

**FOREWORD**

**INTRODUCTION**

**LINALYL ACETATE**

**CAS N°: 115-95-7**

## SIDS Initial Assessment Report

For

### SIAM 14

Paris, France, 26-28 March 2002

- 1. Chemical Name:** Linalyl Acetate
- 2. CAS Number:** 115-95-7
- 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  
e-mail: 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 ?  
This substance is evaluated under the OECD HPV programme and is submitted for first discussion at SIAM 14.

**7. Review Process Prior to the SIAM:**

**8. Quality check process:**

**9. Date of Submission:** May 2002

**10. Date of last Update:**

**11. Comments:** No testing (X) Testing ( )

**SIDS INITIAL ASSESSMENT PROFILE**

<b>CAS No.</b>	115-95-7
<b>Chemical Name</b>	Linalyl acetate
<b>Structural Formula</b>	
<b>RECOMMENDATIONS</b>	
The chemical is currently of low priority for further work.	
<b>SUMMARY CONCLUSIONS OF THE SIAR</b>	
<b>Human Health</b>	
<p>Linalyl acetate is of very low acute toxicity to mammals, the acute oral LD<sub>50</sub> is &gt;13,360 mg/kg, while the inhalation LC<sub>50</sub> is &gt;2740 mg/m<sup>3</sup>. Linalyl acetate has no or a very low potential to irritate the human skin. No information on possible eye irritation is available. Based on the use of linalyl acetate in cosmetics (constituent of perfumes) it is doubted that the substance has significant sensitising properties.</p> <p>Linalyl acetate is an ester that is expected to be hydrolysed to linalool and acetic acid in the gastro-intestinal tract. The main effects of the hydrolysis product, linalool (72.9%), in a 28-day oral rat study 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 was derived for linalool (equivalent to 148 mg/kg bw/d linalyl acetate). In this study no effects on male and female gonads were found.</p> <p>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 for linalool (equivalent to 464 mg/kg bw/d linalyl acetate). The NOAEL on reproduction toxicity and developmental toxicity is 500 mg/kg bw/d (equivalent to 464 mg/kg bw/d linalyl acetate) based on the decreased litter size at birth and pup morbidity/mortality thereafter.</p> <p>Linalyl acetate does not induce gene mutations or chromosomal effects <i>in vitro</i>.</p>	
<b>Environment</b>	
<p>Linalyl acetate is a liquid with a vapour pressure of 0.61 Pa (at 25°C), a water solubility of 30 mg/L and a Log K<sub>ow</sub> of 3.9 (measured). It has a calculated half-life for photo-oxidation of 1.1 hours.</p> <p>Linalyl acetate will partition primarily to water (Mackay level III modelling). In a hydrolysis study linalyl acetate was found to disappear from the test medium within 2.4 hours at pH 4, 7 and 9 (at 50°C) (t<sub>1/2</sub> &lt; 24 hours at 20°C). Hydrolysis products are linalool and acetic acid.</p> <p>Linalyl acetate is readily biodegradable. Based on the log K<sub>ow</sub> a BCF of 412 was calculated. Linalyl acetate has potential for sorption to soil (predicted log K<sub>oc</sub> 2.9), however, in view of the rapid hydrolysis of the substance it is unlikely that significant uptake or sorption may occur.</p>	

Linalyl acetate is toxic to fish and daphnia. All values are based on measurements of the parent compound, which is expected to hydrolyse very quickly. The 96-hour LC<sub>50</sub> in fish is 11 mg/L. The 48-hour EC<sub>50</sub> for daphnia is 6.2 mg/L. In a test with algae (*Scenedesmus subspicatus*, 72-hours exposure), a reduction of biomass was seen at 1.2 mg/L and above. The 72-hour E<sub>b</sub>C<sub>50</sub> was 4.2 mg/L, the E<sub>r</sub>C<sub>50</sub> was 16 mg/L).

The EC<sub>50</sub> for the inhibition of micro-organisms is 415 mg/L (ethanol was used as dispersant).

#### **Exposure**

The market for linalyl acetate is 1000-5000 tonnes. It is used as an intermediate and can be found in consumer products as soaps, cleaning products, cosmetics (perfume), oil paint and extracts. Linalyl acetate is a food additive. Foodstuffs contain between 1.9 (soft drinks) and 13 ppm (chewing gum) linalyl acetate.

There is a potential for occupational exposure. Consumers may be exposed orally and dermally. There is potential exposure to the aquatic compartment arising from the production/formulation and consumer use of this substance.

#### **NATURE OF FURTHER WORK RECOMMENDED**

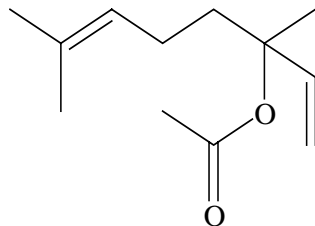
No further work recommended, because this molecule hydrolyzes rapidly.

## SIDS Initial Assessment Report

### 1 IDENTITY

#### 1.1 Identification of the Substance

CAS Number: 115-95-7  
EINECS Number 204-116-4  
Chemical Name 3,7-dimethyl-1,6-octadien-3-yl acetate  
IUPAC Name: 1,5-dimethyl-1-vinylhex-4-enyl acetate  
Molecular Formula: C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>  
Structural Formula\*:



Molecular Weight: 196.29  
Synonyms: Linalyl acetate, linalool acetate, acetic acid linalool ester

\* The compound is a chiral molecule. No data on differences between the enantiomers are available.

#### 1.2 Purity/Impurities/Additives

Purity >96%

#### 1.3 Physico-Chemical properties

Linalyl acetate (CAS no. 115-95-7) is a liquid having the following physical–chemical properties and characteristics, which have been obtained from various reference sources including company substance documentation and handbook data.

**Table 1** Summary of physico-chemical properties

Property	Value
Physical state	Liquid
Melting point	<0°C
Boiling point	220°C at 1013 hPa
Relative density	0.895 (20°C )
Vapour pressure	0.61 Pa (20°C )
Water solubility	30 mg/L (room temperature) (ref. 34)
Partition coefficient n-octanol/water (log value)	log K <sub>ow</sub> 3.9 (ref. 3)
Solubility in organic solvents	Soluble in ethanol and diethyl ether
Flash point	84-85°C

The value for water solubility could not be checked for validity due to the limited information available. However, the result of the test is supported by model calculations with the Syracuse programme (21 mg/L) and the maximum concentrations (~27 mg/L) in the flow-through fish test (ref. 13).

## 2 GENERAL INFORMATION ON EXPOSURE

### Estimated Production or Import Volume

Yearly around 1000-5000 tonnes of linalyl acetate are produced. The following information has been gathered by different authorities in the world. Within the USA the quantity produced, imported and exported is 49 tonnes/year. In Canada 3 to 39 tonnes are imported (data from 1986). In Norway the substance is registered as a component in 37 products with a total quantity of < 0.1 tonne. It is expected that the total quantity used or produced in Norway is less than 1 tonne. The Danish product register indicates that the total quantity of in industrial products was < 1 tonne.

### Uses and Exposure

The substance is used as an intermediate and found in soaps, cleaning products and cosmetics (perfume) (ref. 1). It is a component of oil paint, is used in extracts and as a substitute for petitgrain oil (information from USA). In view of the reported use, both workers and consumers can be exposed.

Linalyl acetate is a food additive. Foodstuffs contain between 1.9 (soft drinks) and 13 ppm (chewing gum) linalyl acetate (ref.1).

The Danish product register indicates that linalyl acetate is a constituent of several industrial products (Odour agents, Cleaning/washing agents, Cosmetics, Absorbents and Adsorbents, Process regulators, Welding and soldering agents, Non-agricultural pesticides and preservatives, Surface treatment). The total amount per product of the substance was 2% or less, except in odour agents (<20%)(The Danish Product Register, 26-02-2002).

The Norwegian Product register indicates that linalyl acetate is used in car polish (wax), ordinary cleaning products and detergents (for textile). The content in the products is between 0 and 1% (The Norwegian Product Register, 27-12-2001).

### 2.1 Environmental Exposure and Fate

Linalyl acetate is not very soluble in water, has a vapour pressure of 0.61 Pa and a calculated Henry's Law constant of  $1.74\text{E-}03 \text{ atm}\cdot\text{m}^3/\text{mol}$  (Epiwin vs 3.10).

For Switzerland an emission limit of  $150 \text{ mg}/\text{m}^3$  is set (mass flux  $\geq 3 \text{ kg}/\text{h}$ ) (ref. 1).

Linalyl acetate is classified as weakly hazardous for water (Germany, ref. 1).

#### 2.1.1 Sources of Potential Release to the Environment

No data on emissions to the environment are available. It can not be excluded that during the production process linalyl acetate is released to the environment. However, in an investigation in rivers of south-west Germany to establish the amount of terpenes, no linalyl acetate was found in the surface water except in one spot (ref. 14). The only conclusion that can be drawn from this report is that it cannot be excluded that linalyl acetate may reach the aquatic environment, since disposal of cosmetic products or chemical processes can lead to emissions to water.

#### 2.1.2 Photodegradation

The atmospheric oxidation potential (AOP, reaction with hydroxyl radicals) predicted from the Epiwin program (vs 3.10, AOP Program v1.90) indicates that linalyl acetate is photo-reactive with a

degradation half-life of about 1.1 hours. A summary of the Epiwin calculations is attached as Appendix A.

### 2.1.3 Stability in Water

In a hydrolysis study performed according to EEC-Directive 92/69, C7, linalyl acetate was found to disappear from the test medium at 50 °C within 2.4 hours at pH 4, 7 and 9 ( $t_{1/2} < 24$  hours) (ref. 24). The hydrolysis products were not identified, but it is expected that an ester like linalyl acetate will be hydrolysed to the corresponding acid and alcohol. For linalyl acetate hydrolysis products would be linalool (CAS 78-70-6, see also corresponding Initial Assessment Report) and acetic acid. In a HCl/citrate buffer (pH 3) linalyl acetate was rapidly hydrolysed, yielding linalool,  $\alpha$ -terpinol and geraniol (51, 22 and 8%, respectively after 25 hours) (ref. 17). Other degradation products were present at levels below 5%. 8.8% was recovered as the parent compound. The half-life of linalyl acetate at this low pH is about 7 hours.

### 2.1.4 Transport between Environmental Compartments

Information available on the transport between environmental compartments has been assessed with the EQC model. Since the substance is soluble in water to some extent, the substance is considered to be a Type I substance. For this assessment the following defaults have been chosen as worst case estimation (in view of the Epiwin, biodegradation and hydrolysis data):

$T_{1/2}$  air: 1 hours,  $t_{1/2}$  water 24 hours,  $t_{1/2}$  soil 360 hours and  $t_{1/2}$  sediment 1440 hours, and using the following physical chemical parameters: water solubility 30 mg/l, vapour pressure 0.6 Pa, Log Kow 3.9, melting point 0°C.

As information on possible emission route is not available, emissions have been considered only to water. The level III fugacity model has been considered and attached as Appendix B. Based on the results of the model it is predicted that 0.3% of the substance will end up in air, 0% in soil, 95% in water and 5% in sediment (see appendix B).

Calculations with the Epiwin model (emission to water only) gave 90% in water, 0.14% in air and 10% in sediment (see appendix A).

From the calculated log  $K_{ow}$  of 3.9 the log  $K_{oc}$  was determined to be 2.9 (EU Technical Guidance Document QSAR, chapter 4 section 4.3, average outcome of two QSARs on esters<sup>1</sup>) indicating a potential for sorption to soil. This sorption was not observed in the modelling results described in the previous paragraph. In fact no sorption is expected in view of the hydrolytic instability of linalyl acetate (see 2.1.3).

The distribution in a sewage treatment plant has been estimated using the SimpleTreat model to be 80.4% degraded, 1.4% to air, 11.4% to water, 6.8% to sludge, based on ready biodegradability, log Kow = 3.9, water solubility = 30 mg/L and vapour pressure = 0.61 Pa.

#### Conclusion:

Based on the relevant physical-chemical, linalyl acetate will partition primarily to water (Mackay level III modelling shows >95% in water). In the sewage treatment plant linalyl acetate will degrade (80%) and be present in the effluent (11%).

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<sup>1</sup>  $\text{LogKoc} = 0.47 \text{ logKow} + 1.09$

$\text{LogKoc} = 0.49 \text{ logKow} + 1.05$



### 2.1.5 Biodegradation

Linalyl acetate is considered to be readily biodegradable (ref. 7) in a MITI-test after incubation for 28 days at 20 °C. The compound turned out to degrade for more than 75%.

#### Conclusion:

Linalyl acetate is considered to be readily biodegradable.

### 2.1.6 Bioaccumulation

The calculated bioconcentration factor is 412 (EU Technical Guidance Document QSAR, chapter 4 section 4.5.2.1).

#### Conclusion:

Based on Log  $K_{ow}$  3.9 a BCF of 412 is calculated. Linalyl acetate is expected to bioaccumulate. However, in view of the rapid hydrolysis of the substance it is unlikely that significant uptake may occur.

## 2.2 Human Exposure

Linalyl acetate is not only used in closed systems (USA, Canada, Denmark). So worker exposure may be possible. Use by consumers is expected (USA, Canada, Denmark).

In the USA it is expected that about 155,491 employees at 11,043 facilities are potentially exposed to linalyl acetate. This will be the case in the manufacturing and applying of oil paints and in the manufacturing of perfume.

For the exposure due to the use in oil paints, area sampling was requested by representatives of artists (painters). 12 artists were interviewed and some of them complained about the odour of the paint and slight dermatitis. No relationship with the use of paint containing linalyl acetate was established (no area samples were taken). Measures to reduce the risks were advised (ref. 29 and data from USA).

Consumers using oil paint and perfume are potentially exposed to linalyl acetate (information from USA).

For occupational exposure no limit values are known.

Linalyl acetate is generally recognised as safe for human consumption (GRAS). The ADI (accepted daily intake) is 0.25 mg/day (ref. 1, 18).

#### Conclusion:

Workers may be exposed during production. But the main exposure is expected with consumers; both oral and dermal exposure may be possible.

### 3 HUMAN HEALTH HAZARDS

#### 3.1 Effects on Human Health

##### 3.1.1 Toxicokinetics, Metabolism and Distribution

Linalyl acetate is hydrolysed in gastric and pancreatic fluids with mean half-lives of 5.5 and 52.6 minutes respectively (ref. 34). As expected hydrolysis occurs more rapidly at the low pH of gastric fluids. The reaction products are linalool and acetic acid (ester hydrolysis). This is supported by the findings of the hydrolysis study (ref. 24) at pH 4, 7 and 9. Therefore it is expected that linalool is the substance that will enter the systemic circulation after oral uptake of linalyl acetate.

Linalool is probably converted to geraniol and its metabolites, 1,5-dimethyl-hexadiene-1,6-dicarboxylic acid and 7-carboxy-5-methylocto-6-enoic acid (ref. 10). The information in this publication was limited to the above mentioned. No indication of the species under investigation was provided.

##### Conclusion

Linalyl acetate will be hydrolysed to linalool and acetic acid in the gastro-intestinal tract.

##### 3.1.2 Acute Toxicity

##### Studies in Animals

###### *Oral*

The information on acute oral toxicity is limited (ref. 31). The results are presented in Table 3.1. Observed effects included depression, coma and wet posterior.

**Table 3.1** Acute oral toxicity

Species	LD <sub>50</sub> (mg/kg bw)
Rat	14550
Mouse	13360

###### *Dermal*

No data available.

###### *Inhalation*

Inhalation exposure of Swiss mice to 2.74 mg linalyl acetate/L air during 90 minutes led to reduced motor activity compared to untreated controls. The effect was more severe in mice of aged 6-8 weeks (up to 100% reduction) than in mice of 6 months (up to 81% reduction). A relationship with dose was suspected, based on the (not reported) results of a separate test with a double dose in old mice (ref. 16).

###### *Other*

No data available

### Human experience

No data available.

### Conclusion:

Linalyl acetate is of very low acute toxicity to mammals, the acute oral LD<sub>50</sub> is >13,360 mg/kg, while the inhalation LC<sub>50</sub> is >2740 mg/m<sup>3</sup>.

## **3.1.3 Irritation**

### Skin Irritation

#### *Studies in Animals*

Linalyl acetate (100%) appeared to be severely irritating to rabbit skin and moderately irritating to the skin of the guinea pig. In a test with miniature swines application of 0.05 g linalyl acetate under a patch for 48 hours, no irritation was observed (ref. 11).

#### *Studies in Humans*

Application of linalyl acetate in acetone (33%) to the back of male volunteers without known allergies during 48 hours under occlusion did not induce signs of irritation up to 120 hours after removal of the patch (ref. 11).

### Conclusion

The data available indicate that linalyl acetate has no or a very low potential to irritate the human skin. A significant species difference was reported. It has to be noted that the concentration tested in humans was lower than the concentration used in animal testing. No guideline studies are available.

### Eye Irritation

No data available.

## **3.1.4 Skin Sensitisation**

In ref. 27 linalyl acetate is identified as one of the constituents of lavender oil that may cause allergic reactions. No testing results were available for linalyl acetate, but lavender oil was positive in a human patch test in a hairdresser (ref. 28).

### Conclusion

Limited information is available. Based on the use of linalyl acetate in cosmetics (constituent of perfumes) it is doubted that the substance has significant sensitising properties. The substance is not listed by the Scientific Committee on Cosmetic and Non-food Products as a compound of concern regarding sensitisation.

### 3.1.5 Repeated Dose Toxicity

#### Studies in Animals

##### *Oral*

Since no reliable studies with linalyl acetate are available and the compound is expected to be hydrolysed to linalool in the gastro-intestinal tract, repeated dose studies on the hydrolysis product linalool are presented in this section.

CrI:CD/BR rats received 160, 400 or 1000 mg/kg bw linalool during 28 days. One male and one female of the high dose group were found dead. Total protein/albumin were increased in males at 400 mg/kg bw and in both sexes at 1000 mg/kg bw. Calcium was increased at 1000 mg/kg bw in males only. Serum glucose levels were decreased in males at 400 and 1000 mg/kg bw. Liver weight was increased dose related and significantly at 400 and 1000 mg/kg bw. Kidney weight was increased in males at 400 mg/kg bw (relative kidney weight) and in all animals at 1000 mg/kg (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 (ref. 23).

The NOAEL derived was 160 mg/kg bw based on effects in liver and kidney.

In a study in rats to establish effects of linalool on drug metabolising enzymes, increased liver weight was reported on day 64. Rats received 500 mg/kg bw linalool by gavage during 64 days. Microsomal protein was increased from day 20 onwards. Cytochrome P450 and cytochrome b5 showed biphasic response (initial depression followed by an increase).

4-Methylumbelliferone glucuronyl transferase increased to 150% by day 64. Alcohol dehydrogenase was initially depressed by 33% on day 3, then increased by 36% on day 7, before regaining normal values by day 14 and thereafter (ref. 21).

The observed effects of linalool are interpreted to represent a physiological adaptation to exposure and not toxicity in a strict sense.

##### *Inhalation*

No data available

#### Conclusion

The 28-day rat study was selected to be the key study. Based on the data present it can be concluded that effects of linalool are limited to the liver and to the kidney. A NOAEL of 160 mg/kg bw could be derived.

#### Observations in man

It is reported that repeated skin exposure to Bergamot oil (45% linalyl acetate) leads to nervous and digestive symptoms. Sensitive persons may develop photodermatitis, eczema and pigment changes (ref. 9).

### 3.1.6 Mutagenicity

#### *In vitro Studies*

An Ames test was performed with linalyl acetate in Salmonella strains TA97, TA98, TA100, TA1535 and TA102 with and without metabolic activation. Linalyl acetate was found to be not mutagenic in this assay (ref. 12).

In a chromosome aberration test with human lymphocytes linalyl acetate did not induce aberrations, both with and without S9-mix (ref. 19).

#### *In vivo Studies*

No *in vivo* data on mutagenicity with linalyl acetate were available.

#### Conclusion

Linalyl acetate does not induce gene mutations or chromosomal effects *in vitro*.

### 3.1.7 Carcinogenicity

Linalyl acetate was tested in a carcinogenicity assay in mice (A/He). Animals received 3 times per week an injection (intra peritoneal (i.p.)) with linalyl acetate at 200 or 1000 mg/kg (total exposure 8 weeks, total 24 injections). Total observation time was 24 weeks. Control animals were included in the study design. Full histopathology was performed on the lungs only. Liver, kidney, spleen, thymus, intestine and salivary and endocrine glands were investigated macroscopically. No increase in tumour bearing animals was reported (ref. 8).

In Swiss mice (ICR/Ha) dermal coapplication of linalyl acetate (3 mg/ in acetone) with benzo[a]pyrene did slightly increase the number of skin papillomas and carcinomas compared to benzo[a]pyrene controls (ref.27).

#### Conclusion

Due to the limited information and shortcomings of the studies (duration of exposure is considered to be short and the intraperitoneal route seems to be not the most suitable route of exposure for linalyl acetate), no conclusions can be drawn from these studies.

### 3.1.8 Toxicity for Reproduction

#### Studies in Animals

An essential oil of coriander containing 72.9% of natural linalool was administered to 10 female rats/treatment from day 7 before mating with untreated males until day 4 after parturition. The dosage levels were 250, 500 and 1000 mg/kg bw. No effects on female fertility became apparent. All treated females showed an increased body weight gain and food consumption during gestation compared to control animals. In the high dose group a decrease of body weight and food consumption was seen during the pre-mating period. Salivation was apparent in females at 500 and 1000 mg/kg. One or two females at the high dose group developed ataxia and/or decreased motor activity. At 1000 mg/kg bw females delivered significantly less live pups than in the other dose groups. During the lactation period pup morbidity and mortality was increased (ref. 22). The NOAEL for maternal toxicity based on clinical signs and effects on body weight and food consumption was 500 mg/kg bw (equivalent to 464 mg/kg bw linalyl acetate). The NOAEL on reproduction toxicity and developmental toxicity is 500 mg/kg bw (equivalent to 464 mg/kg bw linalyl acetate), based on the decreased litter size at birth and morbidity/mortality thereafter.

From the 28-day repeated dose toxicity study with the same essential oil of coriander (ref. 23), no remarkable effects on the primary reproductive organs in both females (ovaries and uteri) and males (testes and epididymides) were noted in any animal from any dosage group up to 1000 mg/kg bw, both macroscopically at dissection and also microscopically during histopathology of every single (10 male, 10 female) high-dose animal.

#### Observations in Humans

No data available.

#### Conclusion

Based on the available data it can be concluded that linalyl acetate has a NOAEL for reproduction/developmental toxicity of 500 mg/kg bw (equivalent to 464 mg/kg bw linalyl acetate). At 1000 mg/kg bw maternal toxicity was observed.

### **3.2 Initial Assessment for Human Health**

Linalyl acetate is of very low acute toxicity to mammals, the acute oral LD<sub>50</sub> is >13,360 mg/kg, while the inhalation LC<sub>50</sub> is >2740 mg/m<sup>3</sup>. Linalyl acetate has no or a very low potential to irritate the human skin. No information on possible eye irritation is available. Based on the use of linalyl acetate in cosmetics (constituent of perfumes) it is doubted that the substance has significant sensitising properties.

Linalyl acetate is an ester that is expected to be hydrolysed to linalool and acetic acid in the gastro-intestinal tract. The main effects of the hydrolysis product, linalool (72.9%), in a 28-day oral rat study 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 was derived for linalool (equivalent to 148 mg/kg bw/d linalyl acetate). In this study no effects on male and female gonads were found.

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 for linalool (equivalent to 464 mg/kg bw/d linalyl acetate). The NOAEL on reproduction toxicity and developmental toxicity is 500 mg/kg bw/d (equivalent to 464 mg/kg bw/d linalyl acetate) based on the decreased litter size at birth and pup morbidity/mortality thereafter.

Linalyl acetate does not induce gene mutations or chromosomal effects *in vitro*.

## 4 HAZARDS TO THE ENVIRONMENT

### 4.1 Aquatic Effects

Data are available on the acute toxicity of linalyl acetate to fish, daphnids and algae.

#### Fish and Invertebrates

In a 96-hour flow-through test with carps (*Cyprinus carpio*), fish were exposed to 10, 18, 32, 56 and 100 mg/L (nominal concentrations). Mean measured concentrations were 7.9, 12.3, 20.1, 27.3 and 27.2 mg/L. At the highest concentrations (32 mg/L and above) all fish died and a precipitate was observed. At all concentrations hypoactive swimming behaviour, loss of equilibrium and/or immobility was observed. A 96-hour LC<sub>50</sub> of 11 mg/L was derived based on measured concentrations (ref.13).

A calculation with ECOSAR yields a 96-hour LC<sub>50</sub> value of 2.86 mg/L

For *Daphnia magna* a 48-hour EC<sub>50</sub> was calculated by the reviewer with the Spearman-Kärber method. The EC<sub>50</sub> derived, based on nominal concentrations in a static test, was 15 mg/L (mean measured 6.2 mg/L). In accordance with the expectation of hydrolysis, the measured concentration after 48 hours was below the detection limit (except in the highest concentration). As the EC<sub>50</sub> for linalool is reported to be 59 mg/L (SIAR on linalool), the toxicity observed can not be attributed to the hydrolysis product only. The EC<sub>50</sub> value based on mean measured concentrations is not very reliable, since this mean concentration overestimates exposure to linalyl acetate (t<sub>1/2</sub> hydrolysis <24 hours). However, the alternative of using the nominal concentrations to derive an EC<sub>50</sub> is even less realistic (ref. 5).

A calculation with ECOSAR yields a 48-hour EC<sub>50</sub> value of 2.91 mg/L

#### Conclusions:

Linalyl acetate is moderately toxic to fish and toxic to daphnia. All values are based on measurements of the parent compound, which is expected to hydrolyse very quickly. The ECOSAR prediction provides an indication for a possible higher toxicity than found in the described tests. The 96-hour LC<sub>50</sub> in fish is 11 mg/L. The 48-hour EC<sub>50</sub> for daphnia is 6.2 mg/L (based on mean measured concentrations).

#### Algae

In a test with algae (*Scenedesmus subspicatus*, 72-hours exposure), a reduction of biomass was seen at nominal concentrations of 4.4 mg/L and above. The 72-hour E<sub>b</sub>C<sub>50</sub> was 16 mg/L and the 72-hour E<sub>r</sub>C<sub>50</sub> was 62 mg/L, both based on nominal concentrations. Analyses showed test concentrations below the limit of detection for all treatments after 72 hours, which is again expected in view of hydrolytic instability of the compound. The EC<sub>50</sub> for linalool is >1000 mg/L (SIAR linalool). Based on the considerations mentioned regarding the daphnia study (see above), the EC<sub>50</sub> were based on mean measured concentrations, E<sub>b</sub>C<sub>50</sub> 4.2 mg/L and E<sub>r</sub>C<sub>50</sub> 16 mg/L (ref.6).

The NOEC for effects on algal growth based on the area under the growth curve is <4.4 mg/L (measured concentration <1.2 mg/L) (ref. 6).

A calculation with ECOSAR yields a 96-hour EC<sub>50</sub> value of 0.244 mg/L

### Conclusions:

Based on the information available linalyl acetate is toxic to algae (72-hour EC<sub>50</sub> 4.2 mg/L). The ECOSAR prediction provides an indication for a possible higher toxicity than found in the described test.

### **Microorganisms**

In a test with activated sludge (according to OECD guideline 209) the EC<sub>50</sub> for the inhibition of micro-organisms was determined to be 415 mg/L. The substance was dissolved in ethanol, which explains that the EC<sub>50</sub> value is above water solubility of the EC<sub>50</sub> (ref. 4).

### Conclusion:

Linalyl acetate is of low toxicity towards aquatic micro-organisms.

### **Determination of PNEC aqua**

Data are available from short term tests at 3 trophic levels. Based on the lowest value (calculated for algae E<sub>b</sub>C<sub>50</sub> 4.2 mg/L) and applying an assessment factor of 100 in accordance with the OECD guidance the resultant PNEC<sub>aqua</sub> is 0.042 mg/L. The same assessment factor would be recommended using the EU TGD as no significant difference in sensitivity between species tested appears to be present.

### Conclusions:

Linalylacetate is of moderate hazard to the aquatic environment with a PNEC<sub>aqua</sub> of 0.042 mg/L.

## **4.2 Terrestrial and Sediment Effects**

No data available.

## **4.3 Other Environmental Effects**

Based on the very low log K<sub>ow</sub> of 3.9, linalyl acetate may accumulate (BCF of 412). However, in view of the rapid hydrolysis of the substance it is unlikely that significant uptake may occur.

## **4.4 Initial Assessment for the Environment**

Linalyl acetate is a liquid with a vapour pressure of 0.61 Pa (at 25°C), a water solubility of 30 mg/L and a Log K<sub>ow</sub> of 3.9 (measured). It has a calculated half-life for photo-oxidation of 1.1 hours.

Linalyl acetate will partition primarily to water (Mackay level III modelling). In a hydrolysis study linalyl acetate was found to disappear from the test medium within 2.4 hours at pH 4, 7 and 9 (at 50°C) (t<sub>1/2</sub> < 24 hours at 20°C). Hydrolysis products are linalool and acetic acid.

Linalyl acetate is readily biodegradable. Based on the log K<sub>ow</sub> a BCF of 412 was calculated. Linalyl acetate has potential for sorption to soil (predicted log K<sub>oc</sub> 2.9), however, in view of the rapid hydrolysis of the substance it is unlikely that significant uptake or sorption may occur.

Linalyl acetate is toxic to fish and daphnia. All values are based on measurements of the parent compound, which is expected to hydrolyse very quickly. The 96-hour LC<sub>50</sub> in fish is 11 mg/L. The 48-hour EC<sub>50</sub> for daphnia is 6.2 mg/L. In a test with algae (*Scenedesmus subspicatus*, 72-hours exposure), a reduction of biomass was seen at 1.2 mg/L and above. The 72-hour E<sub>b</sub>C<sub>50</sub> was 4.2 mg/L, the E<sub>r</sub>C<sub>50</sub> was 16 mg/L).



The EC<sub>50</sub> for the inhibition of micro-organisms is 415 mg/L (ethanol was used as dispersant).

## **5 RECOMMENDATIONS**

The compound is currently of low priority for further work.

Data on all SIDS endpoints are available and are in general of good quality.

**Search criteria**

Only original literature was included in this SIAR, except for internal review reports by the manufacturer of linalyl acetate (ref. 1, 2, and 18). The studies in these rather old reports are not expected to be identified as a key study in view of their age. In general good quality studies were available for all SIDS endpoints.

Key studies are studies with the highest reliability/adequacy. If several studies showed comparable reliability/adequacy, the study with the lowest LC/LD/EC<sub>50</sub> or NOEC/ NOAEL was indicated as the key study.

The following sources were investigated:

Company substance information: older test reports, safety datasheets, information about production and use, specifications etc.

Handbooks and original literature cited therein: CRC Handbook of Chemistry and Physics, Merck Index, Patty Industrial Hygiene and Toxicology, Sax & Lewis Dangerous Properties of Industrial Materials, Ullmann Enzyklopädie der technischen Chemie.

Databases: RTECS, DIMDI.

Also some calculated values are given obtained using Syracuse prediction software (Epiwin) or as indicated in the text.

In addition Medline and Toxline were searched under the CAS number 115-95-7 and the name linalyl acetate in January 2002.

**6 REFERENCES**

	<b>Author</b>	<b>Title</b>	<b>Performing laboratory / source</b>	<b>Year</b>
1	-	Linalyl acetate MSDS	Roche	1996
2	-	Internal report	Roche	1979
3	Schmiedel U.	Determination of the partition coefficient of linalylacetate in n octanol/water	RCC UmweltChemie AG	
4	Calame R, Ronchi W.	Linalyl acetate activated sludge, respiration inhibition test	Givaudan	1989
5	Grade R.	Report on the acute toxicity of linalylacetat on daphnia ( <i>Daphnia magna</i> Strauss 1820)	Ciba-Geigy Ltd.	1993
6	Grade R.	Report on the growth inhibition test of linalylacetat to green algae ( <i>Scenedesmus subspicatus</i> )	Ciba-Geigy Ltd.	1994
7	Rudio J.	Linalyl acetate synthetic determination of the ready biodegradability	Givaudan	1991
8	Stoner G., Shimkin M., Kniazeff A., et al	Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A Mice	Cancer Research 33, 3069-3085	1973
9	Gosselin R., Hodge H., Smith R., et al.	Clinical toxicology of commercial products Acute poisoning	Oil of Bergamot, 154	1981
10	FAO	Toxicological evaluation of some flavouring substances and non-nutrtive sweetening agents	FAO Nutrition Meetings Report Series No. 44A	1967
11	Motoyoshi K., Toyoshima Y, Sato M., et al.	Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man	Cosm. Toil. 94: 41-48	1979
12	Kirchner S.	Mutagenicity evaluation of Ro-8282/000 in the Ames test	Roche	1998
13	Bogers M.	96-hour acute toxicity study with linalylacetate (flow-through)	NOTOX	1998
14	Jüttner F.	Flavour compounds in weakly polluted rivers as a means to differentiate pollution sources	Wat. Sci. Tech. 25 (2): 155-164	1992

15	Weidenhamer J., Macias F., Fischer N., et al.	Just how insoluble are monoterpenes?	J. Chem. Ecology 19 (8):1799-1807	1993
16	Buchbauer G., Jirovetz L., Jäger W.	Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation	Z. Naturforsch. 46c: 1067-1072	1991
17	Clark B., Chamblee T., Iacobucci G.	Micellar-induced selectivity and rate enhancement in the acid-catalyzed cyclization and rearrangement of monoterpenes. The solvolysis of linalyl and geranyl acetates	J. Org. Chem. 54 (5):1032-1036	1989
18	Bauer D.	Occupational and environmental health hazard review: linalylacetate (Ro 02-8282)	Roche	1981
19	Bertens A.	Evaluation of the ability of linalylacetate to induce chromosome aberrations in cultured peripheral human lymphocytes	NOTOX	2000
20	Lewis RJ Sr.		Sax's Dangerous properties of industrial materials, Ninth edition: 2051.	1996
21	Parke DV	Effect of linalool on hepatic drug-metabolizing enzymes in the rat.	Biochem Soc Trans 2: 615-618.	1974
22	Hoberman A.,	Reproductive and developmental toxicity screening test of B10 administered orally via gavage to Crl:CD(SD)BR female rats	Lorillard Inc.	1989
23	Serota D.	28-day oral toxicity study in rats, compound B10.	Lorillard Inc.	1990
24	Brekelmans M.	Determination of the hydrolysis of linalyl acetate as a function of pH	F. Hoffmann-La Roche Ltd.	2001
25	Ghelardini C., et al,	Local anaesthetic activity of the essential oil of <i>Lavandula angustifolia</i>		
26	Ceschel G., et al.	<i>In vitro</i> permeation through porcine buccal mucosa of Salvia desoleana Atzei & Picci essential oil from topical formulations	Intern. J. Pharmaceutics 195: 171-177	2000
27	Van Duuren B., et al.	Cocarcinogenesis studies on mouse skin and inhibition of tumor induction	J. Nat. Cancer Inst. 46(5): 1039-1044	1971

28	Brandão F.	Occupational allergy to lavender oil	Contact Dermatitis 15(4):249-250	1986
29	NIOSH	Health Hazard Evaluation Report	HETA 83-006-1379	1983
30		The Merck Index 12 <sup>th</sup> Ed vs 12.3		2000
31	Jenner P., et al.	Food flavourings and compounds of related structure I. acute oral toxicity	Fd Cosmet. Toxicol. 2:327-343	1964
32	Ishidate M., et al.	Primary mutagenicity screening of food additives currently used in Japan*	Fd Cosmet. Toxicol. 22:623-636	1984
33	Florin I., et al.	Screening of tobacco smoke constituents for mutagenicity using the Ames' test*	Toxicology 15:219-232	1980
34	Hall	Unpublished report from McCormick & Co. Inc. to the flavor and extracts manufacturers' association of the United States	McCormick & Co. Inc. to the flavor and extracts manufacturers' association of the United States, Washington DC, US	1979
35	Oda et al.	Mutagenicity of food flavores in bacteria **	Shokuhin Eisi Hen, 9, 177-181	1978
36	Heck et al.	An evaluation of food flavoring ingredients in a genetic toxicity screening battery	Toxicologist 9, 257	1989
37	Oser	Unpublished report**		1967

\* Reference was not included because it did not provide information on linalyl acetate.

\*\* Reference was not retrievable.

**APPENDIX A****Results of the Epiwin model vs 3.10**

SMILES : O=C(OC(C=C)(CCC=C(C)C)C)C  
CHEM : 1,6-Octadien-3-ol, 3,7-dimethyl-, acetate  
CAS NUM: 000115-95-7  
MOL FOR: C12 H20 O2  
MOL WT : 196.29

## ----- EPI SUMMARY (v3.10) -----

## Physical Property Inputs:

Water Solubility (mg/L): 30  
Vapor Pressure (mm Hg) : -----  
Henry LC (atm-m<sup>3</sup>/mole) : -----  
Log Kow (octanol-water): 3.90  
Boiling Point (deg C) : -----  
Melting Point (deg C) : -----

## Log Octanol-Water Partition Coef (SRC):

Log Kow (KOWWIN v1.66 estimate) = 4.39

## Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPWIN v1.40):

Boiling Pt (deg C): 228.95 (Adapted Stein & Brown method)  
Melting Pt (deg C): -2.09 (Mean or Weighted MP)  
VP(mm Hg,25 deg C): 0.131 (Mean VP of Antoine & Grain methods)  
BP (exp database): 220 deg C  
VP (exp database): 1.11E-01 mm Hg at 25 deg C

## Water Solubility Estimate from Log Kow (WSKOW v1.40):

Water Solubility at 25 deg C (mg/L): 21.35  
log Kow used: 3.90 (user entered)  
no-melting pt equation used

## ECOSAR Class Program (ECOSAR v0.99g):

Class(es) found:  
Esters

## Henrys Law Constant (25 deg C) [HENRYWIN v3.10]:

Bond Method : 1.74E-003 atm-m<sup>3</sup>/mole  
Group Method: Incomplete  
Henrys LC [VP/WSol estimate using EPI values]: 1.128E-003 atm-m<sup>3</sup>/mole

## Probability of Rapid Biodegradation (BIOWIN v4.00):

Linear Model : 0.6443  
Non-Linear Model : 0.9294

## Expert Survey Biodegradation Results:

Ultimate Survey Model: 2.6935 (weeks-months)  
Primary Survey Model : 3.6401 (days-weeks )

## Readily Biodegradable Probability (MITI Model):

Linear Model : 0.6648  
Non-Linear Model : 0.6802

## Atmospheric Oxidation (25 deg C) [AopWin v1.90]:

## Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant = 116.2433 E-12 cm<sup>3</sup>/molecule-secHalf-Life = 0.092 Days (12-hr day; 1.5E6 OH/cm<sup>3</sup>)

Half-Life = 1.104 Hrs

## Ozone Reaction:

OVERALL Ozone Rate Constant = 43.174999 E-17 cm<sup>3</sup>/molecule-secHalf-Life = 0.027 Days (at 7E11 mol/cm<sup>3</sup>)

Half-Life = 38.222 Min

Reaction With Nitrate Radicals May Be Important!

## Soil Adsorption Coefficient (PCKOCWIN v1.66):

Koc : 517.9

Log Koc: 2.714

## Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v1.67]:

Total Kb for pH &gt; 8 at 25 deg C : 4.610E-002 L/mol-sec

Kb Half-Life at pH 8: 174.013 days

Kb Half-Life at pH 7: 4.764 years

## BCF Estimate from Log Kow (BCFWIN v2.14):

Log BCF = 2.303 (BCF = 200.9)

log Kow used: 3.90 (user entered)

## Volatilization from Water:

Henry LC: 0.00174 atm-m<sup>3</sup>/mole (estimated by Bond SAR Method)

Half-Life from Model River: 1.901 hours

Half-Life from Model Lake : 138.2 hours (5.759 days)

## Removal In Wastewater Treatment:

Total removal: 53.44 percent

Total biodegradation: 0.20 percent

Total sludge adsorption: 21.28 percent

Total to Air: 31.97 percent

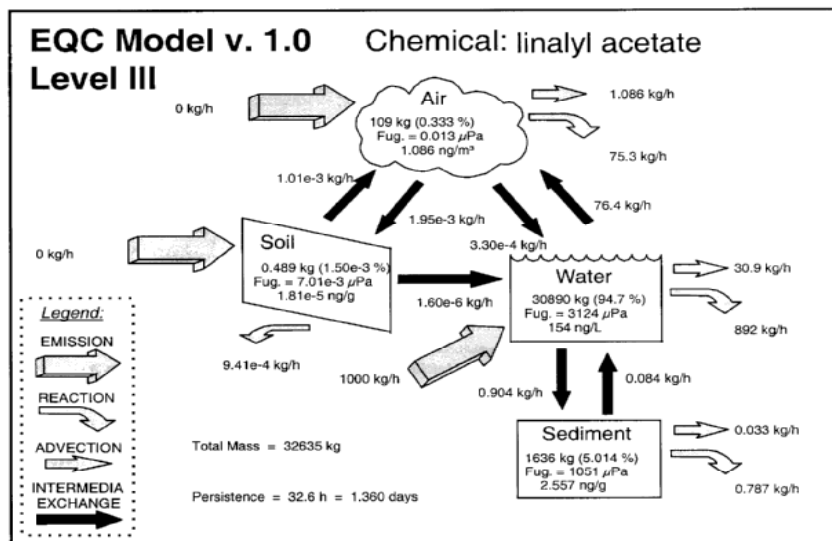
## Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.139	0.494	0
Water	89.9	900	1000
Soil	0.00313	900	0
Sediment	9.97	3.6e+003	0
Persistence Time: 280 hr			



APPENDIX B

EQC model



AM



**SIDS Dossier on the HPV Chemical  
Linalyl acetate**

**CAS no. 115-95-7**

Sponsor Country: Switzerland

Date of submission to OECD:

**List of Abbreviations**

<sup>a</sup>	Absolute to body weight
-	Absent
+	Present
a.i.	Active ingredient
ALP	Alkaline phosphatase
BCF	Bioconcentration factor
CFU	Colony forming units
d	Decrease
dc	Decrease (significant)
DOC	Dissolved organic carbon
DR	Dose related
F	Female
FID	Flame ionisation detection
GC	Gas chromatography
i	Increase
ic	Increase (significant)
LC	Liquid chromatography
LOD	Limit of detection
M	Male
MCV	Mean corpuscular volume
MS	Mass spectrometry
N/A	Not applicable
QC	Quality control
<sup>r</sup>	Relative to body weight
TLC	Thin layer chromatography
UV	Ultra violet
WHC	Water holding capacity

### 1.01. Chemical identity

CAS No. : 115-95-7

OECD name : Linalyl acetate

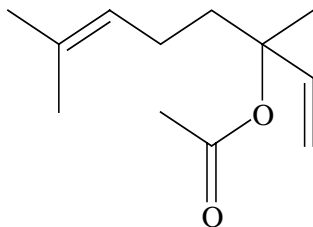
Chemical/IUPAC name : 1,5-dimethyl-1-vinylhex-4-enyl acetate

EINECS number : 2041164

Molecular formula : C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>

Molecular weight : 196.29

Structural formula :



### 1.02. OECD information

Sponsor country : Switzerland

Lead organisation : Dr. Georg Karlaganis  
Swiss Agency for the Environment, Forests and Landscape  
CH-3003 Berne, Switzerland  
e-mail: georg.karlaganis@buwal.admin.ch

Name of responder : This substance is evaluated under the OECD HPV programme  
(leader of consortium)

#### 1.1. General substance information

Type of substance : Organic

Physical state : Liquid

Purity : >96%

#### 1.2. Impurities

Dihydrolinalool, dehydrolinalool, tetrahydrolinalylacetate, linalool

#### 1.3. Additives

#### **1.4. Synonyms**

Linalyl acetate, linalool acetate, acetic acid linalool ester

#### **1.5. Quantity**

Yearly around 1000-5000 tonnes of linalyl acetate are produced.

#### **1.6. Use pattern**

The substance is used as an intermediate and found in soaps, cleaning products and cosmetics (perfume) It is a component of oil paint, is used in extracts and as a substitute for petitgrain oil. Linalyl acetate is a food additive.

#### **1.7. Sources of exposure**

There is a potential for occupational exposure during production/formulation, used not only in closed systems.

Consumers using oil paint and perfume may be exposed orally and dermally.

There is potential exposure to the aquatic compartment arising from the production/formulation and consumer use (cosmetics) of this substance.

#### **1.8. Additional information**

### 2.1. Melting Point

**Title** Safety Data Sheet Linalyl Acetate  
**Date of report** 2000  
**GLP** No data  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** <0 °C  
**Reliability** 4 Secondary literature

**Title** Internal report  
**Date of report** 1979  
**GLP** No  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** <0 °C  
**Reliability** 4 Secondary literature

### 2.2. Boiling Point

**Title** The Merck Index  
**Date of report** 2000  
**GLP** No data  
**Reference** 30  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** 220 °C  
**Reliability** 2 Handbook data

**Title** Safety Data Sheet Linalyl Acetate  
**Date of report** 2000  
**GLP** No data  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** 220 °C  
**Reliability** 4 Secondary literature

**Title** Internal report  
**Date of report** 1979  
**GLP** No  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** 219.7 °C at normal atmospheric pressure  
**Reliability** 4 Secondary literature

**Title** Sax's Dangerous properties of industrial materials, Ninth edition  
**Date of report** 1996  
**GLP** No data.  
**Reference** 20  
**Test substance** Linalyl acetate, purity not indicated  
**Test method** Not indicated  
**Result** 108-110 °C  
**Reliability** 4 Handbook data

### 2.3. Density (relative density)

**Title** Safety Data Sheet Linalyl Acetate  
**Date of report** 2000  
**GLP** No data  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** 0.895 g/cm<sup>3</sup> at 20°C  
**Reliability** 4 Secondary literature

**Title** Internal report  
**Date of report** 1979  
**GLP** No  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** 0.910 g/cm<sup>3</sup> at 20°C  
0.842 g/cm<sup>3</sup> at 100°C  
**Reliability** 4 Secondary literature

**Title** Sax's Dangerous properties of industrial materials, Ninth edition  
**Date of report** 1996  
**GLP** No data.  
**Reference** 20  
**Test substance** Linalyl acetate, purity not indicated  
**Test method** Not indicated  
**Result** 0.898-0.914  
**Reliability** 4 Handbook data

### 2.4. Vapour Pressure

**Title** Safety Data Sheet Linalyl Acetate  
**Date of report** 2000  
**GLP** No data  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** 0.006087 hPa at 20°C  
322.227 hPa at 100°C  
**Reliability** 4 Secondary literature

**Title** Internal report  
**Date of report** 1979  
**GLP** No  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** 0.006087 hPa at 20°C  
322.227 hPa at 100°C  
**Reliability** 4 Secondary literature



## 2.5. Partition Coefficient

**Title** Determination of the partition coefficient of linalylacetat in n-octanol/water  
**Date of report** July 17, 1995.  
**GLP** Yes.  
**Reference** 3.  
**Test substance** Linalylacetat, purity 97.0%.  
**Guidelines** 92/69/EEC, A.8; OECD 107.  
**Procedure** Octanol and water were mutually saturated with each other. 25 mL of a stock solution of linalylacetat in octanol (corresponding to 44 mg of linalylacetat) was transferred to a glass vessel. Additionally 15 mL octanol and 40 mL water, 25 mL octanol and 25 mL water or no octanol and 50 mL water was added. The vessels were sealed and subsequently shaken for 5 min at 25 rpm, 20-25°C. The mixtures were centrifuged (2000 rpm, 5 min), each phase was sampled in duplicate and analysed by GC-FID after dilution with acetone (octanol-phase) or extraction with n-pentane (water phase) using calibration curves.  
**Findings** QCs for analytical method in water phase fortified at 1.0, 2.5 and 3.5 mg/L were 103-111% of nominal (note 1), method validation with known amount of test substance 98-104%.

<i>treatment</i>	<i>A1</i>	<i>A2</i>	<i>B1</i>	<i>B2</i>	<i>C1</i>	<i>C2</i>
amount of test substance [mg]	44	44	44	44	44	44
volume of octanol phase [mL]	40	40	50	50	25	25
volume of water phase [mL]	40	40	25	25	50	50
concentration in octanol phase [mg/L]	1164	1181	919	958	1981	2014
concentration in aqueous phase [mg/L]	0.14	0.14	0.11	0.06	0.21	0.23
recovery [%]	106	108	105	109	113	115
$P_{ow}$	8281	8622	8096	16814*	9416	8922
$\log(P_{ow})$	3.9	3.9	3.9	4.2	4.0	4.0
average $P_{ow}$	8452		8096		9169	
average $P_{ow} \pm RSD$ [%]	<b>8668 <math>\pm</math> 6.1%</b>					
$^{10}\log(P_{ow})$	<b>3.9</b>					

\* Outlier, not included in calculation

**Conclusion**  $^{10}\log(P_{ow})$  3.9.

**Rev. note**

- For the analytical method in the water phase QCs were included at high fortification rates (1.0-3.5 mg/L) in relation to the concentrations measured in n-pentane during the study (0.26-1.02 mg/L). Since calibration curves were drawn using duplicate samples of concentrations ranging between 0.1 and 10 mg/L, the method is still acceptable.
- Temperature was reported to be within the range 20-25°C and pH was not reported. A constant temperature and pH are necessary for a stable system. Since the  $\log(P_{ow})$  values were within a range of  $\pm 0.3$ , the stability of the system is guaranteed. The results of the replicate C2 were not included in the calculation of the  $\log(P_{ow})$  because they are not in accordance with the other 5 values found. Probably the concentration in the water phase was incorrect.

**Reliability** 1

**Critical study for SIDS endpoint**

### 2.6.1. Water Solubility and Dissociation Constant

**Title** Report on the hydrolysis of linalylacetate and ethylformate by artificial gastrointestinal juices  
**Date of report** April 1979.  
**GLP** No.  
**Reference** 34.  
**Test substance** Linalyl acetate, purity not indicated.  
**Test method** Not specified.  
**Procedure** Water solubility was measured at room temperature.  
**Results** Water solubility 30 mg/L  
 Little amounts of linalool were present (determined by GC)  
**Rev. note** No further details were available.  
**Reliability** 4.

**Title** Epiwin vs 3.10  
**Date of report** 2002  
**GLP**  
**Reference** Epiwin vs 3.10  
**Test substance** Linalyl acetate  
**Test method** Calculation based on Kow of 3.9  
**Result** 21.35 mg/L at 25 °C  
**Reliability** 4

**Title** Safety Data Sheet Linalyl Acetate  
**Date of report** 2000  
**GLP** No data  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** < 1 g/L at 20 °C  
**Reliability** 4 Secondary literature

**Title** Just how insoluble are monoterpenes?  
**Date of report** 1993.  
**GLP** No.  
**Reference** 15.  
**Test substance** Linalyl acetate, purity not indicated.  
**Test method** Not specified.  
**Procedure** A saturated aqueous solution was prepared by adding an excess linalyl acetate to 1.5 mL water in test vials. The vials were sealed and sonicated for 30 min in a water bath (25-30°C). The vials were equilibrated for three days at ambient temperatures. Analyses were performed by GC-FID and quantification was based on peak area.  
**Conclusion** Water solubility linalyl acetate <10 mg/L.  
**Rev. note** 1. Four important remarks should be made about the test, partly due to the limited description of the test available in the report:  

- Nothing was said about temperature control during the equilibration (OECD 30°C). The test vials were reported to be equilibrated at ambient temperatures. Because temperature is an important factor in the water solubility of the test substance and therefore should be kept constant, the study reliability is lowered.
- The pH is not reported. Therefore it can not be excluded that esters were hydrolysed in water.
- The purity of the test substance was not specified and impurities could have a disturbing effect on the water solubility.
- Sonication and equilibration times should be long enough to be sure the measured water concentration equals the solubility of the test substance. Since no variations were made in sonication and equilibration times, the measured concentrations were not proved to be the actual maximum water solubility concentration.

2. *Minor remark.* Number of replicates not indicated.  
**Reliability** 3 Secondary literature (note 1).

### 2.6.2. Solubility in organic solvents

**Title** Safety Data Sheet Linalyl Acetate  
**Date of report** 2000  
**GLP** No data  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** Soluble in ethanol and diethyl ether  
**Reliability** 4 Secondary literature

### 2.7 Flash Point

**Title** Safety Data Sheet Linalyl Acetate  
**Date of report** 2000  
**GLP** No data  
**Reference** 1  
**Test substance** Linalyl acetate  
**Test method** Not indicated  
**Result** 84 °C  
**Reliability** 4 Secondary literature

**Title** Sax's Dangerous properties of industrial materials, Ninth edition  
**Date of report** 1996  
**GLP** No data.  
**Reference** 20  
**Test substance** Linalyl acetate, purity not indicated  
**Test method** Not indicated  
**Result** 185 °F (~85 °C)  
**Reliability** 4 Handbook data

### 3.1. Stability

#### A Photodegradation

<b>Reference</b>	Epiwin vs 3.10
<b>Test substance</b>	Linalyl acetate
<b>Test method</b>	Calculation with AOPWIN vs1.9, based on: SMILES : O=C(OC(C=C)(CCC=C(C)C)C) CHEM : 1,6-Octadien-3-ol, 3,7-dimethyl-, acetate MOL FOR: C12 H20 O2 MOL WT : 196.29
<b>Result</b>	----- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----- Hydrogen Abstraction = 3.0433 E-12 cm <sup>3</sup> /molecule-sec Reaction with N, S and -OH = 0.0000 E-12 cm <sup>3</sup> /molecule-sec Addition to Triple Bonds = 0.0000 E-12 cm <sup>3</sup> /molecule-sec Addition to Olefinic Bonds = 113.2000 E-12 cm <sup>3</sup> /molecule-sec Addition to Aromatic Rings = 0.0000 E-12 cm <sup>3</sup> /molecule-sec Addition to Fused Rings = 0.0000 E-12 cm <sup>3</sup> /molecule-sec  OVERALL OH Rate Constant = 116.2433 E-12 cm <sup>3</sup> /molecule-sec HALF-LIFE = 0.092 Days (12-hr day; 1.5E6 OH/cm <sup>3</sup> ) HALF-LIFE = 1.104 Hrs  ----- SUMMARY (AOP v1.90): OZONE REACTION ----- OVERALL OZONE Rate Constant = 43.174999 E-17 cm <sup>3</sup> /molecule-sec HALF-LIFE = 0.027 Days (at 7E11 mol/cm <sup>3</sup> ) HALF-LIFE = 38.222 Min
<b>Reliability</b>	4

#### B Stability in Water

<b>Title</b>	Determination of the hydrolysis of linalylacetate as a function of pH.																									
<b>Date of report</b>	2001 (finalisation date).																									
<b>GLP</b>	Yes.																									
<b>Reference</b>	24.																									
<b>Test substance</b>	Linalyl acetate, purity 97.6%..																									
<b>Test method</b>	EEC-Directive 92/69, C.7.																									
<b>Procedure</b>	Test system: A sterile 0.05 M acetate buffer pH 4, a sterile 0.05 M phosphate buffer pH 7 and a sterile 0.05 M borate buffer pH 9. Method: 400 µL of a linalyl acetate solution (1080 mg/L acetonitrile) was added to 50 mL of each of the buffer solutions under a nitrogen atmosphere. The test solutions were incubated in duplicate at 50°C in the dark. The concentration of linalyl acetate in n-hexane extract was analysed by GC-MS immediately after preparation and after 2.4 hours of incubation. The pH was measured at room temperature at the beginning and end of the test.																									
<b>Results</b>	<table border="1"> <thead> <tr> <th>pH</th> <th>Measured pH</th> <th>Sampling time (hours)</th> <th>Rel. concentration test substance (%)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">4</td> <td>4.0</td> <td>0</td> <td>100</td> </tr> <tr> <td>4.0</td> <td>2.4</td> <td>2</td> </tr> <tr> <td rowspan="2">7</td> <td>7.0</td> <td>0</td> <td>100</td> </tr> <tr> <td>7.0</td> <td>2.4</td> <td>3</td> </tr> <tr> <td rowspan="2">9</td> <td>9.0</td> <td>0</td> <td>100</td> </tr> <tr> <td>9.0</td> <td>2.4</td> <td>4</td> </tr> </tbody> </table>	pH	Measured pH	Sampling time (hours)	Rel. concentration test substance (%)	4	4.0	0	100	4.0	2.4	2	7	7.0	0	100	7.0	2.4	3	9	9.0	0	100	9.0	2.4	4
pH	Measured pH	Sampling time (hours)	Rel. concentration test substance (%)																							
4	4.0	0	100																							
	4.0	2.4	2																							
7	7.0	0	100																							
	7.0	2.4	3																							
9	9.0	0	100																							
	9.0	2.4	4																							
<b>Conclusion</b>	At each pH, a decrease in concentration > 50% was observed after 2.4 hours (half-life time at 25°C < 1 day). Hence it was concluded that linalyl acetate is hydrolytically unstable in aqueous solutions buffered at pH 4, pH 7 and pH 9.																									
<b>Rev. note</b>	1. The hydrolysis products, which are linalool and acetic acid, were not identified.																									
<b>Reliability</b>	1.																									

**Critical study for SIDS endpoint**

**C Stability in Soil**

**3.2. Monitoring Data**

<b>Title</b>	Flavour compounds in weakly polluted rivers as a means to differentiate pollution sources
<b>Date of report</b>	1992.
<b>GLP</b>	No.
<b>Reference</b>	14.
<b>Test substance</b>	Linalyl acetate, purity not relevant.
<b>Test method</b>	Not specified.
<b>Test system</b>	The occurrence of different Volatile Organic Compounds (VOCs) in eighth rivers and brooks of different origin (industry, agriculture, wood preserving, etc.) in South-West-Germany was investigated. 10 L samples were taken from the middle of the river. The mixture of VOCs from the sampled water was brought onto Tenax cartridges and subsequently a GC-MS analyses was performed. Reference standards were used to compare retention times and mass spectra.
<b>Results</b>	28 different mono- and sesquiterpenes were identified in the different rivers or brooks. Linalyl acetate was identified only in Stockacher Aach.
<b>Conclusion</b>	Linalyl acetate was found in one river.
<b>Rev. note</b>	No individual data were available to check the occurrence of linalyl acetate. The amount of linalyl acetate in Stockacher Aach was also not clear. The only conclusion that can be drawn from this study is that linalyl acetate can reach the aquatic environment.
<b>Reliability</b>	4 Secondary literature.

**3.3 Transport and Distribution between Environmental Compartments**

<b>Title</b>	Epiwin vs 3.10
<b>Date of report</b>	2002
<b>GLP</b>	
<b>Reference</b>	Epiwin vs 3.10
<b>Test substance</b>	Linalyl acetate
<b>Test method</b>	Calculation with Epiwin vs 3.10, based on: Chem Name : 1,6-Octadien-3-ol, 3,7-dimethyl-, acetate Molecular Wt: 196.29 Henry's LC : 0.00174 atm-m <sup>3</sup> /mole (Henrywin program) Vapor Press : 0.131 mm Hg (Mpbpwin program) Log Kow : 3.9 (user-entered) Soil Koc : 3.26e+003 (calc by model)

Emission to water only

Result	Mass Amount	Half-Life	Emissions		
	(percent)	(hr)	(kg/hr)		
Air	0.139	0.494	0		
Water	89.9	900	1000		
Soil	0.00313	900	0		
Sediment	9.97	3.6e+003	0		

	Fugacity	Reaction	Advection	Reaction	Advection
	(atm)	(kg/hr)	(kg/hr)	(percent)	(percent)
Air	4.84e-013	545	3.89	54.5	0.389
Water	1.11e-008	194	252	19.4	25.2
Soil	5.5e-014	0.00675	0	0.000675	0
Sediment	7.82e-009	5.37	0.558	0.537	0.0558

Persistence Time: 280 hr  
 Reaction Time: 376 hr  
 Advection Time: 1.09e+003 hr  
 Percent Reacted: 74.4  
 Percent Adverted: 25.6

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 0.4944  
 Water: 900  
 Soil: 900  
 Sediment: 3600  
 Biowin estimate: 2.693 (weeks-months)

Advection Times (hr):

Air: 100  
 Water: 1000  
 Sediment: 5e+004

**Reliability** 4

**Title** EQC v 1.0

**Date of report** 2002

**GLP**

**Reference** EQC v 1.0

**Test substance** Linalyl acetate

**Test method** Calculation:

Since the substance is soluble in water to some extent, the substance is considered to be a Type I substance.

Defaults:

T<sub>1/2</sub> air: 1 hours, t<sub>1/2</sub> water 24 hours, t<sub>1/2</sub> soil 360 hours and t<sub>1/2</sub> sediment 1440 hours

Physical chemical parameters:

Water solubility 21 mg/l, vapour pressure 0.6 Pa, Log Kow 3.9, melting point 0°C.

Emissions have been considered to water only.

**Result** Air: 0.3%

Soil: 0%

Water: 95%

Sediment: 5%

**Reliability** 4

### 3.4. Biodegradation

<b>Title</b>	Linalyl acetate synthetic Determination of the ready biodegradability.
<b>Date of report</b>	February 25, 1991.
<b>GLP</b>	No.
<b>Reference</b>	7.
<b>Test substance</b>	Linalyl acetate, purity 96.0%.
<b>Test method</b>	OECD 301C.
<b>Test system</b>	<p><b>Treatment</b> Activated sludge (30 mg/L): prepared from soil of river bank, sludge of a municipal treatment plant and sludge of an industrial sewage plant.</p> <ul style="list-style-type: none"> <li>- 2 flasks Treated (basal culture medium + activated sludge + linalyl acetate (100-102 mg/L));</li> <li>- 1 flask Positive Control (basal culture medium + activated sludge + Aniline (92 mg/L));</li> <li>- 1 flask Blank Control (basal culture medium + activated sludge).</li> </ul> <p><b>Procedure</b> Incubation was performed for 28 days at 20°C. The oxygen consumption was determined daily with a volumetric respirometer.</p> <p><b>Results</b> <b>Table below</b> Biodegradation values for linalyl acetate and positive control. Values are corrected for blank control values.</p>

Treatment	Mean % biodegradation [% of ThOD] on day:							
	1	4	7	10	14	18	22	28
Linalylacetate	4	33	54	62	68	71	73	75
Positive control	0	9.4	72	74	77	78	80	84

<b>Conclusion</b>	Ready biodegradability.
<b>Rev. note</b>	<ol style="list-style-type: none"> <li>1. Only limited information is available on the test. No information about the composition of the medium, pH during the test, light regime and shaking during the study. All of these are important factors in the degradation of the test substance.</li> <li>2. In a curve showing the oxygen consumption over 28 days, beside a sludge control (30 mg/L) also a blank control (100 mg/L) is included. This is probably due to a mistake, because in the report no information is given about an abiotic control included in this study.</li> </ol>
<b>Reliability</b>	2 Limited information (note 1).
<b>Critical study for SIDS endpoint</b>	

<b>Title</b>	Micellar-induced selectivity and rate enhancement in the acid-catalyzed cyclization and rearrangement of monoterpenes. The solvolysis of linalyl and geranyl acetates
<b>Date of report</b>	1989.
<b>GLP</b>	No.
<b>Reference</b>	17.
<b>Test substance</b>	Linalyl acetate, purity 96%.
<b>Test method</b>	Not specified.
<b>Procedure</b>	90 mL of a buffer with pH 3.1 (36 mM HCl; 15 mM sodiumcitrate) with or without 38 mM SDS was deaerated with Argon and treated with 5.4 mg linalyl acetate (final conc. 0.30 mM). Additionally a test was included without SDS, but with a deaerated mixture of buffer/methanol (44/1) treated with 5.4 mg linalyl acetate (final conc. 0.30 mM). Each sample was stirred, deaerated again, sonicated for 15 minutes and subsequently stirred at 25°C. Samples (10 mL) were taken at approximately 7, 25, 50 and 240 h and analysed by extraction/concentration/GC-MS (analysis in duplicate).
<b>Results</b>	The half-life of linalyl acetate was ~7 h in all tests. For product distribution after 25 h: see table below.

Products	Concentration product, mole %		
	HCl/citrate buffer*	HCl/citrate buffer/2% MeOH	SDS/HCl/citrate buffer
linalylacetate	8.8	9.0	7.1
linalool	51	46	54
a-terpineol	22	19	8.7
neryl acetate	2.4	2.3	0.90
geranyl acetate	4.2	4.1	1.6
nerol	2.8	2.6	4.2
geraniol	7.7	7.2	16
<b>Total</b>	<b>99</b>	<b>91</b>	<b>92</b>

\* Mean of duplicate test.

<b>Conclusion</b>	$T_{1/2}$ : ~7 h (pH 3); with SDS product ratios of acyclic/cyclic alcohols were higher during the first 50 h.
<b>Rev. note</b>	This test is not a standard investigation according to the OECD guidelines. The extreme conditions (pH 3) made it impossible to deduce a reliable $DT_{50}$ -value under normal circumstances in the aquatic environment. Further no validation of the analysis method was reported.
<b>Reliability</b>	2



#### 4.1. Acute Toxicity to fish

<b>Title</b>	96-hour acute toxicity study in carp with linalylacetate (flow-through)	
<b>Date of report</b>	December 23, 1998.	
<b>GLP</b>	Yes.	
<b>Reference</b>	13.	
<b>Test substance</b>	Linalyl acetate, purity 97.6%.	
<b>Guideline</b>	EEC 92/69, C.1; OECD 203.	
<b>Stat. method</b>	Maximum likelihood estimation method (Probit analysis; Finney, 1971)	
<b>Test system</b>	<b>Species</b>	Carp ( <i>Cyprinus carpio</i> ), length 28.8±1.5 mm.
	<b>No. of fish</b>	7/treatment.
	<b>Concentrations</b>	Nominal: 10, 18, 32, 56 and 100 mg/L (no vehicle), untreated control.
	<b>Test conditions</b>	96-h flow-through test with ~10 renewals/24 h; 21-22°C in 38 L glass vessels containing 30 L of water (hardness 250 mg/L CaCO <sub>3</sub> ); 16 h light; unfed; not aerated; loading 0.011 g/L/d.
	<b>Analysis</b>	At 0 h and 24 h or 96 h for all treatments by extraction/dilution/GC-FID.
	<b>Phys. meas.</b>	Daily in all replicates: overall ranges for pH 8.0-8.1; O <sub>2</sub> 100-105%; temperature (only in control vessel) 21-22°C.
	<b>Observations</b>	Mortality/symptoms at 2, 20, 44, 72 and 96 h.
<b>Results</b>	<b>Analysis</b>	Mean measured concentrations for 10, 18, 32, 56 and 100 mg/L were respectively 79, 68, 63, 49 and 27% of nominal (note 1). At test concentrations 32, 56 and 100 mg/L a test substance film was observed.
		Method recovery of QCs fortified at 1, 10 and 100 mg/L: 88-108% (n = 3-6).
	<b>Reference test</b>	A reference test was performed with pentachlorophenol about 11 months earlier; 24-h LC <sub>50</sub> 0.18 mg/L, which is in accordance with historical control values.

##### Biological results.

Parameter	Time [h]	Mean measured concentration [mg/L]					
		0	7.9	12.3	20.1	27.3	27.2
Mortality [%]	96	0	0	71	100	100	100
Symptoms*	0-96		+	+	+	+	+

\* Symptoms included hypoactive swimming, loss of equilibrium and/or immobility.

**Conclusion** 96-h LC<sub>50</sub> 11 mg/L (95% CI, 10-14 mg/L).

- Rev. note**
- The analytical results at 24 h were not reported. For treatment levels in which all fish had died at 24 h (32, 56 and 100 mg/L) only the 0-h result was available. Since it is a flow-through test and the duplicate analytical results in the lowest two concentrations were comparable, the single values are acceptable in this test.
  - The measured concentrations were below the nominal, because of the maximum solubility of the test substance and because of hydrolysis of the test substance. In a static pretest a large amount of a hydrolysis product was found. In the flow-through test the same hydrolysis product was observed, but in significant lower amounts.
  - Minor remarks.* Food was withheld for 48 h before the start of the test (OECD 203, 24 h).

**Reliability** 1

**Critical study for SIDS endpoint**

#### 4.2. Acute Toxicity to Aquatic Invertebrates (Daphnia)

<b>Title</b>	Report on the acute toxicity test of linalylacetat on <i>Daphnia</i> ( <i>Daphnia magna</i> Straus 1820)	
<b>Date of report</b>	December 16, 1994.	
<b>GLP</b>	Yes.	
<b>Reference</b>	5.	
<b>Test substance</b>	Linalyl acetate, purity 97.1%.	
<b>Test method</b>	OECD 202, part I.	
<b>Stat. method</b>	Berkson, Jasa 48 (1953), 569-599.	
<b>Test system</b>	<b>Species</b>	<i>Daphnia magna</i> , ≤24 h old.
	<b>No. of daphnids</b>	5/replicate, 4 replicates/treatment.
	<b>Concentrations</b>	Nominal: 10, 18, 32, 58 and 100 mg/L (no vehicle), untreated controls.
	<b>Test conditions</b>	Static without aeration in the dark; at 20±1°C in beakers, covered with glass



\* Precipitate at 72 h.

**Conclusions** E<sub>p</sub>C<sub>50</sub> (0-72h): 16 mg/L based on nominal concentrations ⇔ 4.2 mg/L corrected for mean measured concentrations (26% of nominal);  
E<sub>r</sub>C<sub>50</sub> (0-72h): 62 mg/L based on nominal concentrations ⇔ 16 mg/L corrected for mean measured concentrations (26% of nominal);  
72-hour NOEC <4.4 mg/L. based on nominal concentrations ⇔ <1.2 mg/L corrected for mean measured concentrations (26% of nominal).

**Rev. note**

1. The LOD was reported to be 0.7 mg/L in a separate analytical report, but 0.2 mg/L in the study report itself. Further test concentrations at 72 h were below the LOD for all concentrations. The mean measured concentrations are probably still an overestimation of the mean exposure concentrations. Probably the concentrations of test substance disappeared in less than 72 h from the test solutions. The study reliability is lowered because of this.
2. *Minor remarks.* The test flasks were not reported to been shaken during the study; this is necessary for the transfer of CO<sub>2</sub> formed during the test. Since the rises in pH of >1 unit were only seen in the two lowest test concentrations (1.1 unit), the algae in test flasks were probably kept in suspension. The pH rises of 1.1 unit were probably associated with strong cell growth, due to CO<sub>2</sub> depletion from test media.

**Reliability** 2 Overestimation concentration.  
**Critical study for SIDS endpoint**

#### 4.4. Toxicity to Bacteria

**Title** Linalyl acetate Activated sludge, respiration inhibition test

**Date of report** March 2, 1989 (completion study).

**GLP** No.

**Reference** 4.

**Test substance** Linalyl acetate, purity 96.7%.

**Test method** OECD 209, ISO 8192.

**Procedure** The test was performed in duplicate 500 mL flasks (Reference product single flask). To each flask were added synthetic sewage feed, a solution of linalyl acetate or reference product 2,5-dichlorophenol in ethanol and sludge. The test concentrations were 96, 304 and 912 mg/L (for the reference product 272 mg/L). Each flask was aerated at 20±2°C for 3 hours, after which period the O<sub>2</sub> consumption was measured (at low concentrations for 10 minutes).

**Results** See table below.

Test solution	Concentration [mg/L]	Respiration rate	Inhibition [%]
Control	0	1.212	-
Control	0	1.250	-
Linalylacetate-100	96	1.212	3
Linalylacetate-100	96	1.176	6
Linalylacetate-300	304	0.667	47
Linalylacetate-300	304	0.657	48
Linalylacetate-900	912	0.471	62
Linalylacetate-900	912	0.494	60
Reference product	272	0.375	70

**Conclusions** 3-h EC<sub>50</sub> 415 mg/L (calculated by the reviewer using 39% trimmed SPK).

**Rev. note** Only limited information was available. The information provided was essentially confined to the above included. There was no information about the composition of the synthetic sewage feed and also the source of the sludge was not reported. The study reliability is lowered.

**Reliability** 2 Limited information.

## 5.1. Pharmacokinetics

## 5.2. Acute Toxicity

**Title** Food flavourings and compounds of related structure I. acute oral toxicity  
**Date of report** 1964  
**GLP** No.  
**Reference** 31.  
**Test substance** Linalyl acetate, purity not indicated.  
**Guideline** Not indicated.  
**Stat. method** Lichfield & Wilcoxon  
**Test system** **Species** Rat (Osborne-Mendel).  
**No. of animals** 5/sex/treatment.  
**Dosage** Oral by gavage not specified  
**Observations** Mortality, clinical signs (frequency not indicated).  
**Results** Deaths occurred between 4 hours and 4 days after treatment.  
 Clinical signs: Depression soon after treatment, coma, wet posterior.  
**Conclusions** LD<sub>50</sub> 14,550 mg/kg bw (95% CI 12,300-17,1070 mg/kg bw)  
**Rev. note** The report is limited to the above mentioned.  
**Reliability** 4  
**Critical study for SIDS endpoint**

**Title** Food flavourings and compounds of related structure I. acute oral toxicity  
**Date of report** 1964  
**GLP** No.  
**Reference** 31.  
**Test substance** Linalyl acetate, purity not indicated.  
**Guideline** Not indicated.  
**Stat. method** Lichfield & Wilcoxon  
**Test system** **Species** Mouse.  
**No. of animals** 5/sex/treatment.  
**Dosage** Oral by gavage not specified, not fasted before treatment.  
**Observations** Mortality, clinical signs (frequency not indicated).  
**Results** Deaths occurred between 1 and 3 days after treatment.  
 Clinical signs: Depression within 10-15 min. after treatment.  
**Conclusions** LD<sub>50</sub> 13,360 mg/kg bw (95% CI 11,920-15,000 mg/kg bw)  
**Rev. note** The report is limited to the above mentioned.  
**Reliability** 4  
**Critical study for SIDS endpoint**

**Title** Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation  
**Date of report** August 8, 1991  
**GLP** No.  
**Reference** 16.  
**Test substance** Linalyl acetate, purity not indicated.  
**Guideline** Not indicated.  
**Stat. method** Student's *t*-test, F-test.  
**Test system** **Species** Mouse (Swiss), 6-8 weeks and 6 months, mean weight 28.5 g.  
**No. of animals** 4/dose level.  
**Dosage** Inhalation exposure to 2.74 mg/L during 90 minutes; untreated controls.  
**Analysis** By GC and GC-MS after capture in activated charcoal and elution with carbon disulfide.  
**Procedure** After 60 min adaptation, animals were exposed (young and old animals separately) (whole body, 8.4L). Motor activity was determined pretest (during adaptation) and at 30, 60 and 90 min. during treatment by the number of interruptions of a light beam. Blood was withdrawn at 0, 30, 60 and 90 min. and analysed by GC.

**Results** The results of analyses (air and blood) were not reported.  
Motor activity of control animals was arbitrarily fixed as 100%.  
An additional test with old animals (6 months) was performed at a higher dose (not specified), leading to a significant reduction of motility.

Exposure level (mg/l)		0		2.74	
Effect	Time	Young	Old	Young	Old
% of activity	30	100	100	42	76
	60	100	100	11	65
	90	100	100	0	19

**Conclusions** Effect at 2.74 mg/l.

**Rev. note**

- Both male and female mice were included in the test without specification. It was indicated that no sex difference exists between the motor activity of male and female mice.
- Exposure was limited to 90 minutes. It is not clear what the result of longer exposure times will be.
- The differences between young and old animals may be explained by the higher amount of fat in older animals and a concomitant higher storage in fat and thus lower plasma levels.

**Reliability** 4 Limited report, secondary literature.

**Critical study for SIDS endpoint**

### 5.3. Corrosiveness/irritation

#### A Skin irritation/corrosion

**Title** Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man

**Date of report** August 1979.

**GLP** No.

**Reference** 11.

**Test substance** Linalyl acetate, purity >95%.

**Guideline** Not applicable.

**Stat. method** Not applicable.

*Test 1*

**Test system**

**Species** Angora rabbit (weight 2.3-3.0 kg).

**No. of animals** 6 (sex not indicated).

**Procedure** Application of 0.1 g test substance on the clipped dorsal skin (3 x 3 cm) without dressing (solvent not indicated) at 0, 24 and 72 h; after 72 h Evans blue was injected i.v., animals were killed after 1 h and dorsal skin was removed.

**Observations** Skin reaction on living skin at 24 and 72 h; on removed skin dilation rate, oedema, capillary permeability and bleeding rate; skin histopathology.

*Test 2*

**Test system**

**Species** Guinea pig (Hartley, weight 350-500 g), rat (Wistar, weight 250-350 g).

**No. of animals** 6 males/test.

**Procedure** Application of 0.1 g test substance on the clipped dorsal skin without dressing (solvent not indicated) at 0, 24 and 72 h; after 72 h Evans blue was injected i.v., animals were killed after 1 h and dorsal skin was removed.

**Observations** Skin reaction on living skin at 24 and 72 h; on removed skin dilation rate, oedema, capillary permeability and bleeding rate; skin histopathology.

*Test 3*

**Test system**

**Species** Miniature swine (Pitman-Moore, age 1 month).

**No. of animals** 6 (sex not indicated).

**Procedure** Application of 0.05 g test substance on the clipped and cleaned dorsal skin under a Ø 15 mm patch (solvent not indicated) for 48 h; after 48 h Evans blue was injected i.v., animals were killed after 1 h and dorsal skin was removed.

**Observations** Skin reaction on living skin at 48 h; on removed skin dilation rate, oedema, capillary permeability and bleeding rate; skin histopathology.

*Test 4*

**Test system**

**Species** Human (male volunteers without known allergies).

**No.** 50

**Procedure** Application of 0.05 mL test substance (32% solution in acetone) on the back under a Ø 15 mm patch for 48 h.

**Observations** Skin reaction at 48, 72, 96 and 120 h.

**Results** Animal scores based on erythema, oedema, dilation rate and capillary permeability: <4 mildly irritating, 4-8 moderate irritating, >8 severely irritating.

Human scores: positive reactions <10% non-irritating 10-40% mildly irritating, 40-70% moderate irritating, >70% severely irritating.

Species	Test results				
	Rabbit	Guinea pig	Rat	Miniature swine	Human
	Severely irritating	Moderately irritating	Not reported	Not irritating	Not irritating

**Conclusion** -

**Rev. note** 1. *Minor remark.* In the rabbit test each animal was treated with 3 different test substances and a positive control (n-hexadecane). Two areas were left free and served as untreated controls.  
2. The method used to calculate scoring was not fully described.

**Reliability** 2 Scoring method not fully elucidated (note 2), secondary literature.

## B Eye irritation/corrosion

### 5.4. Skin Sensitisation

### 5.5. Repeated Dose Toxicity

**Title** 28-Day oral toxicity study in rats, compound B10.

**Date of report** January 26, 1990.

**GLP** Yes.

**Reference** 23.

**Test substance** B10: essential oil of coriander containing 72.9% of natural linalool. Additional constituents were identified as 3.9% alpha-pinene, 0.6% camphene, 0.9% myrcene, 4.0% p-cymene, 2.7% limonene, 3.6% gamma-terpinene, 4.6% camphor, 0.8% alpha-terpineol and 1.2% geranyl acetate. The total of ingredients identified by gas chromatography is 95.5% (area-%), the remainder being minor peaks in the chromatogram.

**Guideline** Not indicated.

**Stat. method** ANOVA.

**Test system** **Species** Rat (CrI:CD/BR), 4-week-old males and females.

**No. of animals** 10/sex/treatment.

**Dosage** Daily oral administration by gavage of 160, 400 and 1000 mg/kg bw (vehicle is 1% methyl cellulose in dist. water; dosing volume 10 ml/kg). Test mixtures were prepared fresh weekly.

**Exposure period** 28 days.

**Post exposure period** 1 day.

**Investigations** **General** Clinical signs (daily); mortality (twice daily); food consumption (weekly); body weight (weekly); physical examination and clinical observation (weekly).

**Clinical pathology** 10 Animals per sex were taken at random from the pool of healthy animals not selected for the study as baseline group for clinical chemistry and haematology. Haematology: leukocyte count, erythrocyte count, haemoglobin, haematocrit, platelet count, leukocyte 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 CO<sub>2</sub>, total protein, albumin, total bilirubin, blood urea nitrogen, creatinine, glucose, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase and alkaline phosphatase.

**Necropsy** Macroscopy: external body surface, orifices, cranial cavity, carcass, nasal cavity and paranasal sinuses, cervical tissues and organs, external surface of brain and

spinal cord, thoracic, abdominal and pelvic cavities and viscera.  
Organ weights: brain, spleen, liver, heart, kidneys, testes with epididymides, thyroid with parathyroids, adrenal glands, ovaries and pituitary.  
Microscopy: all organs investigated macroscopically and femoral bone marrow, lung, any lesion, oesophagus, stomach, duodenum, jejunum, ileum, colon, caecum, rectum, pancreas, urinary bladder and mesenteric lymph nodes.

**Analysis Results** Concentration of the test substance in each concentration for administration was verified by analysis.

Dose	0 mg/kg		160 mg/kg		400 mg/kg		1000 mg/kg		Dose related	
	M	F	M	F	M	F	M	F	M	F
Mortality (A)	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10		
Clinical Signs	No treatment related effects.									
Body weight	No treatment related effects.									
Food consumption	No treatment related effects.									
Haematology	No treatment related effects.									
<b>Clinical chemistry</b>										
Total protein					i		i	i	x	x
Albumin					i		i	i	x	x
Calcium							i		x	
Glucose							d	d	x	
<b>Necropsy</b>										
Macroscopy (B)							+	+	x	x
Liver weight			i	i	ic	ic	ic	ic	x	x
Kidney weight					ic <sup>f</sup>		ic <sup>a</sup>	ic <sup>a</sup>	x	x
Microscopy (C)						+		+	+	+

Where i=increase; d=decrease.

- (A) One female was found dead on day 2 and was replaced by another female that was dosed for the full time of the test. One male was found dead on day 9, probably by a handling accident.  
(B) Thickened liver lobes, pale areas in the kidneys and thickened stomach mucosa.  
(C) All treated female groups showed hepatocellular cytoplasmic vacuolisation while the high-dose males had an increase in degenerative lesions in the renal cortex. Middle- and high-dose females also had lesions in the nonglandular part of the stomach, with some erosion, subacute inflammation and acanthosis.

**Conclusions** NOAEL = 160 mg/kg bw based on histological effects in liver and kidney.(equivalent to ~ 148 mg/kg bw linalyl acetate)  
LOAEL = 400 mg/kg bw based on histological effects in liver and kidney (equivalent to ~371 mg/kg linalyl acetate)

- Rev. note**
- No remarkable effects on the primary reproductive organs in both females (ovaries and uteri) and males (testes and epididymides) were noted in any animal from any dosage group up to 1000 mg/kg bw, both macroscopically at dissection and also microscopically during histopathology of every single (10 male, 10 female) high-dose animal.
  - 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.
  - The dose was converted to equivalents linalyl acetate, making a correction for the purity (72.9%) and the molecular weight.

**Reliability** 1.  
**Critical study for SIDS endpoint**

**Title** Effect of linalool on hepatic drug-metabolizing enzymes in the rat.  
**Date of report** 1974.  
**GLP** No.  
**Reference** 21.  
**Test substance** Linalool, purity ≥96%.  
**Guideline** Not indicated.

<b>Stat. method</b>	Not indicated.
<b>Test system</b>	<b>Species</b> Rat (Wistar), 4-week-old males. <b>No. of animals</b> At least 24. <b>Dosage</b> Daily intragastric intubation of 500 mg/kg bw as a 25% (w/v) solution in propylene glycol. Controls: similar volume of propylene glycol. <b>Exposure period</b> 0-64 days.
<b>Method</b>	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 cervical dislocation, the livers rapidly excised, freed from adhering connective tissue and weighed. Liver homogenates and microsomal fraction were then prepared according to published literature.
<b>Analysis Results</b>	No data. There were no deaths over the 64-day period, nor was there any significant effect on body weight gain. No clinical signs were observed. 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 by 36% ( $P < 0.001$ ) on day 7; normal values were regained by day 14 and thereafter there was no significant difference between test animals and controls.
<b>Conclusions</b>	NOAEL = 500 mg/kg bw
<b>Rev. note</b>	1. The information available is limited to the above. 2. 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-metabolising enzymes (especially 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.
<b>Reliability</b>	2.

## 5.6. Genetic Toxicity

### A Chromosomal Aberration

<b>Title</b>	Evaluation of the ability of linalylacetate to induce chromosome aberrations in cultured peripheral human lymphocytes
<b>Date of report</b>	June 22, 2000.
<b>GLP</b>	Yes.
<b>Reference</b>	19.
<b>Test substance</b>	Linalylacetate, purity 96.7%.
<b>Guideline</b>	OECD 473, 67/548/EEC B10, Draft EEC 23.07.1999.
<b>Stat. method</b>	Chi-square test.
<b>Test system</b>	<b>Cell line</b> Human lymphocytes. <b>Metabolic activation</b> Rat S9 mix (Aroclor 1254-induced). <b>Test concentrations</b> 10-180 µg/ml (based on precipitation).



**Controls** Negative: vehicle controls (DMSO).  
Positive: mitomycin-C (-S9), cyclophosphamide (+S9).  
**Procedure** -S9: 3 h exposure + 24 h fixation.  
24 and 48 h exposure + 24 and 48 fixation.  
+S9: 3 h exposure + 24 h fixation.  
3 h exposure + 48 h fixation.  
Colchicine was added for the last 3 hours.

**Results**

Exposure/fixation (h)	Metabolic activation	Doses evaluated [ $\mu\text{g/ml}$ ]	Aberrations [%]	Test result <sup>(A)</sup>
3/24	Without	33, 100, 130	0.5, 0.5, 1	-
3/24	With	100, 130, 180	2.5, 0.5, 3	-
3/48	With	100, 130, 180	1, 1.5, 0.5	-
24/24	Without	33, 100, 130	1.5, 1.5, 2.5	-
48/48	Without	56, 100, 130	3.5, 3, 1	-

(A) +/- : positive/negative result; positive controls gave expected responses.

**Conclusion** Not clastogenic.

**Rev. note** The 3.5% aberrations seen at the lowest examined dose (48 h treatment, 48 h fixation) was statistically significant. Since no increase was seen at the higher concentrations, it was considered to be without biological significance.

**Reliability** 1

**Critical study for SIDS endpoint**

**B Gene Mutation**

**Title** Mutagenicity evaluation of Ro 02-8282/000 in the Ames test

**Date of report** June 15, 1998.

**GLP** Yes.

**Reference** 12.

**Test substance** Linalyl acetate, purity 97.6% (solvent DMSO).

**Guideline** OECD 471, 79/831/EEC. B.14, ICH.

**Stat. method** Not performed.

**Test system** **Bacterial strains** TA97, TA98, TA100, TA1535 and TA102.

**Metabolic activation** Male rat liver S9 mix (phenobarbital/ $\beta$ -naphthoflavone induced).

**Test concentration** 5, 15, 50, 150 and 500  $\mu\text{g/plate}$  or tube (based on toxicity).

**Controls** Negative: vehicle (DMSO).

Positive:

Without activation: sodium azide (TA1535, TA100), ICR191 (TA97), 2 nitrofluorene (TA98), mitomycin C (TA102) and 2-aminoanthracene (all strains).

With activation: 2-aminoanthracene (all strains).

**Procedure** Plate incorporation and preincubation tests according to OECD 471.

**Results** Toxicity in the plate incorporation assay at  $\geq 500 \mu\text{g/plate}$ , in the preincubation test  $\geq 50 \mu\text{g/plate}$  (without S9) and  $\geq 100 \mu\text{g/plate}$  (with S9).

Tester strain	Test result <sup>(A)</sup>			
	Plate incorporation assay		Preincubation test	
	Without activation	With activation	Without activation	With activation
TA97	-	-	-	-
TA98	-	-	-	-
TA100	-	-	-	-
TA1535	-	-	-	-
TA102	-	-	-	-

(A) +/- : positive/negative result; positive controls gave expected responses.

**Conclusion** Not mutagenic.

**Rev. note** *Minor remark.* The initial number of cells (0.37-1.65E08) was only reported in an EEC-Sheet which was included in the report.

**Reliability** 1

**Critical study for SIDS endpoint**

**Title** An evaluation of food flavoring ingredients in a genetic toxicity screening battery  
**Date of report** 1989.  
**Reference** 36.  
**Test substance** Linalyl acetate, purity indicated.  
**GLP** No data.  
**Result** 63 substances were tested in the Ames test, mouse lymphoma test and in the UDS test. Linalylacetate was not among substances with a positive result in any of these tests  
**Rev. note** Abstract  
 It is not clear whether linalyl acetate was tested in the assay  
**Reliability** 4.

### 5.7. Carcinogenicity

**Title** Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice  
**Date of report** December 1973.  
**GLP** No.  
**Reference** 8.  
**Test substance** Linalyl acetate, purity  $\geq 85\%$ .  
**Guideline** Not indicated.  
**Stat. method** Chi-quadrat test, likelihood principle (Zweifel, 1966).  
**Test system** **Species** Mouse, (A/He), age 6-8 weeks, mean weight 18-20 g.  
**No. of animals** 30 females/treatment.  
**Dosage** 3-weekly injection (i.p.) for 8 weeks of 200 and 1000 mg/kg bw (total 24 doses  $\rightarrow$  4.8 and 24 g/kg bw); untreated and vehicle (tricaprylin) controls.  
**Observations** Body weights every 2 weeks.  
 At termination (24 weeks after study initiation):  
 Fixation of the lungs to count white nodules on the surface; macroscopic and microscopic examination of the lungs; macroscopy of liver, kidney, spleen, thymus, intestine and salivary and endocrine glands.

#### Results

Dose [mg/kg bw] \ effect	0 (untr.)	0 (veh.)	200	1000	DR
Mortality	2/50	3/80	6/30	4/30	
Body weight	Not reported				
Tumour bearing animals	8/50	16/80	4/30	4/30	

**Conclusions** No evidence of carcinogenic activity  
**Rev. note** 1. The report was limited to the above mentioned.  
 2. The test duration was too short for full development of possible carcinogenic effects. However, urethan used as a positive control showed a 100% response.  
 3. The number of animals in the treated groups was too small to allow proper statistical evaluation of the results. No histopathological evaluation of the tumours found was reported.  
 4. Dose selection was based on the maximum tolerated dose in 5 mice receiving 6 i.p. injections of the test substance over a 2-week period (recovery 1-2 months).  
 5. The route of administration is not representative for the possible routes of exposure (mainly dermal and/or inhalatory).  
**Reliability** 4 Route of exposure less suitable (note 5).

**Title** Cocarcinogenesis studies on mouse skin and inhibition of tumor induction.  
**Date of report** 1971.  
**Reference** 27.  
**GLP** No data.  
**Test substance** Linalyl acetate, purified by distillation.  
**Guideline** Not indicated.  
**Test system** **Species** ICR/Ha Swiss mice, age: 6-8 weeks; female.  
**Source** Millerton Research Farms, Millerton, N.Y.  
**No. of animals** 20/treatment.  
**Dosage** 3 mg linalyl acetate with and without 5  $\mu$ g benzo[a]pyrene; application by

micropipet in 0.1 ml acetone 3 times weekly for the duration of the experiment; controls: benzo[a]pyrene or acetone only and no treatment

	<b>Exposure period</b>	67 weeks.
<b>Investigations</b>		Tumors greater than 1 mm in diameter were counted; only tumors persisting for 30 days or more were counted in the cumulative totals. Animals bearing carcinomas were killed ca. 2 months after the tumors were classified as malignant. All animals were necropsied. Tumor specimens were analysed histologically.
<b>Results</b>		The available table states that coapplication of linalyl acetate and benzo[a]pyrene yields 10 papillomas and 4 carcinomas on the skin (it takes 276 days to the first papilloma). Application of benzo[a]pyrene alone takes 266 days to show the first papilloma and 8 papillomas and 1 carcinoma in total have been formed.
<b>Conclusions</b>		Linalyl acetate has weak cocarcinogenic activity.
<b>Rev. note</b>		1. The information in the report is limited to the above. 2. No necropsy data were presented. Histological evaluation is not reported.
<b>Reliability</b>		4.

## 5.8. Reproductive toxicity

### A Fertility

### B Developmental Toxicity

<b>Title</b>	Reproductive and developmental toxicity screening test of B10 administered orally via gavage to Crl:CD(SD)BR female rats.	
<b>Date of report</b>	April 12, 1989.	
<b>GLP</b>	Yes.	
<b>Reference</b>	22.	
<b>Test substance</b>	B10: essential oil of coriander containing 72.9% of natural linalool. Additional constituents were identified as 3.9% alpha-pinene, 0.6% camphene, 0.9% myrcene, 4.0% p-cymene, 2.7% limonene, 3.6% gamma-terpinene, 4.6% camphor, 0.8% alpha-terpineol and 1.2% geranyl acetate. The total of ingredients identified by gas chromatography is 95.5% (area-%), the reminder being minor peaks in the chromatogram.	
<b>Guideline</b>	US Food and Drug Administration (1966): Guidelines for reproduction studies for safety evaluation of drugs for human use.	
<b>Stat. method</b>	Not indicated.	
<b>Test system</b>	<b>Species</b>	Rat (Crl:CD(SD)BR), 71-day-old at gestation day 0, weight 228-383 g.
	<b>Source</b>	Charles River Laboratories.
	<b>No. of animals</b>	10 mated females/dose group.
	<b>Dosage</b>	Oral gavage at 0 (vehicle only), 250, 500 and 1000 mg/kg bw; the vehicle is corn oil.
	<b>Procedures</b>	Female rats were mated with untreated stock males (1/1) from the same strain and source. The day of observation of a vaginal plug or vaginal smear was defined as day 0 of gestation. Females were treated daily from 7 days prior to and subsequently through cohabitation, gestation, delivery and a 4-day lactation period. All dams were observed for clinical signs, death and/or delivery of a litter. Body weights were recorded during the whole dosage period. Feed consumption was determined on days 0, 6, 10, 14, 16, 20 and 25 of presumed gestation as well as on days 1 and 4 of lactation. On day 4, all females were subjected to macroscopic examination. All litters were examined for number, viability, body weight, sex ratio and external anatomy of the pups. Delivered pups were also examined for viability, clinical observations and body weight during the 4-day postpartum period.

#### Results

Dose (mg/kg bw)	0	250	500	1000	DR
<i>Maternal data</i>					
<b>Mortality</b>	0/10	0/10	1/10	0/10	
<b>Clinical signs</b>			+(A)	+(A),(B)	x
<b>Body weight gain</b>		ic	ic	dc/ic <sup>(C)</sup>	x

<b>Feed consumption</b>	ic	ic	dc/ic <sup>(C)</sup>	x
<b>Necropsy</b>	No treatment related effects			
<b>No. of pregnant females</b>	No treatment related effects			
<b>Duration of cohabitation</b>	No treatment related effects			
<b>No. of implantation sites /dam</b>	No treatment related effects			
<b>Duration of gestation</b>	No treatment related effects			
<b>No. live pups/ dam</b>			dc	x
<i>Foetal data</i>				
<b>No. of pups</b>			dc	x
<b>Pup sex ratio/ pup weight/gross morphology</b>	No treatment related effects			

(A) Excessive salivation (p<0.05).

(B) Urine-stained abdominal fur (p<0.01) during the pre-mating period, one or two showed ataxia and/or decreased motor activity during pre-mating and gestation.

(C) Significant decrease during pre-mating for high dosage group, and significant increase during gestation and small increase during lactation for all treated groups.

**Conclusions** NOAEL for maternal toxicity is 500 mg/kg/d based on body weight gain, feed consumption and clinical signs (equivalent to ~464 mg/kg bw linalyl acetate).  
NOAEL for developmental/reproductive toxicity is 500 mg/kg based on increased fetal mortality in utero and after parturition (equivalent to ~464 mg/kg bw linalyl acetate).

**Rev. note**

- Effects on offspring are only present at maternally toxic doses.
- The dose was converted to equivalent linalyl acetate, making a correction for the purity (72.9%) and the molecular weight.
- Males were not treated before mating.

**Reliability** 2

**Critical study for SIDS endpoint**

### 5.9. Other Relevant Information

**Title** Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents

**Date of report** 1967.

**GLP** No.

**Reference** 10.

**Test substance** Linalyl acetate, purity ≥ 90% or ≥ 96%.

**Guideline** Not indicated.

**Results** *Metabolism:*  
Probably hydrolysed to linalool and acetic acid. Linalool is converted to geraniol and its metabolites, 1,5-dimethyl-hexadien-1,6-dicarboxylic acid and 7-carboxy-5-methylocto-6-enoic acid.  
*Acute toxicity (oral):*  
Mouse: LD50 13360 mg/kg bw  
Rat: LD50 14550 mg/kg bw  
*Repeated dose:*  
Rat: 12 week feeding study: LOAEL 24.3 mg/kg (growth retardation)

ADI: 0.25 mg/kg bw.

**Rev. note** The repeated dose study was performed with mixed esters, without further explanation.

**Reliability** 4 Secondary literature

**Title** Occupational and environmental health hazard review: linalylacetate (Ro 02-8282)

**Date of report** 1981.

**GLP** No.

**Reference** 18.

**Test substance** Linalyl acetate.

**Guideline** Not applicable.

<b>Results</b>	<p><i>Acute oral (oral LD<sub>50</sub>):</i> Rat 14500 mg/kg bw. Mouse 13360 mg/kg bw, &gt;8000 mg/kg bw, 15000 mL/kg bw. <i>Skin irritation:</i> see ref. 11. Rabbit (5% solution): not irritating. <i>Subacute toxicity:</i> Rabbits were exposed by inhalation of steam containing 9 and 27 mg/kg H<sub>2</sub>O: effects at 27 mg/kg H<sub>2</sub>O consisted of weak bronchomucotropic action (some augmentation of volume output of respiratory tract fluid). <i>Chronic toxicity:</i> LOAEL female rats 24 mg/kg bw (growth inhibition). Linalyl cinnamate and linalylisobutyrate were fed in diet to rats during 17-18 weeks. No effect on growth, haematology and macro- and microscopic findings. <i>Carcinogenicity;</i> Not carcinogenic in strain A mice (ref. 8). Weak carcinogenic when applied simultaneously and repeatedly with benzo(a)pyrene.</p>
<b>Rev. note</b>	<p>ADI 0.25 mg/kg bw. 1. The report is limited to the above mentioned. 2. From the subacute toxicity study no actual dose levels can be established. 3. It is not clear whether the reported results from the chronic study came from a study with linalyl acetate.</p>
<b>Reliability</b>	<p>4 Secondary literature</p>
<b>Title</b>	Local anaesthetic activity of the essential oil of <i>Lavandula angustifolia</i> .
<b>Date of report</b>	1999.
<b>Reference</b>	25.
<b>Test substance</b>	Linalyl acetate, purity 43.6% as constituent of essential oil of <i>Lavandula angustifolia</i> and pure linalyl acetate, purity 97%.
<b>GLP</b>	No data.
<b>Result</b>	The local anaesthetic activity of the essential oil of <i>Lavandula angustifolia</i> is evaluated. 1. This essential oil and pure linalyl acetate (0.01-10 µg/ml) were able to drastically reduce, in a dose-dependent manner, the electrically evoked contractions of rat phrenic-hemidiaphragm. This finding excludes antimuscarinic activity of linalyl acetate. 2. A rabbit conjunctival reflex test treatment with a solution of the same test substances (30-2500 µg/ml administered in the conjunctival sac) results in a dose-dependent increase in the number of stimuli necessary to provoke the reflex (i.e. suppression of the reflex).
<b>Conclusion</b>	The local anaesthetic activity is not caused by antimuscarinic activity of these compounds, but is suggested to be related to effects on the Na <sup>+</sup> and /or Ca <sup>++</sup> channels.
<b>Rev. note</b>	Secondary literature (journal article)
<b>Reliability</b>	4.
<b>Title</b>	<i>In vitro</i> permeation through porcine buccal mucosa of <i>Salvia desoleana</i> Atzei & Picci essential oil from topical formulations.
<b>Date of report</b>	2000.
<b>Reference</b>	26.
<b>Test substance</b>	Linalyl acetate, 26.8% as constituent of essential oil of <i>S. desoleana</i> .
<b>GLP</b>	No data.
<b>Result</b>	In this article it was determined that permeation of the test substance through the porcine buccal mucosa is possible <i>in vitro</i> .
<b>Rev. note</b>	Secondary literature (journal article)
<b>Reliability</b>	4.
<b>Title</b>	Report on the hydrolysis of linalylacetate and ethylformate by artificial gastrointestinal juices
<b>Date of report</b>	April 1979.
<b>GLP</b>	No.
<b>Reference</b>	34.
<b>Test substance</b>	Linalyl acetate, purity not indicated.
<b>Test method</b>	Not specified.

**Procedure** Test system:  
Artificial gastric and pancreatic juices (made according to method of Longland, 1977)  
Method:  
Linalyl acetate was added to 110 mL gastric or pancreatic juices (37°C). At intervals 10 mL aliquots were removed and analysed by GC with FID.  
Half-lives were calculated from the exponential concentration vs. time curve (A) and using the least square method based on log concentration vs. time (B)

	Gastric		Pancreatic	
	Time (min)	Concentration (mg/mL)	Time (min)	Concentration (mg/mL)
	0	30	0	27
	2.5	16.6	2.1	7
	10.4	9.7	2.8	25
	17.6	5.8	17.6	16.6
	25.7	2.4	42.2	15.0
			76.6	10.4
			106.3	6.8
			136.2	4.1

**Conclusion** Half-life in gastric fluid 3.6 (A) and 7.3 (B) minutes  
Half-life in pancreatic fluid 52.2 (A) and 52.8 (B) minutes

**Rev. note** For gastric juices first order kinetics and for pancreatic juices zero order kinetics followed by first order kinetics. The first phase of the test in pancreatic fluids was assumed to be influenced by reduced solubility due to the less acidic environment compared to the situation in gastric fluids.

**Reliability** 2.

### 5.10. Experience with Human Exposure

**Title** Clinical toxicology of commercial products Acute poisoning  
**Date of report** 1981.  
**GLP** No.  
**Reference** 9.  
**Test substance** Oil of Bergamot, linalyl acetate 45%.  
**Guideline** Not applicable.  
**Results** Repeated skin exposure leads to nervous and digestive symptoms.  
Persons sensitive develop photodermatitis, eczema and pigment changes.  
**Rev. note** Statement, limited to the above mentioned.  
**Reliability** 4

**Title** Occupational allergy to lavender oil  
**Date of report** 1986  
**Reference** 28.  
**Test substance** Lavender oil (one of the constituents was linalyl acetate)  
**GLP** No data.  
**Result** Case study: a hairdresser showed a strong positive response in a patch test, both 48 and 96 hours after application of lavender shampoo. Lavender oil was the positive substance in the shampoo. The allergen of lavender oil has not been identified, but linalyl acetate is suspected (but was not tested).  
**Rev. note** Secondary literature (journal article)  
**Reliability** 4.

**Title** Health Hazard Evaluation Report  
**Date of report** 1983  
**Reference** 29.  
**Test substance** Lavender oil (main constituent linalyl acetate)  
**GLP** Not applicable  
**Result** For the exposure due to the use in oil paints, area sampling was requested by representatives of artists (painters and potters). 12 artists were interviewed and some of them complained about the odour of the paint and slight dermatitis (no area samples were taken).  
**Rev. note** The complaint was related to odour only and was withdrawn before the end of the project.  
**Reliability** 4.

	<b>Author</b>	<b>Title</b>	<b>Performing laboratory / source</b>	<b>Year</b>
1.	-	Linalyl acetate MSDS	Roche	1996
2.	-	Internal report	Roche	1979
3.	Schmiedel U.	Determination of the partition coefficient of linalylacetate in n octanol/water	RCC UmweltChemie AG	
4.	Calame R, Ronchi W.	Linalyl acetate activated sludge, respiration inhibition test	Givaudan	1989
5.	Grade R.	Report on the acute toxicity of linalylacetat on daphnia (Daphnia magna Strauss 1820)	Ciba-Geigy Ltd.	1993
6.	Grade R.	Report on the growth inhibition test of linalylacetat to green algae (Scenedesmus subspicatus)	Ciba-Geigy Ltd.	1994
7.	Rudio J.	Linalyl acetate synthetic determination of the ready biodegradability	Givaudan	1991
8.	Stoner G., Shimkin M., Kniazeff A., et al	Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A Mice	Cancer Research 33, 3069-3085	1973
9.	Gosselin R., Hodge H., Smith R., et al.	Clinical toxicology of commercial products Acute poisoning	Oil of Bergamot, 154	1981
10.	FAO	Toxicological evaluation of some flavouring substances and non-nutrtive sweetening agents	FAO Nutrition Meetings Report Series No. 44A	1967
11.	Motoyoshi K., Toyoshima Y, Sato M., et al.	Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man	Cosm. Toil. 94: 41-48	1979
12.	Kirchner S.	Mutagenicity evaluation of Ro-8282/000 in the Ames test	Roche	1998
13.	Bogers M.	96-hour acute toxicity study with linalylacetate (flow-through)	NOTOX	1998
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