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DECOS and SCG Basis for an Occupational Standard

Lactate esters

*Per Lundberg*

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### ARBETE OCH HÄLSA

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## Preface

An agreement has been signed by the Dutch Expert Committee on Occupational Standards (DECOS) of the Dutch Health Council and the Swedish Criteria Group for Occupational Standards (SCG) of the Swedish National Institute for Working Life. The purpose of the agreement is to write joint scientific criteria documents for occupational exposure limits. The numerical limits will be developed separately by The Netherlands and Sweden according to their different national policies.

The evaluation of health effects of Lactates is a product of this agreement. The draft document was written by Dr Per Lundberg at the Department of Occupational Medicine, National Institute for Working Life, Solna, Sweden. The document has been reviewed by the Dutch Expert Committee as well as by the Swedish Criteria Group.

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## 1. Introduction

Lactate esters (esters of lactic acid) are used as food additives, in pharmaceuticals and cosmetics and are currently finding new uses as solvents. Some esters have been used for many years as solvents for nitro and ethyl cellulose, gums, oils, dyes and in paints. The esters are potentially alternative solvents to glycol ethers and are non-ozone-depleting and biodegradable.

The main information on the toxicity of lactate esters has been presented in two recent reviews (9, 10).

## 2. Chemical Identification

Two enantiomeric isomers (mirror images) of lactate esters exist, the D- and the L-form. Often the two isomers are mixed to give the so called DL-form.

**Table 1.** Name, CAS number, formula and molecular weight for some lactate esters

Lactate	CAS nr	Formula	MW
Methyl	547-64-8 (27871-49-4)	C <sub>4</sub> H <sub>8</sub> O <sub>3</sub>	104.1
Ethyl	97-64-3 (687-47-8)	C <sub>5</sub> H <sub>10</sub> O <sub>3</sub>	118.1
Isopropyl	617-51-6 (63697-00-7)	C <sub>6</sub> H <sub>12</sub> O <sub>3</sub>	132.2
Propyl	616-09-1 (53651-69-7)	C <sub>6</sub> H <sub>12</sub> O <sub>3</sub>	132.2
sec-Butyl	18449-60-0	C <sub>7</sub> H <sub>14</sub> O <sub>3</sub>	146.2
Isobutyl	585-24-0 (702-84-0)	C <sub>7</sub> H <sub>14</sub> O <sub>3</sub>	146.2
n-Butyl	138-22-7 (34451-19-9)	C <sub>7</sub> H <sub>14</sub> O <sub>3</sub>	146.2
Isoamyl	19329-89-6	C <sub>8</sub> H <sub>16</sub> O <sub>3</sub>	160.2
Amyl	6382-06-5	C <sub>8</sub> H <sub>16</sub> O <sub>3</sub>	160.2
2-Ethylhexyl	6283-86-9 (186817-80-1)	C <sub>11</sub> H <sub>22</sub> O <sub>3</sub>	202.3
n-Octyl	5464-71-1 (5110-33-4)	C <sub>11</sub> H <sub>22</sub> O <sub>3</sub>	202.3
n-Decyl	42175-34-8 (51191-35-6)	C <sub>13</sub> H <sub>26</sub> O <sub>3</sub>	230.3
Lauryl	6283-92-7	C <sub>15</sub> H <sub>30</sub> O <sub>3</sub>	258.4
Myristyl	1323-03-1	C <sub>17</sub> H <sub>34</sub> O <sub>3</sub>	286.5
Cetyl	35274-05-6	C <sub>19</sub> H <sub>38</sub> O <sub>3</sub>	314.5

CAS numbers are for DL-forms of the esters. CAS number for the L-forms are given within parenthesis.

## 3. Physical and Chemical Properties

Physical and chemical properties are given for the main lactate esters for which effects are discussed in the document. For some other esters data on physical and chemical properties are given in the Appendix.

*Methyl lactate*

Melting point	- 66 °C
Boiling point	144 °C
Flash point	57 °C
Density	1.092 g/ml (20 °C)
Vapor pressure	0.34 kPa (20 °C); 23 kPa (100°C)
Saturation vapor concentration	3302 ppm (20°C)
Partition coefficient (log P <sub>octanol/water</sub> )	- 0.53
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 4.3 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.23 ppm

Methyl lactate is a colorless transparent liquid. It is soluble/miscible in water at room temperature. Methyl lactate is also soluble in alcohol and ether (10).

*Ethyl lactate*

Melting point	- 25 °C
Boiling point	153 °C
Flash point	61 °C
Density	1.033 g/ml (20 °C)
Vapor pressure	0.22 kPa (20 °C); 17 kPa (100 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	0.06
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 4.9 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.20 ppm

Ethyl lactate is at room temperature a colorless liquid with a mild, characteristic odor. Ethyl lactate is miscible in water, alcohols, ketones, esters, hydrocarbons, ether and oil (10). The odor threshold is reported to be 0.89 mg/m<sup>3</sup> and the odor nuisance threshold to be 65 mg/m<sup>3</sup> (9).

*Isopropyl lactate*

Boiling point	157 °C
Flash point	60 °C
Density	0.991 g/ml (20 °C)
Vapor pressure	0.17 kPa (20 °C); 15 kPa (100 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	0.39
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 5.5 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.18 ppm

Isopropyl lactate is soluble in water, alcohol, ether and benzene (10).

*Isobutyl lactate*

Boiling point	182 °C
Flash point	76 °C
Density	0.979 g/ml (20 °C)
Vapor pressure	0.05 kPa (20 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	1.10
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 6.1 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.165 ppm

Isobutyl lactate is soluble in water; 5.1 g/100 ml at 20 °C (9).

*n-Butyl lactate*

Melting point	- 43 °C
Boiling point	187 °C
Flash point	79 °C
Density	0.984 g/ml (20 °C)
Vapor pressure	0.03 kPa (20 °C); 4.7 kPa (100 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	1.10
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 6.1 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.165 ppm

n-Butyl lactate is at room temperature a water-white liquid with a mild odor. It is miscible with many lacquer solvents, diluents and oils. It is slightly soluble in water (4.5 g/100 ml), miscible in alcohol and ether, and hydrolyzes in acids and alkalis to lactic acid and butyl alcohol (10). The odor threshold is 0.095 mg/m<sup>3</sup> and the odor nuisance threshold is 9 mg/m<sup>3</sup> (9). In a review (2) the odor threshold for n-butyl lactate is reported as 7 ppm (42.6 mg/m<sup>3</sup>) but the actual source or basis is not cited.

*2-Ethylhexyl lactate*

Boiling point	246 °C
Flash point	113 °C
Density	0.940 g/ml (20 °C)
Vapor pressure	0.002 kPa (20 °C); 0.6 kPa (100 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	3.17
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 8.4 mg/m <sup>3</sup>

The solubility of 2-ethylhexyl lactate in water is 30 mg/100 ml (9). The odor threshold limit is reported as 0.45 mg/m<sup>3</sup> and the odor nuisance threshold as 40 mg/m<sup>3</sup> (9).

#### *Myristyl lactate*

Density	0.892 - 0.904 (25 °C)
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 11.9 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.08 ppm

Myristyl lactate is a white to yellow liquid or soft solid. Myristyl lactate is soluble in ethyl alcohol and propylene glycol, dispersible in mineral oil, and insoluble in water and glycerine (10).

#### *Cetyl lactate*

Melting point	23 - 41 °C
Boiling point	170 °C (at 2.8 10 <sup>-3</sup> kPa)
Density	0.893 - 0.905 (25 °C)
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 13.05 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.077 ppm

Cetyl lactate is a white to yellow soft waxy solid with a slight, characteristic, pleasant odor. It is soluble in ethyl alcohol and propylene glycol (10).

## 4. Occurrence, Production and Use

*Methyl lactate* is used as a cellulose acetate solvent (22).

*Ethyl lactate* is both a commercially produced and a naturally existing compound. Ethyl lactate is used as a solvent for nitrocellulose, cellulose acetate, and many cellulose ethers and resins. It is also used in lacquers, paints, enamels, varnishes, stencil sheets, safety glass and flavoring. Ethyl lactate is furthermore used in some cosmetic formulations in soaps, detergents, creams and lotions with a maximum concentration of 0.2 % (10). Ethyl lactate is reported to be found in apple, citrus fruits, pineapple, peas, sauerkraut, vinegar, bread, beer, grape brandy, rum, whisky, cider, sherry, wine, cocoa, banty beer, plum brandy and pear brandy. It has been approved by the US FDA for food use (4). According to earlier editions of Patty's Industrial Hygiene and Toxicology ethyl lactate was used for treatment of acne but this information has been withdrawn in the most recent edition (6). In recent years it has been used as degreaser as a substitute for trichloroethylene (8).

In Sweden the yearly import of *ethyl lactate* is about 23 tonnes in 22 different products. There is no information on other lactates (personal communication, Ulf Rick, Swedish Chemicals Inspectorate)

*Butyl lactate* is used as a solvent for nitrocellulose, ethyl cellulose, oils, dyes, natural gums, many synthetic polymers, lacquers, varnishes, inks, stencil pastes, anti skinning agent, dry-cleaning fluids, and adhesives. It is also used in cosmetic products up to a maximum concentration of 0.03 % (10). It has been approved by the US FDA for food use (3).

*Ethylhexyl lactate* has in recent years been used as degreaser (8).

*Myristyl lactate* functions as a skin-conditioning agent - emollient in a variety of cosmetic product categories. The concentrations are reported to range from >1.5 % in makeup and skin-care preparations to 15 % in eye shadow formulations. In the US myristyl lactate was (1984) used in 292 cosmetic formulations at a concentration of  $\leq 50$  %, usually in the range of 5 - 10 % (10).

*Cetyl lactate* is used as a non-ionic emollient and to improve the feel and texture of pharmaceutical preparations (22). Cetyl lactate functions as a skin-conditioning agent. In 1984 it was used in the US in 224 cosmetic formulations at a concentration of  $\leq 25$  %, usually in the range of 1 - 5 % (10).

## 5. Occupational Exposure

According to the Documentation of the TLVs (1), prolonged exposures to n-butyl lactate at concentrations of 7 to 11 ppm resulted in headache and irritation of the pharyngeal and laryngeal mucosa in all workers. The information is based on a personal written communication to the TLV Committee.

In a Swedish company, the average air concentration of ethyl lactate around degreasing of metal products was found to be 0.6 ppm. Around some operations near a cleaning tunnel the concentration was considerably higher and peaks close to 10 ppm were registered. The 8 h average, however, was calculated to be 4.2 ppm (8).

## 6. Sampling and Analysis of Substance at Work Place

For the two lactate esters, n-butyl lactate and ethyl lactate, the US OSHA has given information on sampling and analysis. In both cases charcoal tubes (100/50 mg sections, 20/40 mesh) are used for sampling. As solvent methylene chloride: methanol (95:5) is preferred. Maximal sampling volume is 10 L with a maximum flow of 0.2 L/min. For analysis gas chromatography (GC/FID) is used. According to the OSHA the method is partially validated, but no data are given (18).

The concentration of ethyl lactate in air can also be evaluated by using FTIR (Fourier-Transform Infra Red) spectrophotometry. By FTIR absorbance over a large portion of the IR-spectrum is registered. Obtained spectra are checked against a library of absorption spectra for different substances. The instrument uses a cuvette of 2.3 L volume and a fixed beam of 10 m (8).

## 7. Toxicokinetics

### 7.1. Uptake and distribution

There are no quantitative data on respiratory uptake of lactate esters. From animal inhalation studies it can be concluded that the esters, or the hydrolysis products, are taken up.

When a preparation containing ethyl [<sup>14</sup>C] lactate was applied to the skin of rats for up to 24 hours, most of the radioactivity was traced in sebaceous glands, but it appeared also in hair follicles, epidermis and dermis (19). Ethyl lactate was detected in portal blood of rats following intragastric instillation, indicating partial absorption before hydrolysis.

### 7.2. Biotransformation

Enzymatic hydrolysis of lactate esters to lactic acid and alcohol has been reported after oral administration as well as after skin application (7). The in vitro hydrolysis of various lactate esters in the rat nasal epithelium is demonstrated to be rapid (9). The in vitro and in vivo hydrolysis of ethyl lactate in the gastrointestinal tract of rats has also been demonstrated.

In an in vitro study, rat plasma hydrolyzed 80 % of ethyl lactate in 60 min at room temperature (9). In various rat tissue homogenates of the nasal epithelium, liver and skin the  $K_m$  values of ethyl lactate was similar (0.06-0.36 mM). The value in cecum was intermediate while blood and small intestinal mucosa showed high  $K_m$  values or first order kinetics (9).

The hydrolysis of 2-ethylhexyl lactate has been investigated in rat organs. The most rapid hydrolysis was observed in the intestinal mucosa followed by cecum, blood, and skin. The kinetic values for the blood were equal to the values for the nasal tissues (9).

Lactic acid/lactate ion is an endogenous metabolite. Effects of the hydrolysis products of lactate esters are shortly discussed in chapter 9.

### 7.3. Tissue clearance and elimination

There are no quantitative data of clearance and elimination of lactate esters. Due to the relatively rapid hydrolysis the elimination pathways are the same as for lactic acid and alcohols, respectively.

## 8. Methods of Biological Monitoring

Today, there is no suitable method described for biological monitoring of lactate esters.

## 9. Mechanisms of Toxicity

Lactic acid, the hydrolysis or metabolic product of all lactate esters, is a normal and natural metabolite in humans. Lactic acid toxicity is mainly related to its acidity. Concentrated lactic acid is a potential eye and skin irritant. The oral LD<sub>50</sub> is 3.73 g/kg body weight in rats and 1.81 g/kg in guinea pigs.

Alcohols, the other hydrolysis product of lactate esters, have generally a low acute toxicity but may produce mild eye and skin irritation at high concentrations. Specific alcohols have been reported to cause certain effects. Large doses of methyl alcohol can produce blindness and death. Ethyl alcohol is a developmental hazard in humans. Several 2-ethylhexyl compounds have been reported to be carcinogenic in animals, probably due to peroxisome proliferation (12). A toxicological evaluation of 2-ethyl-1-hexanol did not indicate genotoxicity nor carcinogenicity (11). An oral gavage study showed that ethylhexanol was not carcinogenic in rats but a weak trend of hepatocellular carcinomas was noted in high-dose mice (5).

## 10. Effects in Animals and in vitro Studies

### 10.1. Irritation and sensitisation

#### *Irritation*

Many lactate esters are irritating to the eye and skin, probably due to hydrolysis which produces lactic acid (9).

*Methyl lactate* has been classed as non-irritant to the eyes of guinea pigs (20). Besides in vivo eye irritation tests also an in vitro chicken enucleated eye test was conducted. Tests of ocular irritation have demonstrated that *ethyl lactate* in vivo causes moderate to severe irritation. *Propyl lactate* was shown to severely irritate the eye in vivo and had an irritative, probably corrosive, effect in vitro. Also *butyl* and *amyl lactate* caused severe irritation in the eye. *Lauryl lactate* caused in vivo minimal to mild irritation and in vitro minimal to moderate irritation. *Myristyl lactate* caused in vivo no to mild irritation and in vitro minimal to mild irritation and *cetyl lactate* caused in vivo no to severe irritation and in vitro minimal to mild irritation. For the in vivo studies albino rabbits were used and in the in vitro studies the Eyetex assay protocol was used (9, 10, 13).

No skin irritation was observed when the primary potential of a formulation containing 50 % *ethyl lactate* was evaluated in single insult patch test using rabbits (10). No irritation was reported when ethyl lactate was applied under occlusive gauze pads, 2 cm<sup>2</sup>, to the shaved abdominal skin of rabbits, but intradermal injection of 0.1 mL ethyl lactate into the shaved abdominal skin of guinea pigs produced severe irritation (13).

Application of *butyl lactate* to 10 rabbits produced moderate and marked erythema in eight and two animals, respectively, and slight and moderate edema in one and nine animals, respectively. The lactate was assumed to be applied undiluted under occlusive patches to intact and abraded skin for 24 hours (10).

No skin irritation was observed when *propyl lactate* or *isopropyl lactate* were tested (9).

Mild to minimal irritation was observed when the primary potential of two cosmetic formulations containing *lauryl lactate* was evaluated in single insult occlusive patch tests using rabbits. The same results were obtained when formulations containing *myristyl lactate* or *cetyl lactate* were tested. The maximum concentration of the lactate esters in the formulations was 12 % (10).

As a measure of cytotoxicity rabbit and human skin cell proliferation were determined in skin culture. The data indicate that human skin cells are less sensitive than rabbit skin cells. Furthermore, higher molecular weight esters seem to be more toxic than those with lower molecular weight (9).

In a sensory irritation study *ethyl* and *butyl lactates* were used in mice and rats. The  $RD_{50}$  values (50 % decrease in respiratory rate) for both esters were approximately 750 - 800 mg/m<sup>3</sup> (9).

### *Sensitisation*

The allergic contact sensitisation potential of *lauryl lactate* was evaluated in a modified Magnusson-Kligman maximization test using 10 female guinea pigs. The induction phase consisted of intradermal injections of 0.05 mL of 5 % lauryl lactate in propylene glycol, 50 % aq. Freund's adjuvant (FCA), and 5 % lauryl lactate and 50 % aq. FCA. One week after induction, a topical booster of 50 % lauryl lactate in petrolatum was applied to the induction site. Two weeks after the booster, occlusive patches of 5 and 25 % lauryl lactate in petrolatum were used for the challenge. At 72 hours after challenge, none of the animals had reacted to the 5 % concentration. With the 25 % challenge 30 % of the animals reacted (10).

The allergic contact sensitisation potential of a formulation containing 0.75 % *cetyl lactate* was evaluated in the same test system as above using 10 female guinea pigs. The induction phase was as above with 50 % of the formulation. One week after the induction, a topical booster of 100 % of the test formulation in petrolatum was applied. Two weeks after the booster, occlusive patches of 50 and 100 % of the test material in petrolatum were used for the challenge. The sites were scored 48 and 72 hours after patch application. None of the animals reacted and a formulation containing 0.75 % cetyl lactate was not considered a sensitizer (10).

These high molecular lactate esters are probably not sensitizers.

## **10.2. Effects of single exposure**

In acute inhalation studies using rats exposed nose-only for 4 hours, the target concentration was 5000 mg/m<sup>3</sup>. Clinical observations, mortality, body weights and gross pathological changes were recorded during a 14 day observation period. Clinical signs indicated acute irritation but no mortality was noted. The 4 h  $LC_{50}$  was for all tested lactate esters above 2400 mg/m<sup>3</sup>. The esters tested were methyl-, ethyl-, butyl-, isobutyl-, and isoamyl-ester (9).

Oral  $LD_{50}$  has been determined in rats for several lactate esters. No mortality was seen for any lactate ester at 2000 mg/kg body weight, the highest concentration

tested (9). The oral LD<sub>50</sub> for rats of a nail enamel corrector formulation containing 50 % *ethyl lactate* was determined in studies where fasted female rats were given 5, 10 or 15 g/kg body weight. There were no deaths at 5 g/kg, 4 deaths of 5 rats at 10 g/kg and all animals in the highest dose group died. The LD<sub>50</sub> was calculated to be 8200 mg/kg body weight (10).

Using 10 rats the oral LD<sub>50</sub> of *ethyl lactate* was >5000 mg/kg body weight. One animal died during the 14-day observation period (10). In another study the LD<sub>50</sub> of ethyl lactate for white mice was 2.5 mL/kg ( $\approx$  2.6 g/kg bw) and the LD<sub>100</sub> was 4.0 mL/kg ( $\approx$  4.1 g/kg bw). The minimum toxic dose (producing hypnotic signs in one of four mice) was 0.4 mL/kg ( $\approx$  0.4 g/kg bw) and the maximum non toxic dose was 0.2 mL/kg ( $\approx$  0.2 g/kg bw) (13).

For toxicological experiments esters were injected intramuscularly into the upper part of the leg of guinea pigs. The animals were observed continuously for several hours and then examined daily for a week. Lactate esters used in this unusual type of study were *ethyl lactate* and *isopropyl lactate*. For ethyl lactate a given dose of 2.5 mL/kg ( $\approx$  2.6 mg/kg bw) was lethal. At 1.0 mL/kg ( $\approx$  1.0 g/kg bw) the animals had labored respiration and were dyspneic. For isopropyl lactate the lethal dose was the same 2.5 mL/kg ( $\approx$  2.5 g/kg bw). At the given dose of 1.25 mL/kg ( $\approx$  1.25 g/kg bw) the animals demonstrated lack of muscular control (14).

When 5 g/kg body weight of *butyl lactate* was given orally to 10 rabbits there were no deaths, demonstrating that the LD<sub>50</sub> >5000 mg/kg body weight (10).

The acute oral toxicity of a number of freshener formulations containing *lauryl lactate* has been evaluated. In all cases was the LD<sub>50</sub> >5000 mg/kg body weight. Similarly the rat oral LD<sub>50</sub> for formulations containing *myristyl lactate* was >10000 mg/kg body weight. The same results were obtained with formulations containing *cetyl lactate* (10).

Acute dermal toxicity has been tested in rats at 2 g/kg body weight. Slight dermal encrustation was noted in one third of the rats on day 3. No mortality or gross treatment-related necropsy observations were observed (9).

There were no deaths during a 7-day observation period in 10 rabbits when 5 g/kg body weight of *ethyl lactate* was applied to the skin. Thus, the dermal LD<sub>50</sub> was >5000 mg/kg body weight. The maximum tolerated dose applied to mouse skin was 250 mg/kg body weight (10).

When 5 g/kg body weight of *butyl lactate* was applied to the skin of 10 rabbits there were no deaths. The dermal LD<sub>50</sub> was, thus, >5000 mg/kg body weight (10).

The estimated average lethal dose for the female rat following i.p. injection of *methyl lactate* was >2000 mg/kg body weight. Observations included narcosis, respiratory distress and peritoneal adhesions. The estimated non toxic dose and estimated maximum dose without gross lesions at necropsy was 500 mg/kg body weight (20).

Approximately 1000 mg/kg body weight was the estimated average lethal dose for the female rat following i.p. injection of *ethyl lactate*. The estimated maximum non toxic dose was 750 mg/kg body weight and the estimated maximum dose without gross lesions at necropsy was >500 mg/kg body weight (20).

The subcutaneous LD<sub>50</sub> of *ethyl acetate* for white mice was 2.5 mL/kg body weight ( $\approx$  2.6 g/kg bw), and the i.v. LD<sub>50</sub> was 0.6 mL/kg body weight ( $\approx$  0.6 g/kg bw). The maximum non toxic dose after s.c. administration was 0.8 mL/kg ( $\approx$  0.8 g/kg bw) and after i.v. administration 0.2 mL/kg body weight ( $\approx$  0.2 g/kg bw) (13).

### 10.3. Effects of short-term exposure

Inhalation studies have been conducted in rats, where groups of males and females were exposed during 28 days, 5 days/week, 6 h per day. Two studies were conducted on *ethyl lactate*. In one of the studies the exposure levels were 0, 150, 600 or 2500 mg/m<sup>3</sup> and in the other 0, 25, 75 or 200 mg/m<sup>3</sup>. No treatment-related clinical signs, changes in body or organ weights (e.g. increased adrenal and testes weights), hematology or biochemistry were observed in doses up to 600 mg/m<sup>3</sup>. In the highest dose group decreased body weight gain, decreased absolute liver weight, decreased food consumption and increased blood glucose (males) were significantly different from the control. At the two highest concentrations degenerative changes of the nasal olfactory epithelium were seen, and in addition hyperplasia of the goblet cells (9). See also Table 2 in chapter 12.

In a similar study *isobutyl lactate* was tested at 0, 100, 200, 400 or 800 mg/m<sup>3</sup>. Hyperplasia of the nasal respiratory epithelium was noted in all animals at 800 mg/m<sup>3</sup> and most animals at 400 mg/m<sup>3</sup>. At the highest dose level disarrangement of the nasal olfactory epithelium was noted in 60 % of the animals. No other treatment-related changes were reported (9). See also Table 2 in chapter 12.

When *n-butyl lactate* was tested at 0, 75, 200 or 600 mg/m<sup>3</sup> in a similar way, only slight focal hyperplasia of the nasal epithelium was seen in the highest dose group. No other treatment-related effects were reported (9). See also Table 2 in chapter 12.

In a 28-day study an aerosol of *2-ethylhexyl lactate* was used. Groups of rats of both sexes were exposed 5 days/week, 6 h per day to 0, 75, 200, 600 or 1800 mg/m<sup>3</sup>. Histopathological changes of the respiratory tract were observed in all treated groups. In the lowest exposure group changes were seen only in the nasal cavity, but in all other treated groups also larynx, trachea and lungs showed changes. In the highest exposure group a doubling of peroxisome proliferation was observed. In a follow-up, comparative study groups of male rats were exposed to an aerosol or vapors of 2-ethylhexyl lactate. The concentration was 75 mg/m<sup>3</sup> and the rats were exposed nose-only for 4 weeks, 5 days/week, 6 h per day. The effects of aerosol exposure were similar to the previous study, slight focal hyperplasia of the nasal respiratory epithelium. The response was less in the vapour exposed animals (9). See also Table 2 in chapter 12.

Groups of 20 Sprague-Dawley rats, 10 per sex, were dosed orally with 0, 0.5, 2.5 or 5.0 mg/kg body weight *myristyl lactate* 5 days/week for 13 weeks. All animals survived. Body weight gain was significantly decreased in males in the high dose group. Statistically significant changes were observed in some clinical chemistry values especially in the high dose group. At necropsy, three males of the

high dose group, one of the mid-dose group and three females of the high dose group had enlarged livers. Liver weight was significantly increased in males and females of the two highest dose groups. Dose-related effects were also seen in the gastrointestinal tract, including enlargement or thickening of the walls of the stomach and duodenum. At microscopic examination of selected tissues, alterations found included a dose-related diffuse mucosal hyperplasia in the duodenum of treated animals, inflammatory and/or proliferative lesions in the non-glandular stomach of several mid- and high-dose rats, and hepatic changes, primarily Kupffer cell hypertrophy and a slight disorganization of hepatic cords in some areas, in four males and three females of the high-dose group. The researchers concluded that "because of the exaggerated conditions used in the study, myristyl lactate is considered safe for use in oral area cosmetic products" (10).

A group of 15 female rats were used to determine the toxicity of a lipstick formulation containing 7.5 % *cetyl lactate*. The animals were dosed orally with 1000 mg/kg of the formulation in corn oil once daily 5 days/week for 6 weeks. The control animals received corn oil. The serum alkaline phosphatase values were significantly increased in dosed animals. Also the kidney weights were significantly greater than in controls. None of these differences were considered toxicologically significant. All other measurements were similar between the groups and no microscopic lesions were found (10).

A group of 15 male rats were used to determine the dermal toxicity of an after-shave moisturizer containing 0.75 % *cetyl lactate*. The formulation at a dose of 1870 mg/kg body weight was applied by gentle inunction to a shaved dorsal site once daily 5 days/week for 13 weeks for a total of 68 doses. No statistically toxicologically significant differences between dosed animals and controls were observed. Similarly, the dermal toxicity of a moisturizing cream formulation containing 1 % cetyl lactate has been tested. The total dose of the formulation was 920 mg/kg body weight given as 67 applications. No toxicologically significant differences between dosed animals and controls were found (10).

*Ethyl lactate* was reportedly a good energy source and enhanced growth in a group of 8 male weanling rats fed a diet containing 5 % of this ester (approximately equivalent to 5 g/kg bw) over a period of 12 days. One of 8 animals died during the course of the experiment. There was no indication of the cause of death. No adverse effects were observed in the surviving animals (23, 24).

#### **10.4. Effects of long-term exposure and carcinogenicity**

No data available.

#### **10.5. Mutagenicity and genotoxicity**

*Ethyl lactate* has been tested for mutagenicity in the Ames test using the strains TA 98, 100, 1535, 1537 and 1538 with and without metabolic activation. No mutagenic activity was observed in any tester strain. Lack of mutagenic activity has also been demonstrated for *2-ethylhexyl lactate* in *Salmonella* or *E. coli* bacteria (9).

## 10.6. Reproductive and developmental toxicity

*Ethyl lactate* was applied percutaneously on the back of groups of pregnant rats on days 6 to 15 of gestation. Applied doses were 0, 517, 1551 or 3619 mg/kg body weight. Slight erythema and desquamation was observed in treated animals at the application site. No other clinical signs or necropsy observations were noted. No effects were observed on the development (9).

Pregnant rats were exposed to an aerosol of *2-ethylhexyl lactate*. Twelve rats per group were exposed for 6 hours per day from day 6 to 15 of gestation for 0, 200 or 600 mg/m<sup>3</sup>. There were no signs of maternal toxicity. The only treatment-related effect was a significant reduced feed consumption at 600 mg/m<sup>3</sup> and a slight decrease in the low-dose group. Delayed ossification of the frontalis, metatarsals, and hind limb phalanges was observed in both treatment groups. These effects were regarded as related to stress rather than the manifestation of toxicity by the ester itself (9).

## 10.7. Immunotoxicity

No data available.

# 11. Observations in Man

## 11.1. Effects by contact and systemic distribution

The lack of data suggest that lactate esters in general are not skin sensitizers. However, a single case of skin sensitisation has been reported where *ethyl lactate* was used as a component in an acne medicine (9). This is probably the same case as that of Marot et al who reported a case of allergic contact dermatitis to *ethyl lactate*. A gel containing 10 % ethyl lactate as the active ingredient gave acute rash on the cheeks, diagnosed as allergic contact dermatitis. Patch tests performed six weeks later, gave a positive response to the gel and to 1 % ethyl lactate in petrolatum. Control patients were all negative (16).

A 44-year-old woman had applied a moisturizing cream daily to her face for at least 5 years. For the past three months, itching had occurred a few hours after application and for the past 2 weeks there had been dermatitis on her face. She was patch tested with the ingredients of the cream, including myristyl lactate 0.5 % /maleated soybean oil 1.5 % and *myristyl lactate* 0.5 %. The patient showed a positive reaction to myristyl lactate/maleated soybean oil. Myristyl lactate gave a negative response. No reactions were seen in 20 control persons. The authors suggest that maleated soybean oil was the cause of this allergic reaction (21).

## 11.2. Effects of repeated exposure on organ systems

An unpublished report to the ACGIH TLV-committee states that prolonged exposure to *n-butyl lactate* at concentrations of about 7 ppm ( $\approx$  43 mg/m<sup>3</sup>) with

short peak exposures of 11 ppm ( $\approx 67 \text{ mg/m}^3$ ) resulted in headache and irritation of the pharyngeal and laryngeal mucosa with coughing in all workers. Some workers complained of sleepiness and headache after work. Occasional nausea and vomiting were experienced. Complaints of irritation of the conjunctiva were not confirmed by examination. Blood and urine routine clinical analyses were normal. Some of the symptoms (headache, coughing, pharyngitis) were related to an air concentration of 4 ppm ( $\approx 24 \text{ mg/m}^3$ ) measured by personal monitoring. No signs of symptoms were seen when the concentration was below 1.4 ppm ( $\approx 8 \text{ mg/m}^3$ ) (1).

In a subsequent study, unpublished, using improved analytic methods it was stated that levels of 7 ppm ( $\approx 43 \text{ mg/m}^3$ ) n-butyl lactate did produce a readily discernible odor, but was not found to be injurious or objectionable (1).

### **11.3. Genotoxic effects**

No data available.

### **11.4. Carcinogenic effects**

No data available.

### **11.5. Reproductive and developmental effects**

No data available.

## **12. Dose-Effect and Dose-Response Relationships**

For many of the lactate esters toxicological data are very sparse and it is not possible to describe a dose-effect and/or a dose-response relationship.

There are practically no human data which can be used for evaluation of dose-effect and dose-response relationships.

Data from animal inhalation studies are summarized in Table 2.

The  $\text{RD}_{50}$  for *ethyl lactate* as well as for *n-butyl lactate* has been estimated to be 750-800  $\text{mg/m}^3$  both for rats and mice.

In studies where *myristyl lactate* was given orally to rats, liver weights were significantly increased at a daily dose of 2.5  $\text{mg/kg}$  body weight or above. The NOAEL for oral exposure to myristyl lactate was found to be 0.5  $\text{mg/kg}$  body weight.

**Table 2.** Effects of some lactate esters on rats exposed 28 days, 5 days/week, 6 hours/day. (From ref 9)

Lactate	Exposure		Effect
	mg/m <sup>3</sup>	ppm	
ethyl (vapor)	2500	500	Significantly decreased body weight gain Significantly decreased absolute liver weight Significantly decreased food consumption Significantly increased blood glucose Degenerative changes of nasal olfactory epithelium Hyperplasia of goblet cells
	600	120	Degenerative changes of nasal olfactory epithelium Hyperplasia of goblet cells
	200	40	NOAEL
n-butyl (vapor)	600	99	Slight focal hyperplasia of nasal epithelium
	200	33	NOAEL
isobutyl (vapor)	800	132	Disarrangements of nasal olfactory epithelium Hyperplasia of nasal respiratory epithelium
	400	66	Hyperplasia of nasal respiratory epithelium
	200	33	NOAEL
2-ethylhexyl (aerosol)	1800	216	Histopathological changes in nose, larynx, trachea, lungs Doubling of peroxisome proliferation
	600	72	Histopathological changes in respiratory passages
	200	24	Histopathological changes in respiratory passages
	75	9	Histopathological changes in nasal cavity LOAEL
(vapor)	75	9	Focal hyperplasia of nasal respiratory epithelium LOAEL

### 13. Previous Evaluations by (Inter)national Bodies

ACGIH in their documentation for the TLV<sup>®</sup> of *n-butyl lactate* recommends a TWA occupational exposure limit of 5 ppm as levels below 7 ppm were not injurious to workers. The level of 5 ppm is recommended to prevent irritation of mucosa and headache. The recommendation is mainly based on unpublished written communications to the TLV committee (1).

The Swedish Criteria Group in 1995 conclude in their consensus report on "Lactates" that available data are too sparse to allow a dose-response or dose-effect relationship to be identified. The little amount of data indicate that the critical effect of occupational exposure to n-butyl lactate and ethyl lactate is irritation of mucous membranes. For other lactates there are no data indicating a critical effect (15). Based on given scientific and other information an OEL of 5 ppm was adopted by the Swedish National Board of Occupational Safety and Health for the two lactates (17).

## 14. Evaluation of Human Health Risks

### 14.1 Groups at extra risk

No special occupational or constitutional groups seem to be at extra risk by occupational exposure to lactate esters.

### 14.2 Scientific basis for an occupational exposure limit

The lactate esters are not very toxic. In animal inhalation studies the NOAEL for ethyl-, n-butyl- and isobutyl lactate is 200 mg/m<sup>3</sup>. Of the lactate esters tested in rats only 2-ethylhexyl gave an effect on the nose at a lower dose and a LOAEL for this ester is 75 mg/m<sup>3</sup>. Also the 4 h LC<sub>50</sub> value for all esters tested is above 2400 mg/m<sup>3</sup> and the oral LD<sub>50</sub> values have been more than 2 g/kg body weight.

In studies where *myristyl lactate* was given orally to rats, liver weights were significantly increased at a daily dose of 2.5 mg/kg body weight or above. The NOAEL for oral exposure to myristyl lactate was found to be 0.5 mg/kg body weight.

The similarities in toxicity response for low molecular weight lactate esters suggest that the acidity of lactic acid is most likely the cause of toxicity. For high molecular weight lactate esters also the exposure to aerosol must be of concern.

In humans only one study is reported which implies effects. The study reports effects after exposure to n-butyl lactate at levels above 7 ppm ( $\approx 43$  mg/m<sup>3</sup>), but it does not give any details and has not been published.

Based on the limited amount of data it is concluded that the critical effect for occupational exposure to lactate esters is irritation of the mucous membranes in nose and throat. The effect is probably due to lactic acid.

## 15. Research Needs

The lack of studies for several lactate esters implies that studies should be performed, although most of the lactate esters seem not to be very toxic.

No carcinogenesis studies have been reported. Such a study might be of interest for 2-ethylhexyl lactate as an increase in peroxisome proliferation has been seen in rats exposed for 28 days. On the other hand the mechanism of carcinogenicity from peroxisome proliferators is probably not of interest in the human situation.

## 16. Summary

Lundberg P. Lactate esters. DECOS and SCG Basis for an Occupational Standard. *Arbete och Hälsa* 1999;9:1-21.

Lactate esters (esters of lactic acid) are used as food additives, in pharmaceuticals and cosmetics and are currently finding new uses as solvents. Lactate esters are hydrolyzed to lactic acid and alcohol. Lactic acid is a normal metabolite in humans. The toxicity of lactate esters is most likely due to the acidity of lactic acid. Based on animal data the critical effect of occupational exposure to lactate esters is irritation of the mucous membranes in nose and throat. Only unpublished studies in humans are available.

*Keywords:* Hazard assessment, Irritation, Lactate esters, Lactic acid, Occupational Exposure Limit, Toxicity.

## 17. Summary in Swedish

Lundberg P. Lactate esters. DECOS and SCG Basis for an Occupational Standard. *Arbete och Hälsa* 1999;9:1-21.

Laktatestrar (mjölksyrestrar) används som additiv till matvaror, i farmaceutiska och kosmetiska produkter och på senare tid som lösningsmedel. Estrarna hydrolyseras till mjölksyra och alkohol. Mjölksyra är en naturlig metabolit i människokroppen. Laktatestrarnas toxicitet beror troligtvis på mjölksyrans surhetsgrad. Baserat på djurdata är den kritiska effekten vid yrkesmässig exponering för laktatestrar irritation av slemhinnor i näsa och svalg. För människa finns endast opublicerade studier.

*Nyckelord:* Hygieniskt gränsvärde, Irritation, Laktatestrar, Mjölksyra, Riskbedömning, Toxicitet.

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## 19. Data Bases Used in Search for Literature

In the search for literature the following data bases were used:

- NIOSHTIC
- Cancerline
- Chemical Abstracts
- Medline
- Toxline
- RTECS

The latest search was performed in October, 1998, at the library of the Swedish National Institute for Working Life. In order not to miss any references the only search-words used were the CAS numbers and the names of the substances.

# Appendix

Physical and chemical properties for some of those lactate esters where data on effects are scarce or missing.

## *Propyl lactate*

Boiling point	170 °C
Flash point	69 °C
Density	1.005 g/ml (20 °C)
Vapor pressure	0.11 kPa (20 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	0.51
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 5.5 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.18 ppm

Propyl lactate is miscible with water at room temperature (9).

## *sec-Butyl lactate*

Boiling point	174 °C
Flash point	70 °C
Density	0.973 g/ml (20 °C)
Vapor pressure	0.11 kPa (20 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	1.01
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 6.1 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.165 ppm

Sec-butyl lactate is soluble in water; 14.4 g/100 ml at 20 °C (9).

## *Isoamyl lactate*

Boiling point	202 °C
Flash point	85 °C
Density	0.961 g/ml (20 °C)
Vapor pressure	0.02 kPa (20 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	1.62
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 6.8 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.15 ppm

Isoamyl lactate is slightly soluble in water; 0.3 g/100 ml (9).

*Amyl lactate*

Boiling point	207 °C
Flash point	87 °C
Density	0.964 g/ml (20°C)
Vapor pressure	0.01 kPa (20 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	1.62
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 6.8 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.15 ppm

Amyl lactate is slightly soluble in water at room temperature; 0.3 g/100 ml (9).

*n-Octyl lactate*

Boiling point	258 °C
Flash point	126 °C
Density	0.943 g/ml (20 °C)
Vapor pressure	0.0001 kPa (20 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	3.17
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 8.4 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.12 ppm

The solubility of n-octyl lactate in water is 30 mg/100 ml (9).

*n-Decyl lactate*

Boiling point	283 °C
Flash point	136 °C
Density	0.942 g/ml (20 °C)
Vapor pressure	0.0002 kPa (20 °C)
Partition coefficient (log P <sub>octanol/water</sub> )	4.21
Conversion factor (20 °C; 101.3 kPa)	1 ppm = 9.4 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.106 ppm

The solubility of n-decyl lactate in water is 20 mg/100 ml (9).