Lactate esters

Health-based recommended occupational exposure limit

Aanbiedingsbrief

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Health-based recommended occupational exposure limit

report of the Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of The Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

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Samenvatting en advieswaarde

Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in lucht op de werkplek waaraan beroepsmatige blootstelling kan plaatsvinden. Deze aanbevelingen vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden (MAC-waarden).

In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan lactaatesters en presenteert zij, indien mogelijk, een gezondheidskundige advieswaarde voor die stoffen.

Het voorliggende rapport over lactaatesters is tot stand gekomen in samenwerking met de Zweedse Criteria Groep, die de Zweedse regering van advies dient. Het gezamenlijke rapport over de gezondheidskundige implicaties van blootstelling aan lactaatesters, dat in 1999 in Zweden is gepubliceerd, is opgenomen in deel 2 van dit advies. Deel 1 bestaat voornamelijk uit een gezondheidskundige risicobeoordeling door de Commissie WGD.

De conclusies van de commissies zijn gebaseerd op wetenschappelijke publicaties die vóór december 1998 zijn verschenen. Wetenschappelijke publicaties verschenen tussen 1998 en 2000 gaven de commissie geen aanleiding haar aanbevelingen te wijzigen.

Fysische en chemische eigenschappen

Er zijn vijftien verschillende lactaatesters, met een molekuulmassa variërend van 104,1 tot 314,5. De meeste lactaatesters zijn vluchtige vloeistoffen met een karakteristieke geur. De kleur van de individuele lactaatesters varieert tussen transparant, wit en geel. De laagmolekulaire lactaatesters zijn oplosbaar in water, terwijl de hoogmolekulaire lactaatesters vooral goed oplossen in alcoholen.

Lactaatesters worden gebruikt in de voedings-, geneesmiddelen- en cosmetica industrie, als onder andere oplosmiddel en ontvetter.

Monitoring

Bij normale temperatuur en luchtdruk zijn sommige lactaatesters dampvormig en komen enkele anderen als aerosol- of stofdeeltje voor. Bij bemonstering van lucht moet hiermee rekening worden gehouden.

Damp- of gasvormige lactaatesters kunnen met een koolstofbuisje worden gevangen, terwijl aerosol- of stofdeeltjes bemonsterd kunnen worden met een gravimetrische techniek. Over het bepalen van de hoeveelheid bemonsterde lactaatesters is weinig bekend. Alleen voor de dampvormige n-butyl- en ethyllactaat is een gaschromatografische analysemethode (GC/FID) beschreven.

Methoden voor biologische monitoring zijn niet bekend.

Grenswaarden

Op dit moment vigeert in Nederland voor n-butyllactaat (CAS no. 138-22-7) een bestuurlijke MAC-waarde van 25 mg/m^3, gemiddeld over een achturige werkdag. Ook de ACGIH (VS) heeft deze waarde voorgesteld. Verder geldt in Zweden een beroepsmatige blootstellingslimiet (OEL) van 25 mg/m^3 voor n-butyl- en ethyllactaat. Voor de andere lactaatesters bestaan geen beroepsmatige grenswaarden.

Kinetiek

Er zijn geen kwantitatieve humane gegevens over de opname van lactaatesters via luchtwegen, mond en huid. Dierexperimentele onderzoeken hebben echter aangetoond dat lactaatesters, of hun afbraakproducten, worden opgenomen na inademing. Verder is ethyllactaat aangetroffen in bloed van ratten die deze stof via de maag ingebracht hebben gekregen.

Lactaatesters worden in het lichaam omgezet in melkzuur en alcohol. Dit kan snel gaan en al plaatsvinden waar lactaatesters voor het eerst in contact komen met het lichaam, zoals in de neus bij inademing. Hoewel niet duidelijk is hoe lactaatesters zich verdelen over het lichaam, is uit laboratoriumexperimenten wel bekend dat verschillende organen, waaronder bloedplasma, slijmvliezen van de dunne en dikke darm en de huid in staat zijn ethyllactaat af te breken.

Er zijn geen kwantitatieve gegevens over de uitscheiding van lactaatesters, maar door de relatief snelle omzetting zal de uitscheiding vergelijkbaar zijn met die van melkzuur en alcohol.

Effecten

Er zijn geen epidemiologische gegevens beschikbaar van werknemers die zijn blootgesteld aan lactaatesters. Tot nu toe is slechts één geval gepubliceerd van contactdermatitis na het opbrengen van een gel met 10% ethyllactaat in een vrijwilligersstudie.

Dierexperimenteel onderzoek wijst uit dat veel (L)-lactaatesters oog- en huidirritaties kunnen veroorzaken. Volgens *in vitro* onderzoeken variëren de uitkomsten van zeer sterk irriterend tot corrosief voor propyl-, butyl- en amyllactaat, tot matig prikkelend voor ethyl-, 2-ethylhexyl- en octyllactaat.

Er zijn inhalatie-onderzoeken uitgevoerd met zowel mannelijke als vrouwelijke ratten (n=5/sexe), die gedurende 28 dagen (5 dagen/week, 6 uur/dag) zijn blootgesteld aan verschillende concentraties ethyl-L-lactaat (25, 75, 150, 200, 600 of 2500 mg/m^3), n-butyl-L-lactaat (75, 200 of 600 ,g/m^3), isobutyl-L-lactaat (100, 200, 400 of 800 mg/m^3) of 2-ethylhexyl-L-lactaat (75, 200, 600 of 1800 mg/m^3) in de lucht. Het geen-waargenomen-nadelig-effect-niveau (NOAEL) van zowel ethyl-L-lactaat, als n-butyl- en isobutyl-L-lactaat was 200 mg/m^3. Hogere luchtconcentraties resulteerde in irritaties van het neusslijmvlies. Het hoogmolekulaire 2-ethylhexyl-L-lactaat (aerosol) is toxischer dan de drie laagmolekulaire lactaatesters (dampen), in die zin dat bij alle gebruikte luchtconcentraties afwijkingen zijn waargenomen in de neusholte, keelholte en de longen. Bij 75 mg/m^3 was dit beperkt tot afwijkingen in de neusholte. Voor 2-ethylhexyl-L-lactaat is een laagst-waargenomen-nadelig-effect-niveau (LOAEL) vastgesteld van 75 mg/m^3.

Verder zijn twee onafhankelijke onderzoeken gepubliceerd waarin ratten oraal werden blootgesteld met myristyl- en cetyllactaat. In het onderzoek waarin myristyllactaat (0.5, 2.5 of 5 mg/kg lichaamsgewicht/dag) werd gegeven gedurende 13 weken (5 dagen/week), werd een NOAEL van 0.5 mg/kg lichaamsgewicht/dag vastgesteld. Hogere doseringen leidde tot leververgroting, gecombineerd met een groter levergewicht. In het andere onderzoek werd 75 mg/kg lichaamsgewicht

cetyllactaat gegeven aan vrouwelijke ratten gedurende 6 weken (5 dagen/week). Na die periode werd een verhoogde alkalische fosfatase activiteit in het plasma en een gewichtstoename van de nieren vastgesteld, hoewel dit laatste niet gepaard ging met histopathologische afwijkingen. De commissie stelt voor 75 mg/kg lichaamsgewicht als LOAEL voor 2-ethylhexyllactaat te beschouwen.

Gegevens over effecten na langdurige blootstelling en over mogelijke kankerverwekkende eigenschappen van lactaatesters ontbreken geheel. Ethyl- en 2-ethylhexyllactaat scoorden negatief in bacteriële mutageniteitsproeven. Van de andere lactaatesters zijn geen mutageniteitsgegevens bekend.

Effecten op het nageslacht zijn bestudeerd in twee onderzoeken waarin zwangere ratten respectievelijk ethyl-L-lactaat intradermaal (527, 1551 of 3619 mg/kg lichaamsgewicht/dag) of 2-ethylhexyl-L-lactaat inhalatoir (200 of 600 mg/m^3; 6 uur/dag) kregen toegediend tussen de 6de en 15de dag van hun zwangerschap. In beide onderzoeken werden geen bijzondere effecten of afwijkingen op het nageslacht gevonden.

Evaluatie en advies

Wegens een gebrek aan humane gegevens zijn de gezondheidskundige advieswaarden afgeleid van dierexperimentele onderzoeken. De commissie stelt dat het kritische effect bij beroepsmatige blootstelling het ontstaan van irritaties in neus- en keelholte is. Verder onderkent de commissie dat niet voor alle lactaatesters een gezondheidskundige advieswaarde voor beroepsmatige blootstelling voorgedragen kan worden.

Voor dampen van ethyl-, isobutyl- en n-butyl-L-lactaat stelt de commissie de gezondheidskundige advieswaarde voor beroepsmatige blootstelling op 20 mg/m^3, gemiddeld over een achturige werkdag. Deze waarde is afgeleid van de NOAEL van 200 mg/m^3 met inachtneming van een veiligheidsfactor van 10, samengesteld uit een factor 3 voor intrasoort verschillen, een factor 3 ter compensatie voor de korte duur van de blootstelling en een factor 1 voor verschillen tussen soorten, daarmee rekening houdend met de ernst van het kritisch effect. Een zelfde advieswaarde wordt door de commissie voorgesteld voor de dampen propyl- en isopropyl-L-lactaat. Ondanks dat over deze twee stoffen geen toxiciteitsgegevens bekend zijn, geeft de commissie toch een advieswaarde, omdat propyl- en isopropyllactaat sterke fysische, chemische en mechanistische overeenkomsten vertonen met ethyl-, n-butyl- en isobutyllactaat.

Uitgaande van een LOAEL van 75 mg/m^3, stelt de commissie een gezondheidskundige advieswaarde van 4 mg/m^3 voor 2-ethylhexyl-L-lactaat voor als aerosoldeeltjes, gemiddeld over achturige werkdag. De commissie hanteert hierbij een

veiligheidsfactor van 20, bestaande uit en factor 10 zoals hierboven genoemd en een extra factor van 2 voor de extrapolatie van een LOAEL naar een NOAEL.

Aangezien van myristyl- en cetyllactaat geen inhalatoire gegevens bekend zijn kan de commissie geen advieswaarde voordragen. Ook kan de commissie geen gezondheidskundige advieswaarde afleiden voor de andere lactaatesters, namelijk methyl-, sec-butyl-, isoamyl-, amyl-, n-octyl-, n-decyl- en lauryllactaat, door het volledig ontbreken van toxiciteitsgegevens.

Samengevat stelt de commissie de volgende gezondheidskundige advieswaarden voor beroepsmatige blootstelling op, gemiddeld over een achturige werkdag:

- 20 mg/m^3 voor ethyl-L-lactaat (damp)
- 20 mg/m^3 voor n-butyl-L-lactaat (damp)
- 20 mg/m^3 voor isobutyl-L-lactaat (damp)
- 20 mg/m^3 voor propyl-L-lactaat (damp)
- 20 mg/m^3 voor isopropyl-L-lactaat (damp)
- 4 mg/m^3 voor 2-ethylhexyl-L-lactaat als inhaleerbare aerosoldeeltjes.

Wegens een gebrek aan goede gegevens is het volgens de commissie niet mogelijke voor de overige (L)-lactaatesters een advieswaarde voor te stellen.

Executive summary

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure that leads to legally binding limit values.

The present report on lactate esters was prepared in co-operation with the Swedish Criteria Group, which advises the Swedish government. The joint report on the health implication of exposure to lactate esters, published in Sweden in 1999, is included in Part 2 of this document. Part 1 mainly consists of the health hazard assessment by DECOS. The committee's conclusions are based on scientific publications obtained from data retrieval systems prior to December 1998. Scientific publications between 1998 and 2000 were no reason for the committee to adjust her recommendations.

Physical and chemical properties

Fifteen different lactate esters are known, of which some exist as liquid, whereas others exist as soft waxy solid. The colour varies between transparent, white, or white-yellowish. Lactate esters have a mild, characteristic odour. In general, lactate esters with a low molecular weight are soluble or miscible in water, whereas lactate

esters with a high molecular weight are soluble or miscible in different alcohol's, at room temperature.

Lactate esters are used as food additives, in pharmaceuticals and cosmetics. Furthermore, they serve as a solvent for degreasing metals and for printing.

Monitoring

In ambient air at normal room temperature and pressure, most lactate esters exist as vapours, whereas few exist as aerosol particles (e.g. 2-ethylhexyl lactate) and some may exist as a mixture of vapour and aerosol particles.

For monitoring vapours, charcoal tubes can be used. For monitoring aerosol/dust particles, first their particle size should be determined. Depending on this particle size, the fraction of inhalable aerosol/dust can be measured by the gravimetric sampling technique. In the Netherlands most inhalable dust measurements are carried out with the Dutch 'PAS6' sampling head, of which international equivalents are available.

N-butyl and ethyl lactate vapours are the only lactate esters of which information on analysis is available. They are sampled by charcoal tubes and thereafter analysed by gas chromatography (GC/FID; solvent methylene chloride: methanol (95:5), sample volume 10 L, max. flow 0.2 L/min). According to the OSHA, this method is partially validated. Ethyl lactate can also be analysed by using Fourier-Transform Infra Red (FTIR) spectrophotometry.

No validated methods for biological monitoring are available.

Current limit values

Only n-butyl lactate has an occupational exposure limit in the Netherlands, i.e. an administrative MAC value of 25 mg/m^3, 8 hour TWA (SZW00). In addition, the ACGIH (USA) has also proposed a TLV of 25 mg/m^3, 8 hour TWA (1976) for n-butyl lactate. This TLV is based on preventing irritation of the mucosa of the respiratory tract and in preventing headache (ACG98). The Swedish National Board of Occupational Safety and Health has adopted an OEL of 25 mg/m^3 for n-butyl lactate and ethyl lactate.

Kinetics

There are no human quantitative data about the absorption of lactate esters after respiratory, dermal or oral exposure.

In animal experiments, absorption of lactate esters or its hydrolysis products, after inhalation, have been observed. Furthermore, topical applied radiolabeled ethyl lactate,

present on skin of rats for up to 24 hours, was traced in all parts of the skin. In addition, ethyl lactate was detected in the portal blood of rats following intragastric instillation, indicating partial absorption before hydrolysis.

It has been reported that lactate esters are enzymatically hydrolysed in lactic acid, an endogenous metabolite, and alcohol, after oral administration or topical application. Hydrolysis of ethyl and 2-ethylhexyl esters have been reported to occur in various rat tissue homogenates, such as in plasma, the nasal epithelium, the liver, the skin, the small intestinal mucosa and the cecum.

There are no quantitative data on clearance and elimination of lactate esters. But due to the relative rapid hydrolysis, the elimination pathways are expected to be the same as for lactic acid and alcohols.

Effects

Observations in men

There is a lack of data concerning the occupational health hazards in men. A single case has been reported, in which it was written that ethyl lactate (10% in gel) caused allergic contact dermatitis. Six weeks later, the same subject gave a positive response in the patch test to the gel and to 1% ethyl lactate in petrolatum.

Animal studies

Propyl, butyl, amyl, ethyl, 2-ethylhexyl and octyl lactate, all as liquids, have been reported to be irritating the eyes and skin. These effects were, however, most probably due to the hydrolysis products. Contact sensitization was not observed with lauryl (5%; booster 50%) and cetyl (0.75%; booster 100%) lactate in female guinea pigs (n=10) using a modified Magnusson-Kligman maximization test.

Depending on species, compound and exposure time, the following respiratory LC_{50}, oral LD_{50} and dermal LD_{50} values were estimated:

- respiratory: more than 2,400 mg/m^3 for methyl-, ethyl-, butyl-, isobutyl- and isoamyl-L-lactate;
- oral: more than 5,000 mg/kg b.w. for butyl and lauryl lactate, 8,200 mg/kg b.w. for ethyl lactate, and more than 10,000 mg/kg b.w. for myristyl and cetyl lactate;
- dermal: more than 5,000 mg/kg b.w. for ethyl and butyl lactate.

A series of inhalation studies have been conducted, in which a group of male and female rats (n=5/sex) were exposed to four different L-lactate esters, during 28 days, 5 days/week and 6 hours per day. Animals who inhaled 0, 25, 75, 150, 200, 600 or 2,500 mg/m^3 ethyl lactate showed systemic effects when exposed to 600 and 2,500 mg/m^3. In the highest dose group, decreased body weight gain, liver weight and food

consumption were observed, and increased blood glucose levels, compared with the control group. Since degenerative changes of the nasal olfactory epithelium, a local effect, were observed in animals inhaling 600 mg/m^3, a NOAEL was set on 200 mg/m^3.

The same NOAEL (200 mg/m^3) was set for isobutyl and n-butyl lactate. Both L-lactate esters, used in different concentration ranges (isobutyl lactate, 0,100, 200, 400 or 800 mg/m^3; n-butyl lactate, 0, 75, 200 or 600 mg/m^3 in male (n=6)), caused hyperplasia of the nasal respiratory epithelium above 400 mg/m^3 and 600 mg/m^3 for isobutyl and n-butyl lactate respectively.

The fourth lactate ester studied in the inhalation studies was 2-ethylhexyl-L-lactate, a high molecular aerosol particle. It was found to be more toxic than the other three low molecular lactate esters. Histopathological changes of the respiratory tract, that is the nasal cavity, the larynx, the trachea and the lungs, were observed in all treated groups (75, 200, 600 or 1800 mg/m^3). However, these changes were restricted to the nasal cavity in animals inhaling 75 mg/m^3 2-ethylhexyl lactate. Therefore, the LOAEL was set on 75 mg/m^3.

There are no data on the health effects after inhalationof the other lactate esters.

Published reports about the oral and dermal effects on short-term exposure are very limited. In one study, male and female rats (n=10/sex), orally exposed to myristyl lactate (0, 0.5, 2.5 or 5.0 mg/kg b.w./day) for 13 weeks and 5 days/week, showed enlarged livers and increased liver weights in rats exposed to the two highest dose groups. From these findings a NOAEL of 0.5 mg/kg b.w./day for myristyl lactate was estimated. In another study, female rats (n=10), orally exposed to cetyl lactate (75 mg/mg b.w./day) for 6 weeks, 5 days/week, showed increased serum alkaline phosphatase levels and kidney weights compared with the control group, indicating a LOAEL of 75 mg/kg b.w./day for cetyl lactate.

Data are missing on the toxicity after long-term exposure and on carcinogenicity. Ethyl and 2-ethylhexyl lactate show no mutagenic activity in several *in vitro* tests. No information exists of the other lactate esters.

Doses of 0, 517, 1551 or 3619 mg/kg b.w. percutaneous administered ethyl-L-lactate to pregnant rats, on days 6 to 15 of gestation, did not induce any developmental effects. Maternal effects were restricted to erythema and desquamation of skin at the site of application. In another study, maternal effects, observed in rats (n=12) exposed to 2-ethylhexyl-L-lactate aerosols (200 or 600 mg/m^3) for 6 hours/day during the gestation days 6 and 15, were restricted to reduced (at 600 mg/m^3) or slightly decreased (at 200 mg/m^3) food consumption.

Hazard assessment and health-based occupational exposure limits

There are practically no human data which can be used for assessing the health hazard of lactate esters. Based on the inhalation studies with rats, the committee presumes that the critical effect for occupational exposure to lactate esters is irritation of the mucous membranes in nose and throat. This critical effect is most probably due to lactic acid, an hydrolysis product of lactate esters. Concerning occupational exposure, under normal room temperature and pressure, lactate esters exist as vapours, except 2-ethylhexyl lactate that exists as aerosol/dust particles.

From a no observed adverse effect level (NOAEL) of 200 mg/m^3, the committee advises a health based recommended occupational exposure limit (HBR-OEL) for ethyl-, isobutyl-, n-butyl-, propyl- and isopropyl-L-lactate (vapours) of 20 mg/m^3 as an 8 hour time weighted average concentration, by application of a safety factor of 10. This factor of 10 is composed of a factor of 3 due to intraspecies variability and a factor of 3 due to variability in the exposure duration. Because of the type of critical effect, the committee has taken in consideration a factor of 1 for interspecies differences. For propyl and isopropyl-L-lactate no toxicity data are available. However, the committee is of the opinion that due to similarities in chemical structure, physical characteristics and the analogy of the working mechanism of both compounds with ethyl, n-butyl and iso-butyl lactate, a HBR-OEL of 20 mg/m^3 (TWA 8-hour) is warranted.

For 2-ethylhexyl-L-lactate aerosol particles a LOAEL was set on 75 mg/m^3. Therefore, the committee advises a HBR-OEL of 4 mg/m^3 (TWA 8-hour) for this compound, by application of a safety factor of 20. A factor two for extrapolating the LOAEL to the NOAEL, and a factor of 10 to compensate for uncertainties due to intraspecies variability (factor 3), and to variability in the exposure duration (factor 3). As for ethyl, isobutyl and n-butyl lactate, the committee has taken a factor of 1 for interspecies differences in consideration.

Since no information is available on the inhalation toxicity of myristyl, cetyl and other lactate esters, the committee cannot recommend a HBR-OEL for these compounds.

Summarized, the committee recommends an health-based occupational exposure limit (8 hour TWA) for:

- Ethyl-L-lactate (vapour) of 20 mg/m^3
- Isobutyl-L-lactate (vapour) of 20 mg/m^3
- N-butyl-L-lactate (vapour) of 20 mg/m^3
- Propyl-L-lactate (vapour) of 20 mg/m^3

- Isopropyl-L-lactate (vapour) of 20 mg/m^3
- l2-Ethylhexyl-L-lactate (inhalable aerosol particles) of 4 mg/m^3
- Other (L)-lactate esters, no recommendations made.

Part 1

Health Council: Lactate esters

Chapter 1

Scope

1.1 Background

In the Netherlands occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (Annex A). The purpose of the committee's evaluation is to set a health-based recommended exposure limit for the atmospheric concentration of the substance, provided the database allows the derivation of such a value or that toxic action can be evaluated using a threshold model. In the latter case an exposure-response relationship is recommended for use in the regulatory standard setting.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister on the feasibility of using the health based value as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure, the Minister of Social Affairs and Employment sets the legally-binding OEL.

1.2 Committee and method of work

The present document of lactate esters is a co-production of DECOS and the Swedish Criteria Group (SCG). It is a result of an agreement between both groups to prepare

jointly criteria documents which can be used by the regulatory authorities in the Netherlands and in Sweden for establishing exposure limits. The draft document has been prepared by Dr P Lundberg from the Department of Occupational Medicine, National Institute for Working Life in Solna, Sweden, and was reviewed by the DECOS and subsequently by the SCG. The resulting document, as published by the Swedish National Institute of Occupational Health (Arbete och Hälsa 1999:9), is included in Part 2 of the present report.

Part 1, contains additional considerations used by the DECOS, hereafter called the committee, to recommend a health-based occupational exposure limit for lactate esters. The members of the committee and of the SCG are listed in annex B. The first draft of this part of the report was prepared by Dr AAE Wibowo and Dr MM Verberk, both from the Coronel Institute of the Academic Medical Center, University of Amsterdam, by contract with the Ministry of Social Affairs and Employment.

In 2000 the president of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of part 1 of this report.

1.3 Data

After publication of the DECOS and SCG report, an additional data search was conducted from 1998 to October 2000, using on-line databases Medline, EMBASE, BIOSYS Previews, Health, Elsevier Biobase, PASC, Current Contents, Toxline and Science Citation Index. No additional data were found.

Chapter 2

Evaluation of human health hazard

2.1 Assessment of health hazard

The assessment of the health hazard is based on data presented in the joint report, published in Sweden, which is included in part 2 of this document.

There are practically no human data which can be used for assessing the health hazard of lactate esters.

Of the fifteen lactate esters known, only some have been studied in animal studies, of which the relevant ones are described below.

Two series of inhalation studies have been performed in male and female rats, which differed only in the dose given to the animals. In more detail, rats (n=5/sex) inhaled ethyl-L-lactate (0, 25, 75, 150, 200, 600 or 2500 mg/m^3), isobutyl-L-lactate (0, 100, 200, 400 or 800 mg/m^3), n-butyl-L-lactate (0, 75, 200 or 600 mg/m^3) or 2-ethylhexyl-L-lactate (0, 75, 200, 600 or 1800 mg/m^3) for 28 days, 5 days per week and 6 hours per day. From the four lactate esters tested, 2-ethylhexyl-L-lactate were aerosol particles, whereas the others were vapours.

The lowest concentrations at which local degenerative effects, such as hyperplasia of the nasal epithelium were observed, were 600, 400, and 600 mg/m^3 for ethyl, isobutyl and n-butyl lactate respectively. The highest dose of ethyl lactate (2500 mg/m^3) caused, furthermore, systemic effects, such as decreased body weight gain, liver weight and food consumption, and increased levels of blood glucose. The observations indicate a NOAEL of 200 mg/m^3 for these three lactate esters (Cla98).

The high molecular 2-ethylhexyl lactate showed to be more toxic than the low molecular lactate esters. In all treatment groups, histological changes in the nasal the cavity, the larynx, the trachea and the lungs were observed, although in the lowest dose group (75 mg/m^3) this was restricted to the nasal cavity. Therefore, a LOAEL was indicated of 75 mg/m^3 for 2-ethylhexyl lactate (Cla98).

For myristyl and cetyl lactate only oral ingestion studies are available. In Sprague-Dawley rats (n=10/sex), orally dosed with 0, 0.5, 2.5 and 5 mg myristyl-(L)-lactate per kg b.w. for 13 weeks (5 days/week), a few systemic effects, such as liver aberrations, in the two highest dose groups have been reported. Therefore, a NOAEL is indicated of 0.5 mg/kg b.w./day for myristyl lactate. In another study, using female rats (n=15), which were orally dosed with 75 mg cetyl-(L)-lactate per kg b.w. for 6 weeks (5 days/week), increased levels of serum alkaline phosphatase and kidney weights have been found. Based on the findings of that study, a LOAEL is indicated of 75 mg/kg b.w./day for cetyl lactate.

The committee has summarized the available and relevant data in the table below, which includes the experimental design, the critical effect, and the threshold levels.

(L-)lactate ester	experimental design	critical end-point	threshold levels
ethyl	inhalation: 6 h/d, 5 d/w, 28 d	degenerative changes of nasal epithelium	NOAEL: 200 mg/m^3
isobutyl	inhalation: 6 h/d, 5 d/w, 28 d	degenerative changes of nasal epithelium	NOAEL: 200 mg/m^3
n-butyl	inhalation: 6 h/d, 5 d/w, 28 d	degenerative changes of nasal epithelium	NOAEL: 200 mg/m^3
2-ethylhexyl	inhalation: 6 h/d, 5 d/w, 28 d	degenerative changes of nasal epithelium	LOAEL: 75 mg/m^3
myristyl	ingestion: 5 d/w, 13 weeks	histopathological changes of the liver	NOAEL: 0.5 mg/kg bw/day
cetyl	ingestion:	increase of serum alkaline	LOAEL: 75 mg/kg bw/day

For the other lactate esters (methyl lactate, sec-butyl lactate, isoamyl lactate, amyl lactate, n-octyl lactate, n-decyl lactate, and lauryl lactate), no information is available on their health effects from respiratory or oral exposure.

Furthermore, no information is available on effects after long-term exposure, carcinogenicity and reproduction toxicity of all the fifteen different lactate esters known.

Based on the few inhalation studies with rats, the committee presumes that the critical effect for occupational exposure to lactate esters is irritation of the mucous membranes in nose and throat. This critical effect is most probably due to lactic acid, an hydrolysis product of lactate esters.

From a NOAEL of 200 mg/m^3 for ethyl-, isobutyl- and n-butyl-L-lactate and an uncertainty factor of 10, the committee recommends a HBR-OEL of 20 mg/m^3 (8-hour TWA) for these three compounds. The uncertainty factor of 10 is composed of a factor of 3 to compensate for intraspecies variability and a factor of 3 to compensate for the duration of the exposure. Because on the type of critical effect, the committee has taken in consideration a factor of 1 for interspecies differences.

Furthermore, from a LOAEL of 75 mg/m^3 for 2-ethylhexyl-L-lactate and a safety factor of 20, the committee recommends a HBR-OEL of 4 mg/m^3 (8-hour TWA) for this compound. For this compound a safety factor of 20 is used, 2 to extrapolate from LOAEL to NOAEL and 10 to compensate for uncertainties due to intraspecies variability (factor 3), and to variability in the exposure duration (factor 3). As for ethyl, isobutyl and n-butyl-L-lactate, the committee has taken in consideration a factor of 1 for interspecies differences.

For propyl and isopropyl-(L)-lactate almost no toxicity data are available. However, the committee is of the opinion that due to similarities in the chemical structure, the physical characteristics and the analogy of the working mechanism of both compounds with ethyl, n-butyl and iso-butyl-L-lactate, a HBR-OEL of 20 mg/m^3 (8 hour TWA) is warranted. As for ethyl, n-butyl and isobutyl-L-lactate, both propyl- and isopropyl-(L)-lactate are most probably hydrolysed in lactic acid. Moreover, both n-butyl- and propyl-(L)-lactate are severely irritative, probably corrosive to the eye.

The committee believes that the critical endpoints for myristyl- and cetyl-(L)-lactate should be derived from exposure by inhalation, as it occurs in occupational exposure. Since the threshold levels of myristyl and cetyl lactate were derived from oral administration only, the committee can not recommend a health-based occupational exposure limit. The committee expects, however, that also myristyl and cetyl lactate are irritants to the upper respiratory tract. Interpolation of these compounds, as with propyl and isopropyl lactates, was not possible.

Because of a lack of data, the committee can not recommend a health-based occupational exposure limit for the other lactate esters.

2.2 Groups at extra risk

The committee presumes that hypersensitive subjects may have an increased susceptibility to develop irritation of the mucous membranes in nose and throat, caused by inhalation of lactate esters.

2.3 Health-based recommended occupational exposure limits

The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit of:

- 20 mg/m^3 (8 hour TWA) for ethyl-L-lactate (vapour)
- 20 mg/m^3 (8 hour TWA) for isobutyl-L-lactate (vapour)
- 20 mg/m^3 (8 hour TWA) for n-butyl-L-lactate (vapour)
- 20 mg/m^3 (8 hour TWA) for propyl-L-lactate (vapour)
- 20 mg/m^3 (8 hour TWA) for isopropyl-L-lactate (vapour)
- 4 mg/m^3 (8 hour TWA) for 2-ethylhexyl-L-lactate (inhalable aerosol particles).

Because of a lack of data, the committee cannot recommend a HBR-OEL for the other (L)-lactate esters.

Chapter 3

Recommendations for further research

There is a need to assess the hazardous effects on the upper respiratory tract of many individual lactate esters, since these effects are indicated as critical effects.

Furthermore, to put the hazard assessment on a firmer basis, epidemiological studies are needed. In addition, more specific answers are needed on their kinetics, whether lactate esters can be absorbed through skin, whether they possess long-term effects, and whether they are maybe carcinogenic.

References

ACG98 American Conference of Governmental Industrial Hygienists. TLVs and other occupational exposure values - 1998. CD ROM.

Cla98 Clary JJ, Feron VJ and Velthuijsen JA. Safety assessment of Lactate esters. Regul Toxicol Pharmacol, 1998; 27: 88-97.

SZW00 Ministry of Social Affairs and Employment. Nationale MAC-lijst 2000, Sdu uitgevers.

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

> Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

> The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of

genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.
The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committees

Members of the DECOS

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- VJ Feron
  professor of toxicology; TNO Nutrition and Food Research, Zeist
- DJJ Heederik
  epidemiologist; IRAS, University of Utrecht, Utrecht
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- TM Pal
  occupational physician; Nederlands Centrum voor Beroepsziekten, Amsterdam

- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.
- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and
  professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

Members of the SCG (as of June 1997)

- Johan Högberg, *chairman*
  Toxicologist; Swedish Natl Inst for Working Life, Solna
- Gunnar Johanson, *v. chairman*
  Toxicologist; Swedish Natl Inst for Working Life, Solna
- Olav Axelson
  Occupational physician, epidemiologist; University Hospital, Linköping
- Sven Bergström
  Union representative; Swedish Trade Union Confederation
- Christer Edling
  Occupational physician, epidemiologist; University Hospital, Uppsala
- Lars Erik Folkesson
  Union representative; Swedish Metal Workers' Union
- Francesco Gamberale
  Behavioural neurotoxicologist; Swedish National Institute for Working Life, Solna
- Stig Holmquist
  Union representative; Swedish Confederation of Professional Associations
- Bengt Järvholm
  Occupational physician, epidemiologist; University Hospital, Umeå

- Ulf Lavenius
  Union representative; Swedish Factory Worker's Union
- Bengt Olof Persson, *observer*
  Physician, organic chemist; Sw Natl Board of Occup Safety and Health, Solna
- Bengt Sjögren
  Occupational physician; Swedish Natl Inst for Working Life, Solna
- Jan Wahlberg
  Dermatologist; Swedish Natl Inst for Working Life, Solna
- Kerstin Wahlberg, *observer*
  Chemical engineer; Swedish Natl Board of Occupational Safety and Health, Solna
- Arne Wennberg
  Neurotoxicologist; Swedish Natl Inst for Working Life, Solna
- Olof Vesterberg
  Physician, biochemist; Swedish Natl Inst for Working Life, Solna
- Per Lundberg, *scientific secretary*
  Toxicologist; Swedish Natl Inst for Working Life, Solna

The first draft of the present advisory report was prepared by AAE Wibowo, from the Coronel Institute in Amsterdam, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance was provided by T van der Klugt.
Lay-out: M Javanmardi.

Annex C

Comments on the public review draft

A draft of the present report was released in 2000 for public review. The following organisations or persons commented on the draft document:

- APM Van Dongen, PURAC, Gorinchem, The Netherlands;
- Dr H Lindemann, Bayer AG, Wuppertal, Germany;
- Dr RD Zumwalde, National Institute for Occupational Safety and Health, Cincinnati OH, USA.

Annex **D**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at wAbbreviationshich inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit

ppb	parts per billion (v/v)10^{-9}
ppm	parts per million (v/v)10^{-6}
RD_{50}	concentration at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit
STEL	short term exposure limit
tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Association (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone

GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione
HLiA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration
MFO	mixed function oxidase
NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RLiA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

GM	geometric mean
OR	Odds Ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography

GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Annex **E**

DECOS-documents

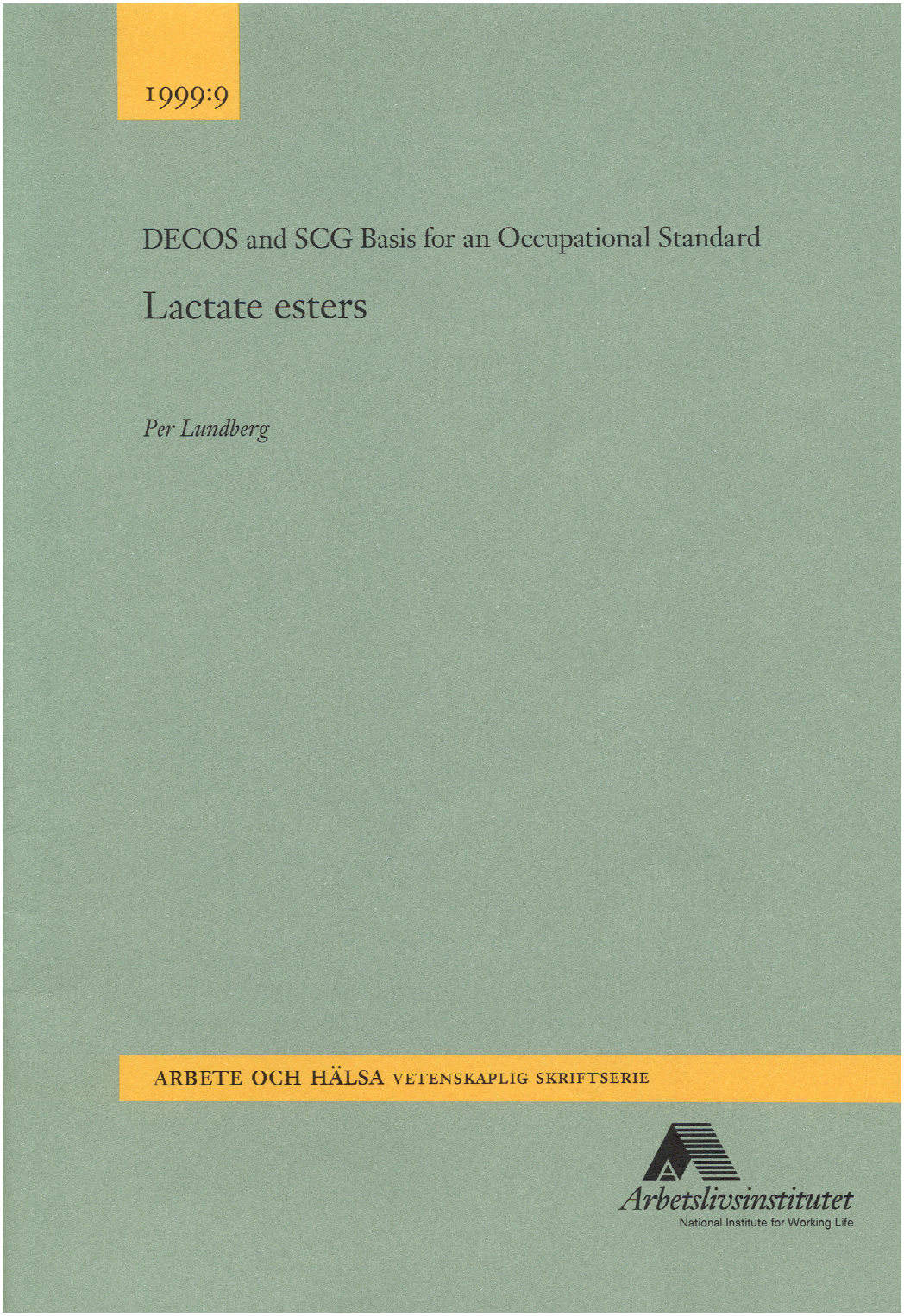
DECOS has produced documents on the following substances.

To be ordered from the Health Council of the Netherlands:

Acetone cyanohydrin	1995/05WGD
p-Aramid fibres	1997/07WGD
Azathioprine	1999/04OSH
Aziridine (ethyl imine)	2000/13OSH
1,2,3-Benzotriazole	2000/14OSH
Bisphenol A and its diglycidylether	1996/02WGD
Bromoethane	1998/10WGD
1,2-and t-Butanol	1994/10
β-Butyrolactone	1999/05OSH
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbadox	1999/06OSH
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
p-Chloroaniline	1998/09WGD
4-Chloro-o-toluidine	1998/08WGD
Chromium and its inorganic compounds	1998/01WGD
Cresols	1998/15WGD
Copper sulphate	1999/01OSH

1996-1997 WGD-rapporten/1996-1997 DECOS reports	1999/01WGD
1,2-Dibromoethane	1999/07OSH
1,2-Dichloroethane	1997/01WGD
Diethylsulphate	1999/08/OSH
Diglycidyl resorcinol ether	1999/09OSH
Diphenylamine	1997/05WGD
<Titeladv>	1998/03WGD
Epichlorohydrin (1-Chloro-2,3-epoxypropane)	2000/10OSH
1,2-Epoxybutane	1998/11WGD
1,2-Ethanediamine	1996/03WGD
Ethyleneglycol ethers	1996/01WGD
Ethylene thiourea	1999/03OSH
Formamide and dimethylformamide	1995/08WGD
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1997/03WGD
Isopropyl acetate	1997/04WGD
Man made mineral fibers	1995/02WGD
2-Meathylaziridine (propylene imine)	1999/10OSH
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
4,4'-Methylene bis (2-Chloroaniline)	2000/09OSH
4,4'-Methylene dianiline	2000/11OSH
Metronidazole	1999/11OSH
2-Nitropropane	1999/13OSH
N-Nitrosodimethylamine (NDMA)	1999/12OSH
2-Nitrotoluene	1998/12WGD
Pentaerythritol	1997/06WGD
Phenol	1996/04WGD
o-Phenylenediamine	1998/06WGD
Piperidine	1997/08WGD
Procarbazine hydrochloride	1999/14OSH
1- and 2-Propanol	1994/24
Propylene oxide	1997/02WGD
Ronidazole	1998/05WGD
Styrene	1998/07WGD
Quartz	1998/02WGD
1,1,1-Thrichloroethane	1995/03WGD
1,2,3-Trichloropropane	1994/25
1,2,3-Trichloropropane	1998/14WGD

Urethane (ethyl carbamate)	200012OSH
Vinylbromide	1999/15OSH
Wood dust	1998/13WGD



Arbete och Hälsa: Lactate esters

Part **2**

Arbete och Hälsa: Lactate esters

Arbete och Hälsa: Lactate esters