg bw/d) and high-dose (1000 mg/kg bw/d) groups. A significant number of high-dose dams had urine-stained fur. One or two of the high-dose group showed ataxia or decreased motor activity during treatment, which are considered toxic (pharmacological) effects of linalool. During the premating period, body weight gain and feed consumption were decreased in the high-dose group, but during gestation significant increases in absolute and relative body weight gain were seen in all three treatment groups including the low-dose group (250

mg/kg bw/d).
In all animals, both controls and from all three treatment groups, both females and males, the primary sexual organs were unremarkable gross-anatomically at dissection after 28 days.
Further, all high-dose animals were additionally examined histopathologically. In every single high-dose male the testes or the epididymides were unremarkable on microscopical examination. Similarly, in every single high-dose female the ovary or the uterus were unremarkable on microscopical examination.
Based on these results, 500 mg/kg bw/d is proposed as the maternal NOAEL while the NOEL was below 250 mg/kg bw/d.

Source: The Flavor and Fragrance High Production Volume Consortia (2001): Contact: Tim Adams, Ph.D., Technical Contact Person of FFHPVC, The Roberts Group, 1620 I Street N W, Suite 925, Washington, D.C. 20006

Test substance: B10: essential oil of coriander containing 72.9% of natural linalool. Additional constituents were identified as 3.9% alpha-pinene (CAS 80-56-8), 0.6% camphene (79-92-5), 0.9% myrcene (123-35-3), 4.0% p-cymene (99-87-6), 2.7% limonene (138-86-3), 3.6% gamma-terpinene (99-85-4), 4.6% camphor (76-22-2), 0.8% alpha-terpineol (98-55-5) and 1.2% geranyl acetate (105-87-3). The total of ingredients identified by gas chromatography is 95.5% (area-%), the remainder being minor peaks in the chromatogram.

Conclusion: Subchronic administration of doses of linalool up to 1000 mg/kg bw/d over 28 days did not lead to macroscopically or microscopically remarkable findings regarding the primary repoductive organs, ovaries and uteri respectively testes and epididymides.

Reliability: (2) valid with restrictions
Reliability judged as 2 because this was not a proper reproductive study, however, the endpoints of macroscopic and, in the case of the high-dose group, also micrioscopic examination of primary reproductive organs were examined under GLP.

Flag: Critical study for SIDS endpoint

08-SEP-2003 (130)

5.9 Specific Investigations

Endpoint:	Immunotoxicity
Type:	other: both IGM antibody plaque-forming cell (PFC) assay and host resistance (HR) assay using Listeria monocytogenes
Species:	mouse
Strain:	B6C3F1 Sex: female
Route of administration:	oral, gavage
No. of animals:	90
Vehicle:	other: 1% methylcellulose
Exposure Period:	5 day(s)
Frequency of treatment:	once daily
Doses:	375, 188, 94 and 0 mg/kg bw/d
Control Group:	other: one concurrent vehicle control group and one positive immunosuppression control group in the PFC assay
Observation Period:	10 days after challenge in the HR assay and 4 days after dosing in the PFC assay
Result:	Linalool is not an immunotoxicant.

Method: other
Year: 1993
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: Animals and keeping
Female B6C3F1 mice from Charles River Labs were obtained at 6-8 weeks of age and kept in a 2-week quarantine prior to experiments. Animals were group-housed in PP cages with hardwood bedding, Purina Rodent Chow and water were available ad libitum. There was a 12-hour light/dark cycle with fluorescent lighting, ambient temperature was 18-26 °C and relative humidity was 10-70%.
Test substances and dose determination
35 lavouring materials of food grade purity including linalool were obtained from commercial suppliers. Linalool was diluted in 1% methylcellulose, made up to test dilutions corresponding to 10 ml solution/kg bw. The high dose for the immunotoxicity test was selected based on a prior 5-day repeated dose acute toxicity test as that dose at which minimal toxicity was produced based on body weight changes or clinical observations; for linalool the high dose was set at 375 mg/kg bw/d. Lower test doses consisted of one-half and one-quarter the high dose, corresponding to 188 and 94 mg/kg bw/d.
Test groups, controls and dosing
Mice were randomised for body weight and assigned in groups of 30 mice to high-, middle- and low-dose groups, another 30-mice group served as the vehicle controls. Mice were dosed with test substance dilutions or vehicle only by gavage once daily for 5 days.
Immunotoxicity tests
1) PFC assay
10 of the treated mice in each group were used for the PFC assay. In addition, for each PFC assay, 24 hours prior to the assay 5 animals were injected ip with 80 mg cyclophosphamide/kg bw; these animals served as positive immunosuppression controls and were compared statistically with naive controls. All animals were observed twice daily during the study period for signs of toxicity. Body weights were measured at dosing initiation, on exposure day 5 and at autopsy on day 9.
For the test, all mice (vehicle controls, test substance treated, naive and positive controls) were injected with 2*10E8 sheep red blood cells (SRBC; Colorado Serum/Western Instrument Co) at the end of the 5-day exposure period. 3 days after SRBC injection, mice in the positive control group received a single ip injection of 80 mg cyclophosphamide/kg bw while the naive control group received an equeal volume of phosphate-buffered saline. 4 days after SRBC injection the mice were killed, spleen and thymus were aseptically removed and weighed and individual organ/body-weight ratios determined.
Single-cell suspensions were prepared from the spleens, cells were counted and viability assessed by trypan blue exclusion. in duplicate, 0.1 ml of spleen cell concentrates were added to 0.1 ml of a mixture of equal volumes of 80% guinea pig complement and 16% washed SRBC. This reaction mixture was filled in Cunningham PFC chambers, sealed and incubated in a humidified atmosphere at 37 °C for 1 h. The resulting immunoglobulin M anti-SRBC plaques were then counted with a plaque viewer. Production of at least 800

PFC/10E6 viable spleen cells in the vehicle and naive control groups as well as a statistically significant (P <= 0.05) depression in PFC/10E6 viable cells in the positive controls, relative to the naive group, constituted the minimum requirement for a valid test.
2) HR assay
A stock culture of L. monocytogenes (ATCC 13932) was prepared by growing the organism on the surface of Petri plates in Brain Heart Infusion broth containing 3.5% agar at 35 °C for 24 h. Listeriae were then harvested, suspended in Difco 0003-01 nutrient broth containing 15 % glycerol (v/v) as a cryoprotective agent, divided into 1-ml aliquots and stored at -70 °C. Prio to infectious challenge the frozen stock was thawed and diluted in 0.85% saline; additional dilutions were made on BHI agar for a colony count/viability determination.
20 mice per experimental and vehicle control group were used for the HR assay. Following the thrid day of dosing they received an injection in the lateral tail vein of 0.2 ml saline containing L. monocytogenes. The inoculum was titred to produce a target LD20 dose in control animals. Test animals were monitored daily for mortality for 10 days after challenge.
Statistics
Dunnett's and chi-square tests were used to evaluate mean survival time and mortality data in the HR assay. For continuous response data, two-tailed analysis of variance and post-hoc comparisons suing Dunnett's test were performed on natural-logarithmic- or logit-transformed PFC data. For the positive control group, pots-hoc comparisons with the naive control group were made using a Student's t-test. The elevel of significance was set at P <= 0.05 in all instances.

Result: In the HR assay there were no statistically significant effects on mortality or survival time caused by any of the test dosages of linalool. Vehicle controls were at 15% mortality, within the targeted range.
In the PFC assay there were no statistically significant negative effects on PFC counts, spleen or thymus weight, organ/body-weight ratios nor spleen cell viability caused by any of the test dosages of linalool compred to vehicle controls. The middle-dose linalool group (188 mg/kg bw/d), but not the high- or low-dose groups, showed soignificantly enhanced PFC counts. Positive, immunosuppressed controls showed significant depression of PFC counts.

Test substance: Test substances (including linalool) were of "food grade purity and were obtained from commercial flavour supply companies".

Conclusion: Based on two tests there is no indication that linalool in dosages up to LOAEL over 5 days has any immunotoxic respectively immunosuppressive effects on mice. On the contrary, in the PFC assay the middle-dose (188 mg/kg bw/d) showed statistically significantly enhanced PFC response, meaning improved immune competence.

Reliability: (2) valid with restrictions
reliability considered as 2, based on very detailed description of materials and methods, clear internal validity criteria, tabulated and statistically analysed results

04-DEC-2001 (55)

Endpoint: other: sedative effects on the central nervous

system
Species: rat
Strain: Wistar Sex:

Year: 2001
GLP: no data
Test substance: no data

Remark: Both studies only seen as the abstract, no doses stated.
Result: Psychopharmacological evaluation of linalool in vivo in rats showed that it has marked dose-dependent sedative effects on the central nervous system, including hypnotic, anticonvulsant and hypothermic properties. The study reports an inhibitory effect of linalool on glutamate binding in the rat cortex.
Conclusion: Linalool is a monoterpene compound reported to be a major component of essential oils in various aromatic species of plants. Several linalool-producing psecies are used in traditional medicine systems, including Aeolanthus suaveolens used as an anticonvulsant in the Brazilian Amazon. It is suggested that the reported neurochemical effect of linalool on glutamate binding in the cortex may be underlining the traditional pharmacological effect. These findings provide a rational basis for many of the traditional medical uses of linalool-producing plant species.
Reliability: (4) not assignable
08-SEP-2003 (38) (39)

Endpoint: Neurotoxicity
Species: other: insects
Result: Linalool is described as a reversible competititve inhibitor of acetylcholinesterase.

Reliability: (4) not assignable
23-JAN-2002 (127)

5.10 Exposure Experience

Type of experience: Health records from industry

Result: Exposure of production workers to linalool is low, both due to synthesis in a quasi-closed system and the low vapour pressure of the substance. Potential exposure to linalool may occur during sampling in production, during discharging of spent Pt-activated-charcoal catalyst for external recycling and during filling of transport containers and barrels.
No occupational health problems due to exposure to linalool have been recorded at the Lalden production plant.
Reliability: (2) valid with restrictions
18-JUL-2001 (145)

Type of experience: Human - Exposure through Food

Method: The highest daily dietary intake of linalool was estimated based on data published by the FAO/WHO Joint Expert Committee on Food Additives (JECFA) and using the following

equation for the daily Per Capita Intake (PCI * 10): (PCI * 10) = (annual poundage [food intake] in kg)/((population/10) * 365 days * 0.6); where it is assumed that only 10% of the population consumes the flavouring substance and that only 60% of production is reported. The NOEL for linalool was based on a NOEL published for linalyl cinnamate by Hagan et al. [1967: Food flavouring compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet Toxicol 5: 141-157] because direct data for linalool by Oser [1967, unpublished; cited in JECFA (1967): Toxicological Evaluation of some flavouring substances an non-nutritive sweetening agents. JECFA 11th Report. FAO Nutrition Meetings Reports Series no. 44. WHO Technical Report Series no. 383] of only 50 mg/kg bw/day were lower by one dimension and were the highest dose tested, indicating that the true NOEL would be higher. The Margin of Safety was determined by dividing the NOEL through the estimated highest daily dietary intake.

Result: The highest daily dietary intake of linalool in Europe or the USA through food and beverages was estimated at 0.0438 mg/kg bw/day. The NOEL for linalool was set at 500 mg/kg bw/day. The Margin of Safety between NOEL and daily intake was calculated to be 11,407.

Conclusion: A very high Margin of Safety exists between highest estimated daily dietary intake and NOEL.

Reliability: (4) not assignable

18-JUL-2001 (106)

Type of experience: Human - Exposure through Food

Remark: Based on data from the International Organisation of the Flavour Industry for Europe and the US National Academy of Sciences, the production volumes of 23 terpene alcohols in Europe is given as 58 t/a in Europe and 15 t/a in the USA; linalool, linalyl acetate, alpha-terpineol and terpinyl acetate are stated to account for approx. 96% of that respective volume in Europe and the USA. Considering the industry information that approx. 12,000 t/a of linalool are produced by chemosynthesis or from natural sources, this would mean that only a very much minor part of linalool would be used as a food or beverage flavour additive.

Result: Daily per capita intake of linalool from its use and that of 8 of its esters (subsequent to hydrolysis in the gut) as flavouring agents was estimated at 4.3 mg/person (corresponding to 72 ug/kg bw/day) in Europe and 1.3 mg/person (corresponding to 21 ug/kg bw/day) in the USA

Reliability: (4) not assignable

23-JAN-2002 (78)

Type of experience: Human - Exposure through Food

Result: Because of ready hydrolysis of linalool esters, in particular due to hepatic esterases, an estimated 28 ug linalool/kg bw/day formed through hydrolysis, would form an important part of the whole daily intake estimated at 72 ug/kg bw/day.

Reliability: (4) not assignable
23-JAN-2002 (78)

Type of experience: other: Sedative effects and sensory evaluation in man

Method: The sedative properties and sensory evaluation of R-, S- and RS-linalools were investigated in 20- to 26-year-old adults. The subjects were exposed to diluted oils at concentrations previously characterised by several judges as "feeling well"; however, no measured doses or concentrations are available. Sedative properties were evaluated based on performance in an Uchida-Kraeplin mental work test, in a physical exercise test and in a listening/environmental sound test and based on conventional forehead surface electroencephalography. Before and after the above-mentioned tests the subjects were asked to rate sensory properties according to the following opposite impression items on an 11-point scale from -5 to +5: fresh-stale, soothing-active, airy-heavy, plain-rich, natural-unnatural, elegant-unrefined, soft-strong, pleasant-unpleasant, warm-cool, comfortable-uncomfortable, woodsy-unwoodsy, floral-peppery and lively-dull. Scores were statistically analysed.

Result: Inhalation of RS-linalool during hearing environmental sounds caused "favourable" impressions with 6/13 impressions significantly more positive. The sensory evaluation spectrum of R-linalool was quite similar to thr RS-from, while S-linalool produced less favourable impressions and in particular had more ratings on the negative side. No details are given as to performace in the work tests. In the EEG studies, 3/5 cases for R-linalool and 4/6 cases for RS-linalool showed a tendency of decreasing beta waves (=sedation), while an opposing tendency of increase was noted in 3/5 cases for S-linalool.

Test substance: R-Linalool was isolated from essential oil of lavender through flash chromatography on silica gel; S-Linalool was isolated from essential oil of coriander through flash chromatography on silica gel; the identity of the R- and S-forms was confirmed by co-GLC analysis with authentic R- and S-standards and by specific rotation. Commercial RS-linalool was repurified by the same method and shown to consist of 50.9% R- and 49.1% S-linalool.

Conclusion: RS-linalool was interpreted to elicit a favourable impression after hearing environmental sound , accompanied by a decrease in beta waves, due to the R-linalool component, while the S-form tended to produce unfavourable impressions along with an increase in beta waves.

Reliability: (4) not assignable
08-SEP-2003 (143)

Type of experience: other: Sedative effects in animals

Remark: See Chapter 5.1.2, Acute Inhalation Toxicity, for details of the study.

Result: Motor activity decreased progressively in both young (6- to

8-week-old) and adult (6-month-old) mice after inhalation of
both essential oil of lavender, linalool and linalyl acetate
after 30, 60 and 90 min of exposure.
Reliability: (2) valid with restrictions
23-JAN-2002 (19)

Type of experience: other: Human odour threshold

Method: Six terpene test compounds commonly found indoors including linalool were dissolved in mineral oil serial dilutions of 1/3 each, ie, 100%, 33%, 11%, 3.7% etc, all percentages as %
v/v. Stimuli were presented to the test subjects from "squeeze bottles". Quantification of the vapour-phase concentration was achieved via direct gas chromatography with flame ionisation detector (GC/FID) of the headspace, using the saturated vapour concentration at room temperature
(approx. 23 °C) of each compound as a reference.
In order to detect odour thresholds, nasal pungency, nasal localisation and eye irritation, 4 anosmic subjects (2 m, 2 f, age range 23-53 years) and 4 normosmic subjects (2 m, 2 f, age range 37-58) participated. Anosmics provided nasal pungency thresholds and normosmics provided odour thresholds. All subjects provided nasal localisation and eye
irritation thresholds. Each type of threshold was measured 8
times (hals with each nostril or eye) per subject-stimulus combination. Typically, each subject participated in a total
of 10-14 sessions held on different days. Each sessions lasted between 1 nad 3 hours. Stimuli were presented via a forced-choice procedure (against the blank mineral oil) with
ascending concentrations over trials. Five correct choices in a row constituted the criterion for threshold.
Result: The odour threshold for linalool in normosmics was ca. 1 ppm
(no exact data given, only graph with log ppm). In anosmics the pungency threshold (nasal irritation) was ca. 180 ppm. However, in 31% of instances linalool failed to produce a pungency threshold.
Reliability: (4) not assignable
23-JAN-2002 (26)

Type of experience: other: Human odour threshold

Result: Odour detection threshold from water = 0.006 ppm
Reliability: (4) not assignable
23-JAN-2002 (62)

5.11 Additional Remarks

Type: other: Acceptable Daily Intake

Remark: Current ADI, Reliability = 1.
Result: ADI (human) for total acyclic and alicyclic terpenoid alcohols in food products (food and beverages) = 0-0.5 mg/kg

bw
Source: JECFA (Joint FAO/WHO Expert Committe on Food Additives), 51st Meeting (1999): Safety evaluation of certain food additives. Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances; first draft prepared by Dr Antonia Mattia. WHO Food Additives Series Number 42. online at Inchem: http://www.inchem.org/documents/jecfa/jecmono/v042je17.htm
Reliability: (1) valid without restriction

23-JAN-2002 (77)

Type: other: Acceptable Daily Intake

Remark: This is the former ADI, which was changed in 1999 by JECFA to 0-0.5 mg/kg/d for total perpenoid alcohols, therefore reliability = 3.
Result: ADI (human) for food products (food and beverages) = 0-0.25 mg/kg bw
Reliability: (3) invalid

23-JAN-2002 (48) (79) (156)

Type: other: Flavour threshold/detection limit

Result: The flavour threshold for linalool (in wine) is cited as 100 ug/l.
Reliability: (4) not assignable

23-JAN-2002 (101)

Type: Biochemical or cellular interactions

Remark: Linalool was without any effect on platelet aggregation in vitro.
Source: BASF AG Ludwigshafen
Test substance: Linalool
Reliability: (4) not assignable

23-JAN-2002 (140)

Type: Biochemical or cellular interactions

Remark: After 150 mg/kg administered i.p. to rats for 3 consecutive days an increase in liver p-nitrobenzoic acid nitro reductase was observed.
Source: BASF AG Ludwigshafen
Test substance: Linalool

Reliability: (4) not assignable

23-JAN-2002 (112)

Type: Cytotoxicity

Remark: Cytotoxic action to Chang, Hela and KB cells
Source: BASF AG Ludwigshafen
Test substance: Linalool
Reliability: (4) not assignable

23-JAN-2002 (107) (140)

Type: other

Remark: Repeated application on sheep skin caused signs comparable to acanthosis.
Source: BASF AG Ludwigshafen
Test substance: Linalool
Reliability: (4) not assignable

23-JAN-2002 (129)

Type: other

Remark: Tobacco ingredients like Linalool might burn down to isoprene and form polycyclic aromatics through the process of smoking.
Source: BASF AG Ludwigshafen
Test substance: Tobacco ingredients, linalool
Reliability: (4) not assignable

23-JAN-2002 (56)

6.1 Analytical Methods

Method: Gas-chromatographic method available
Test substance: Linalool

Reliability: (2) valid with restrictions
04-DEC-2001 (145)

6.2 Detection and Identification

7.1 Function

7.2 Effects on Organisms to be Controlled

Common Name: Grain weevil
Scientific Name: Tribolium castaneum
End Point: other: mortality, LC50
Contact time: 5 hour(s)
Value: = 25000 - ppm

Method: FAO contact method: 0.5-ml-aliquots of serial dilutions using 2% ethanol as an solution aid were pipetted onto 5.5-cm-diameter filter papers and the ethanol was lallowed to evaporate for approx. 1 min. Then, batches of 20 beetles each were transferred onto the papers, confined in Petri plates sealed on top, and placed in an incubator at 28 °C. Mortality was determined after 5 hours by the inability of single insects to satnd up or walk after being toppled by a gentle push with a forceps. Tests were performed in duplicate and also with duplicate controls (ethanol in water only). LC50 concentrations were determined graphically using log-probit paper.
Remark: Test year: 1988
GLP: no data
Result: Linalool proved to be an insecticide with an LC50 of 2.5 * 10E+4 ppm (concentration of the test solution pipetted onto paper disc). In a comparison with gossypol, citral, bornyl acetate and cineole, the relative potency of linalool was a medium-strength insecticide, its LC50 being between citral and bornyl acetate.
From the test it was evident that beetles became paralysed prior to death.
Test substance: Linalool, purity 99%, from Aldrich, England.
Reliability: (4) not assignable
22-JAN-2002 (126)

Common Name: various stored-food pests
Scientific Name: Coleoptera
End Point: other: effective concentration in insect pest control
Value: ca. 2500 - 7500 ppm

Result: Linalool, as dried plant parts or constituent of essential oils, proved effective against major stored-food-product insect pests and for other applications, eg clothes storage. Specifically against the Confused Flour Beetle (Tribolium confusum; Coleoptera, Tenebrionidae), linalool showed repellent action, contact toxicity and fumigant toxicity; in comparison with zimtaldehyde, a rather strong insect toxicant, all of these effects were reported to be moderate. At concentrations of 5-15 ul/l of air, corresponding to approx. 2,500-7,500 ppm by volume, among other substances, essential oils of basil and lavender as well as pure linalool proved to be highly active as a fumigant against the following stored-cereal pests: Rhyzopertha dominica (Coleoptera, Bostrichidae; Lesser Grain Borer), Oryzaephilus surinamensis (Col., Cucujidae; Saw-toothed Grain Beetle), Sitophilus oryzae (Col., Curculionidae; Rice Weevil) and Tribolium castaneum (Col., Tenebrionidae; Rust-red Flour Beetle).
In Rwanda, farmers traditionally add dried leaves of the

basil Ocimum canum to stored dried edible beans for protection against insect damage. Linalool is a major component of O. Canum fresh extract and essential oil. Linalool proved active, ie toxic, against the following important insect stored-food pests in experiments: Zabrotes subfasciatus (Col. Bruchidae; Mexican Bean Weevil), Acanthoscelides obtectus (Col., Bruchidae; Bean Weevil), Rhyzopertha dominica and Sitophilus oryzae.

Reliability: (4) not assignable
22-JAN-2002 (109) (131) (154)

7.3 Organisms to be Protected

7.4 User

7.5 Resistance

8.1 Methods Handling and Storing

Safe Handling:	generally processing in closed systems, if possible under inert gas; when direct contact is possible, during filling of transport containers, manual extraction of spent catalyst or maintenance, personal protection measures
Fire/Exp. Prot.:	processing in closed systems, if possible under inert gas; avoid electrostatic charging - earth installations; local exhaust
Storage Req.:	room temperature (15 to 25 °C), in tightly closing container, protected from light and air
Container:	tightly closing, stainless steel, glass, enamel, polyethylene
Unsuitable Cont.:	aluminium
Add. Information:	test plastic containers for suitability before use

Reliability: (2) valid with restrictions
23-JAN-2002 (141)

8.2 Fire Guidance

Hazards:	combustible liquid
Prot. Equipment:	full fire-fighting equipment including pressure breather
Ext. Medium:	foam, powder, carbon dioxide, water mist
Unsuit. Ex. Med.:	water jet (splash hazard)
Add. Information:	use water spray for cooling containers at risk only
Products arising:	CO, CO2

04-DEC-2001 (141)

8.3 Emergency Measures

Type: injury to persons (skin)

Remark: immediately remove contaminated clothes, wash skin with water and soap only, do not use solvents, if symptoms persist call physician; wash contaminated clothes before re-use
04-DEC-2001 (141)

Type: injury to persons (eye)

Remark: rinse with drinking water for at least 10 minutes, opening eyelids forcibly; consult physician
04-DEC-2001 (141)

Type: injury to persons (inhalation)

Remark: immediately bring affected persons to fresh air and consult physician
04-DEC-2001 (141)

Type: injury to persons (oral)

Remark: immediately call or refer to physician
23-JAN-2002 (141)

Type: other: note for physician: symptomatic treatment

04-DEC-2001 (141)

Type: accidental spillage

Remark: collect spilled material with universal adsorbent and hand over to waste removal service for professional disposal in accordance with regulations

04-DEC-2001 (141)

8.4 Possib. of Rendering Subst. Harmless

Domain: Industry/skilled trades
Process: Destruction
Type of destruction: other: Incineration in approved installation with flue gas treatment

23-JAN-2002 (141)

8.5 Waste Management

Memo: Possibility of destruction: incineration

04-DEC-2001 (141)

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material

Memo: do not use aluminium containers; test plastics before use

04-DEC-2001 (141)

(1) Acros Organics, Belgium: Safety Data Sheet, revision #1, 08.02.2000

(2) Bagley DM, Gardner JR, Holland G, Lewis RW, Regnier J-F, Stringer DA, Walker AP (1996): Skin irritation: reference chemicals data bank. Toxicol in vitro 10: 1-6.

(3) Baraldi R, Rapparini F, Latella A, Ciccioli P (1999): Volatile organic compound emissions from flowers of the most occurring and economically important species of fruit trees. Phys Chem Earth B: Hydrol Oceans Atmosphere 24(6): 729-732 (seen as abstract only).

(4) Bartholome E, Biekert E, Hellmann H, Ley H, Weigert WM, Weise E (1981): Ullmanns Encyklopädie der technischen Chemie, 4. Aufl, Bd. 20, pp. 211-212.

(5) BASF AG (1991): AIDA-Grunddatensatz Linalool, CAS 78-70-6. 15.10.1991.

(6) BASF AG, Analytisches Labor; unveroeffentlichte Untersuchung (J.Nr.106288/14 vom 02.05.1989)

(7) BASF AG, Analytisches Labor; unveroeffentlichte Untersuchung (J.Nr.130569/01 vom 18.07.1988)

(8) BASF AG, Depart. of Toxicology; unpublished data (88/601), 11.10.88

(9) BASF AG, Depart. of Toxicology; unpublished data (88/601), 30.03.89

(10) BASF AG, Labor Oekologie; unveroeffentlichte Untersuchung (1982)

(11) BASF AG, Labor Oekologie; unveroeffentlichte Untersuchung, (0904/88)

(12) BASF AG, Sicherheitsdatenblatt Linalool (17.08.1993)

(13) BASF AG, unpublished test, report dated June 7, 1977.

(14) BASF Technical Data Sheet Linalool, May 1999

(15) Basketter DA, Gerberick GF, Kimber I (2001): Measurement of allergenic potential using the local lymph node assay. Trends Pharmacol Sci 22(6): 264-265.

(16) Benoit-Vical F, Valentin A, Mallié M, Bastide J-M, Bessière J-M (1999): In vitro antimalarial activity and cytotoxicity of Cochlospermum tinctorium and C. planchonii leaf extracts and essential oils. Planta Med 65: 378-381.

(17) BIBRA Toxicity Profile: Linalool; 2nd ed. 1995. TNO/BIBRA International Ltd, Carshalton, Surrey SM5 4DS, United Kingdom

(18) Breheret S, Talou T, Rapior S, Bessière (1997): Monoterpenes in the aromas of fresh wild mushrooms (Basidiomycetes). J Agric Food Chem 45(3): 831-836.

(19) Buchbauer G, Jirovetz L, Jäger W, Dietrich H, Plank C, Karamat E (1991): Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. Z Naturforsch 46c: 1067-1072.

(20) Burdock GA, ed (1994): Fenaroli's handbook of flavor ingredients; 3rd ed., vol. 2. CRC Press, Boca Raton, FL

(21) Bächtold H (1977): Internal Communication no. 7301, F. Hoffmann-La Roche Ltd.

(22) Calame R, Ronchi W (1989): Linalool, activated sludge respiration inhibition test. Givaudan-Roure SA, Dept. TSE, report no. 89-001, May 18th, 1989.

(23) Ceschel GC, Maffei P, Moretti MDL, Demontis S, Peana AT (2000): In vitro permeation through procine buccal mucosa of Salvia desoleana Atzei & Picci essential oil from topical formulations. Int J Pharm 195: 171-177.

(24) Chadha A, Madhava Madyastha K (1984): Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. Xenobiotica 14(5): 365-374.

(25) Chung B (2000): Natural plant extracts; export market opportunities in the USA. Australian Rural Industries Research & Development Corporation, RIRDC publication no. 00/51.

(26) Cometto-Muñiz JE, Cain W, Abraham MH, Kumarsingh r (1998): Sensory properties of selected terpenes: thresholds for dodr, nasal pungency, nasal localisation and eye irritation. Ann NY Acad Sci 55: 648-651.

(27) Cosmetics and Toiletries 94(8): 41 (1979); cited in RTECS Database Online

(28) CTFA Dictionary

(29) de Groot AC (1987): Contact allergy to cosmetics: causative agents. Contact Dermatitis 17: 26-34.

(30) de Groot AC, Bruynzeel DP, Bos JD, van der Meeren HLM, van Joost T, Jagtman BA, Weyland JW (1988): The allergens in cosmetics. Arch Dermatol 124: 1525-1529.

(31) de Groot AC, Liem DH (1983): Facial psoriasis caused by contact allergy to linalool and hydroxycitronellal in after-shave. Contact Dermatitis 9: 230-232.

(32) Demyttenaere JCR, Schamp N (1997): Biotransformation of terpenes by fungi; dissertational abstract. Faculteit van de Landbouwkundige en Toegepaste Biologische Wetenschappen, University of Gent, Belgium.

(33) Di Francesco AM, Chiu PC, Cha DK, Allen HE, Standley LJ, Salvito D (2001): Fate of fragrance materials in sludge-amended soils. Poster, 11th Annual Meeting of SETAC Europe, Madrid, May 6-10, 2001.

(34) Eder E. et al.: Biochem.Pharmacol. 29, 993-998, (1980)

(35) Eder E. et al.: Chem.-Biol. Interactions, 38, 303-315 (1982)

(36) Eder E. et al.: Xenobiotica 12, 831-848, (1982)

(37) EINECS

(38) Elisabetsky E, Brum LF, Souza DO (1999): Anticonvulsant properties of linalool in glutamate-related seizure models. Phytomedicine 6: 107-113.

(39) Elisabetsky E, Marschner J, Souza DO (1995): Effects of linalool on glutamatergic system in the rat cerebral cortex. Neurochem Res 20: 461-465.

(40) EPA Chemical Fact Sheet no. 77, Linalool, Oct 1, 1985

(41) Espinoza Díaz MA, Guetachew T, Landy P, Jose J, Voilley A (1999): Experimental and estimated vapour pressures of aroma compounds. Fluid Phase Equilibria 157: 257-270.

(42) European Collaborative Action: Indoor air quality. EU Joint Research Centre: Annual Report of the Environment Institute 1995.

(43) Evans BK, James KC, Luscombe DK (1978): Quantitative structure-activity relationshsips and carminative activity. J Pharm Sci 67: 277-278; cited in Yalkowsky SH, Dannenfelser R-M (2000): Aquasol Database, PC version, 6th ed (University of Arizona, Tucson, AZ 85721)

(44) F. Hoffmann-La Roche Ltd, internal physical properties database

(45) F. Hoffmann-La Roche Ltd, internal Physical Properties Database

(47) F.Hoffmann-La Roche Ltd, Basle, Safety laboratory (1994): Test results no. BS-5734

(48) FAO (1967): Nutrition Meetings Report Series No. 44A WHO/Food Add./68.33. online at Inchem: http://www.inchem.org/documents/jecfa/jecmono/v44aje23.htm

(49) fish-water partition coefficient = 46.7, which equals a log value of 1.669

(50) Fluka Chemie AG, CH-9471 Buchs: Safety Data Sheet (+/-)-Linalool

(51) Fogleman R.W.: Report to RIFM, (1970) cited in: Opdyke D.L.J.: Food Cosmet.Toxicol. 13, 827-832, (1975)

(52) Food Cosm Toxicol 14: 673 (1976); cited in RTECS Database Online

(53) Fuij T. et al.: Yukagaku 21, 904, (1972) cited in: Opdyke D.L.J.: Food Cosmet.Toxicol. 13, 827-832, (1975)

(54) Fulton A (2000): Food safety of three species of native mint. Rural Industries Research & Development Corporation. RIRDC publication no. 00/38.

(55) Gaworski CL, Vollmuth TA, Dozier MM, Heck JD, Dunn LT, Ratajczak HV, Thomas PR (1994): An immunotoxicity assessment of food flavouring ingredients. Food Chem Toxicol 32(5): 409-415

(56) Gil-Av E. and Shabatai J.: Nature 197, 1065-1066, (1963)

(57) Givaudan Roure Ltd, Market estimate, 2001

(58) Grade R, CIBA-GEIGY Ecotoxicology (1991): Report no. 918163 on the test for ready biodegradability in the Closed Bottle test of linalool. Test sponsored by F. Hoffmann-La Roche Ltd, Dr L Schnurrenberger.

(59) Grade R, CIBA-GEIGY Ecotoxicology (1991): Report no. 918164 on the test for inhibitory concentration on aerobic bacteria of linalool. Test sponsored by F. Hoffmann-La Roche Ltd, Dr L Schnurrenberger.

(60) Greif N.: American Perfumer and Cosmetics 82, 54-57, (1967)

(61) Grosjean E, Grosjean D (1997): Rate constants for the gas-phase reaction of ozone with unsaturated oxygenates. Int J Chem Kinetics 30: 21-29.

(62) Guadagni et al (1996): J Sci Fd Agric 17: 142-144; cited in ECDIN Database online, http://ecdin.etomep.net/cgibin_ecd/

(63) Harder J, Probian C (1995): Microbiol degradation of monoterpenes in the absence of molecular oxygen. Appl Envir Microbiol 61(11): 3804-3808.

(64) Hener U, Braunsdorf R, Kreis P, Dietrich A, Maas B, Euler E, Schlag B, Mosandl A (1992): Chiral compounds of essential oils. X: The role of linalool in the origin evaluation of essential oils. Chem Mikrobiol Technol Lebensm 14: 129-133.

(65) Hink W.F. et al.: J.Med.Entomology 25, 1-4, (1988)

(66) Hjorth N.: Eczematous Allergy to Balsams, Copenhagen, (1961)

(67) Hoberman AM, Christian MS (1989): Reproductive and developmental toxicity screening test of B10 administered orally via gavage to Crl:CD(SD)BR female rats. Argus Research Laboratories Inc, Horsham PA 19044, Protocol 412-005, April 12, 1989. Test commissioned by Lorillard Inc, Greensboro NC 27420, study monitors Dr TA Vollmuth, Dr JD Heck.

(68) http://www.umweltbundesamt.de/wgs/wgs-index.htm

(69) Hutchins SR, Tomson MB, Ward CH (1983): Trace organic contamination of ground water from a rapid infiltration site: a laboratory-field coordinated study. Envir Toxicol Chem 2: 195-216 (1983).

(70) Hylemon PB, Harder J (1999): Biotransformation of monoterpenes, bile acids and other isoprenoids in anaerobic ecosystems. FEMS Microbiol Rev 22: 475-488.

(71) Ikawa M, Mosley S, Barbero B (1992): Inhibitory effects of terpene alcohols and aldehydes on the growth of green alga

Chlorella pyrenoidosa. J Chem Ecol 18(10): 1755-1760.

(72) Ikeda Y, Matsumoto K, Kunihiro K, Uekama K (1982): Inclusion complexation of essential oils with alpha- and beta-caclodextrins. Yakugaku Zasshi (Tokyo) 102: 83-88; cited in Yalkowsky SH, Dannenfelser R-M (2000): Aquasol Database, PC version, 6th ed (University of Arizona, Tucson, AZ 85721)

(73) Ishidate M. et al.: Fd.Chem.Toxic. 22, 623-636, (1984)

(74) Ishidate M.: Chromosomal Aberration Test in vitro, Tokyo, (1983)

(75) IUCLID 4.0

(76) Izvestiya na Instituta po Fiziologiya, Bulgarske Akedemiya na Naukite 15: 149 (1973); cited in RTECS Database Online

(77) JECFA (Joint FAO/WHO Expert Committe on Food Additives), 23rd Meeting

(78) JECFA (Joint FAO/WHO Expert Committe on Food Additives), 51st Meeting (1999): Safety evaluation of certain food additives. Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances; first draft prepared by Dr Antonia Mattia. WHO Food Additives Series Number 42. online at Inchem: http://www.inchem.org/documents/jecfa/jecmono/v042je17.htm

(79) JECFA Evaluation (1979): Linalool. TRS 648-JECFA 23/25. online at Inchem: http://www.inchem.org/documents/jecfa/jeceval/jec_142.htm

(80) Jenner PM, Hagan EC, Taylor JM, Cook EL, Fitzhugh OG (1964): Food flavourings and compounds of related structure. I. Acute oral toxicity. Food Cosmet Toxicol 2: 327-343.

(81) Jirovetz L, Jäger W, Buchbauer G, Nikiforov A, Raverdino V (1991): Investigations of animal blood samples after fragrance drug inhalation by gas chromatography/mass spectrometry with chemical ionization and selected ion monitoring. Biol Mass Spectrom 20: 801-803.

(82) Journal of Scientific and Industrial Research (New Delhi), Section C: Biological Sciences 21: 342 (1962); cited in RTECS Database Online

(83) Jüttner F (1995): Elimination of terpenoid odorous compounds by slow sand and river bank filtration of the Ruhr river, Germany. Wat Sci Tech 31(11): 211-217.

(84) Klarmann E.G.: Ann.Allergy 16, 425-434, (1985)

(85) Kligman A.M.: Report to RIFM, (1970) cited in: Opdyke D.L.J.: Food Cosmet.Toxicol. 13, 827-832, (1975)

(86) Kligman A.M.: Report to RIFM, (1972) as cited in: Opdyke D.L.J.: Food Cosmet.Toxicol. 14, 673, (1976)

(87) Knudsen JT, Tollsten L, Bergström LG (1993): Floral scents - a checklist of volatile compounds isolated by head-space

techniques. Phytochem 33(2): 253-280.

(88) Knöppel H, Schauenburg H (1989): Screening of household products for the emission of organic compounds. Envir Int 15: 413-418.

(89) Kubo I, Muroi H, Kubo A (1995): Structural functions of antimicrobial long-chain alcohols and phenols. Bioorganic Medicinal Chemistry 3(7): 873-880.

(90) Levenstein I.: Report to RIFM, (1972) as cited in: Opdyke D.L.J.: Food Cosmet.Toxicol. 14, 673, (1976)

(91) Li J, Perdue EM, Pavlostathis SG, Araujo R (1998): Physicochemical properties of selected monoterpenes. Envir Int 24(3): 353-358.

(92) Lindfors V, Laurila T, Hakola H, Steinbrecher R, Rinne J (2000): Modeling speciated terpenoid emissions from the European boreal forest. Atmosph Environ 34: 4983-4996.

(93) Lopes G.: Contribution a L' etude experimentale de phenomenes d' allergie, doctoral thesis, Bordeaux, (1955)

(94) Lutz D. et al.: Mutat.Res. 93, 305-315, (1982)

(95) Lutz D. et al.: Naunyn-Schmiedeberg's Arch. Pharmacol. 311(Suppl.), R25, (1980)

(96) Lyon WF (no date given): Pet Pest Management, Bulletin 586, Chemical Control. Ohio State University, Extension Entomology Building, Columbos OH, USA. http://www.ag.ohio.state.edu/~ohioline/b586/b586_4.html

(97) Mackay D (1996): EQC (Equilibrium Concentration Model), v.1.0. http://www.trentu.ca/envmodel/

(98) Mackay D (1999): Level III, Fugacity-based environmental equilibrium partitioning model. http://www.trentu.ca/envmodel/

(99) Madhava Madyastha K (1984): Microbial transformation of acyclic monoterpenes. Proc Indian Acad Sci (Chem Sci) 93(4): 677-686.

(100) Marhold J (1986): Prehled Prumyslove Toxikologie; Organicky Latky. Avicenum, Prague; p. 202; cited in RTECS Database Online

(101) Mateo JJ, Jiménez M (2000): Monoterpenes in grape juice and wines. J Chromat A 881: 557-567.

(102) Meerts, IATM (2001): Micronucleus test in bone marrow cells of the mouse with Linalool. NOTOX Project 328826, NOTOX Substance 112158. Test performed at NOTOX BV, 's-Hertogenbosch, The Netherlands. Test sponsored by F-Hoffmann-La Roche Ltd, Dr. J.O. Straub.

(103) Meyer F, Meyer E (no year given in source): Arzneimittelforschung 8: 516-519.

(104) Misra G, Pavlostathis SG, Perdue EM, Araujo R (1996):

Aerobic biodegradation of selected monoterpenes. Appl Microbiol Biotechnol 45: 831-838

(105) Motoyoshi K, Toyoshima Y, Sato M, Yoshimura M (1979): Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, miniature swine and man. Cosmetics & Toiletries 94: 41-48.

(106) Munro IC, Kennepohl E (2001): Comparison of estimated daily dietary per capita intakes of flavouring substances with no-observed-effect levels from animal studies. Food Chem Toxicol 39: 331-354.

(107) Nachev Ch. et al.: C.r.Acad.bulg.Sci. 20, 1081, (1967) cited in: Opdyke D.L.J.: Food Cosmet.Toxicol. 13, 827-832, (1975)

(108) Oda Y. et al.: Osaka-Fu Koshu Eisei Kenkyu Hokoku, Shokukin Eisei Hen 9, 177-181, (1978)

(109) Ojimelukwe PC, Adler C (1999): Potential of zimtaldehyde, 4-allyl-anisol, linalool, terpineol and other phytochemicals for the control of the confused flour beetle (Tribolium confusum J.d.V) (Col., Tenebrionidae). Anz Schädlingskde/J Pest Sci 72: 81-86.

(110) Opdyke DLJ, ed (1979): Monographs on fragrance raw materials. Published on behalf of the Research Institute for Fragrance Materials (RIFM) by Pergamon Press, Oxford.

(111) Oser BL (1967): unpublished report.

(112) Parke D.V. and Rahman H.: Biochem.J. 113, 12, (1969) cited in: Parke D.V. et al.: Biochem.Soc.Trans. London 2, 615-618, (1974)

(113) Parke DV, Quddusur Rahman KHM, Walker R (1974): Effect of linalool on hepatic drug-metabolizing enzymes in the rat. Biochem Soc Trans 2: 615-618.

(114) Parke DV, Quddusur Rahman KHM, Walker R (1974): The absorption, distribution and excretion of linalool in the rat. Biochem Soc Trans, London 2: 612-615.

(115) Pattnaik S, Subramanyam VR, Bapaji M, Kole CR (1997): Antibacterial and antifungal activity of aromatic constituents of essential oils. Microbios 89(358): 39-46; only seen as the online abstract at http://csa.tsinghua.edu.cn/csa/factsheets/microbiology-c.shtm.

(116) Powers KA, Beasley VR (1985): Toxicological aspects of linalool: a review. Vet Hum Toxicol 27(6): 484-486.

(117) Public information database, Biodegradation of existing chemicals; CERI (Chemicals Evaluation and Research Institute), Tokyo, Japan: http://www.cerij.or.jp/ceri_en/index_e.shtml

(118) Razdan TK, Wanchoo RK, Rain GK, Jotshi CK (1985): Thermodynamic and physical properties of some terpenoids. Parümerie Kosmetik 66(7): 444-449.

(119) Rockwell P. and Raw I.: Nutr.Cancer 1, 10-15, (1979)

(120) Roe FJC, Field WEH (1965): Chronic toxicity of essential oils and certain other products of natural origin. Food Cosmet Toxicol 3: 311-324.

(121) Roffey S.J. et al.: Fd.Chem.Toxic. 28, 403-408, (1990)

(122) Ruberto G, Baratta MT (2000): Antioxidant activity of selected essential oil components in two lipid model systems. Food Chem 69: 167-174.

(123) Rudio J (1991): Linalool synthetic, determination of ready biodegradability. Givauda-Roure SA, Dept. TSE, report no. 90-57/B, February 25th, 1991.

(124) Rudio J (1991): Linalool synthetic; determination of the partition coefficient (octanol/water). Givaudan-Roure SA, Dept. TSE, Report no. 91-57/P, April 22nd, 1991.

(125) Russin WA, Hoesly JD, Elson CE, Tanner MA, Gould MN (1989): Inhibition of rat mammary carcinogenesis by monoterpenoids. Carcinogenesis 10(11): 2161-2164.

(126) Ryan MF, Byrne O (1988): Plant-insect coevolution and inhibition of acetylcholinesterase. J Chem Ecol 14(10): 1965-1975.

(127) Ryan MR, Byrne O (1988): Plant-insect coevolution and inhibition of acetylcholinesterase. J chem Ecol 14: 1965-1975.

(128) Sapporo Igaku Zasshi 3: 73 (1952); cited in RTECS Database Online

(129) Schaaf F.: Dermatologica 123, 362, (1961) cited in: Powers K.A. and Beasley V.R.: Vet.Hum.Toxicol. 27, (1974)

(130) Serota, DG (1990): 28-day oral toxicity study in rats, compound B10. Hazleton Laboratories America Inc, Rockville, MD 20850. HLA study no. 642-460, January 26, 1990. Test commissioned by Lorillard Inc, Greensboro NC 27420.

(131) Shaaya E, Ravid U, Paster N, Juven B, Zisman U, Pissarev V (1991): Fumigant toxicity of essential oils against four major stored-product insects. J Chem Ecol 17(3): 499-504.

(132) Sharp DW (1978): The sensitisation potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9: 261-271.

(133) Shu Y, Kwok ESC, Tuazon EC, Atkinson R, Arey J (1997): Products of gas-phase reactions of linalool with OH radicals, NO3 radicals and O3. Environ Sci Technol 31: 896-904.

(134) Slooff W, Zoetemanm BCJ (1976): Toxicological aspects of some frequently detected organic compounds in drinking water. Report prepared for the Commission of the European Communities under contract nr. 111-75-1 ENV. RID Report 76-15, National Institute of Water Supply, Leidschendam, The Netherlands; cited in: Kool HJ, van Kreijl CF, Zoeteman BCJ

(1982): Toxicology assessment of organic compounds in drinking water. Crit Rev Envir Control 12(4): 307-357.

(135) Smith AM, Rigler E, Kwok ESC, Atkinson R (1996): Kinetics and products of the gas-phase reactions of 6-methyl-5-hepten-2-one and trans-cinnamaldehyde with OH and NO3 radicals and O3 at 296 +- 2 K. Envir Sci & Technol 30(5): 1781-1785.

(136) SPARC On-Line Calculator. http://ibmlc2/chem/uga.edu/sparc/

(137) Stocks BJ, Goldammer J-G, Cahoon DR, Cofer WR (1998): Fire Research in the Boreal Zone. IGAC Activities Newsletter 15: 13-14.

(138) Stoner GD, Shimkin MB, Kniazeff AJ, Weisburger JH, Weisburger EK, Gori GB (1973): Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Res 33: 3069-3085.

(139) Stull (1947): Ind Eng Chem 39: 517. cited in: Jordan TE (1954): Vapor pressure of organic compounds. Interscience Publishers, New York

(140) Subramoniam A. and Satyanarayana M.N.: J.Food Safety 9, 201-214, (1989)

(141) Substance Documentation F. Hoffmann-La Roche Ltd, Basle

(142) Suga T, Shishibori T, Bukeo M (1971): Biosynthesis of linalool in higher plants. Phytochemistry 10: 2725-2726.

(143) Sugawara Y, Hara C, Tamura K, Fujii T, Nakamura K, Masujima T, Aoki T (1998): Sedative effect on humans of inhalation of essential oil of linalool: sensory evaluation and physiological measurements using optically active linalools. Anal Chim Acta 365: 293-299.

(144) Syrres Research Corporation: EPISuite v.3.10; http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

(145) Teranol AG, Visp, internal data

(146) Teranol AG, Visp: Certificate of Analysis 482E1

(147) US National Institute for Occupational Safety and Health (NIOSH): Registry of Toxic Effects of Chemical Substances (RTECS). online access available from National Information Services Corporation NISC, Wyman Towers, 3100 St. Paul Street, Baltimore, Maryland 21218 USA

(148) US National Institute of Standards and Technology, NIST (2001): NIST Chemistry Webbook, online: http://webbook.nist.gov/

(149) US National Library of Medicine: HSDB - Hazardous Substances Data Bank online: http://www.toxnet.nlm.nih.gov/cgi-bin/sis/search

(150) US National Technical Information Service, OTS0543729, no year given; cited in RTECS Database Online

(151) Vial A, CIBA-GEIGY Ecotoxicology (1991): Report no. 918165 on the acute toxicity test of linalool on daphnia (Daphnia magna Straub 1820). Test sponsored by F. Hoffmann-La Roche Ltd, Dr L Schnurrenberger.

(152) Vial A, CIBA-GEIGY Ecotoxicology (1991): Report no. 918166 on the acute toxicity test of linalool to rainbow trout (Salmo gairdneri). Test sponsored by F. Hoffmann-La Roche Ltd, Dr L Schnurrenberger.

(153) Wardle K, Short KC (1982): Effects of isoprenoid alcohols and fatty acids on root elongation, germination and their association with stomatal activity. Biochem Physiol Pflanzen 177: 210-215.

(154) Weaver DK, Dunkel FV, Ntezurubanza L, Jackson LL, Stock DT (1991): The efficacy of linalool, a major component of freshly-milled Ocimum canum SIMS (Lamiaceae), for protection against postharvest damage by certain stored product coleoptera. J stored Prod Res 27(4): 213-220.

(155) Weinzierl R, Henn T (1991): Alternatives in insect management: biological and biorational approaches. North Central Regional Extension Publication 401. Cooperative Extension Service, University of Illinois at Urbana-Champaign.

(156) WHO Tech Rep Ser 383, 18 (1968);
cited in ECDIN Database online,
http://ecdin.etomep.net/cgibin_ecd/

(157) Yoo Y.S.: J. Osaka City Med.Cent. 34, 267-288, (1985)