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Isopropyl acetate

Health-based recommended occupational exposure limit

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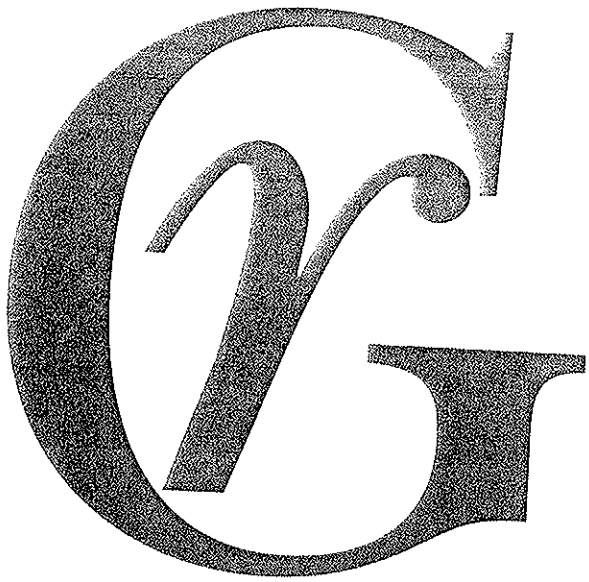
Report of the Dutch Expert Committee on Occupational Standards, a committee of the Health Council of the Netherlands



Gezondheidsraad

1997/04 WGD

Isopropyl acetate

Health-based recommended occupational exposure limit

Gezondheidsraad
Health Council of the Netherlands

Voorzitter

Aan de Minister van Volksgezondheid, Welzijn en Sport
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Onderwerp	: aanbieding advies
Uw kenmerk	: DGV/BMO-U-932542
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Bij brief van 3 december 1993, nr. DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

Per 1 januari 1994 heeft mijn voorganger daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD). De WGD was een door genoemde Minister ingestelde adviescommissie.

Hierbij bied ik u - gehoord de Beraadsgroep Toxicologie - een publicatie van de Commissie WGD aan over 'Isopropyl acetate'.

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

to

the Minister of Health, Welfare and Sport

the Minister and State Secretary of Social Affairs and Employment

No. 1997/04WGD, Rijswijk, 4 September 1997

First draft prepared by J. Th. M. Stouten)

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Contents

Samenvatting en advieswaarde

1 Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor beroepsmatige blootstelling aan toxische stoffen in lucht. Die afleiding is de eerste fase van een drietrapsprocedure die moeten leiden tot wettelijke grenswaarden.

In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan isopropylacetaat in de lucht op de werkplek. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór juni 1995 zijn verschenen.

2 Vóórkomen; fysische en chemische eigenschappen

Isopropylacetaat is een kleurloze, naar fruit ruikende vloeistof die oplosbaar is in water en aceton en zich goed laat mengen met alcohol en ether. De damp van isopropylacetaat is zwaarder dan lucht (dampspanning bij 20 °C: 6,1 kPa) en kan op afstand tot ontbranding worden gebracht.

Isopropylacetaat komt voor in natuurproducten, waaronder bepaalde fruitsoorten, en ook in sommige voedingsmiddelen. De stof wordt gebruikt als oplosmiddel voor verf, drukinkt, celluloseproducten, plastic, oliën en vetten, als chemisch intermediair en bij de productie van parfums en smaakstoffen.

3 Monitoring

Door het Nederlands Normalisatie Instituut en door de Amerikaanse NIOSH zijn gaschromatografische (GC-FID) analysemethoden beschreven voor de bepaling van isopropylacetaat in de lucht op de werkplek. Ook zijn methodes beschreven voor persoonlijke monitoring met diffusiebuisjes of badges.

4 Huidige grenswaarden

In Nederland en de VS geldt als grenswaarde voor beroepsmatige blootstelling 950 milligram per kubieke meter lucht (250 ppm). In Duitsland en het Verenigd Koninkrijk is de grenswaarde 840 mg/m^3 (200 ppm).

5 Kinetiek

Er zijn geen gegevens over de kinetiek van isopropylacetaat. Op grond van gegevens over andere acetaten is te verwachten dat isopropylacetaat gehydrolyseerd wordt door carboxyl esterases tot azijnzuur en isopropanol, in de lever, de dunne darm en de luchtwegen. Vermoedelijk vindt in bloed betrekkelijk langzame ontleding plaats.

6 Effecten

Er zijn, inzake de gevolgen bij de mens van blootstelling aan isopropylacetaat, slechts verouderde gegevens over irritatie. Die gegevens duiden erop dat vloeibaar respectievelijk dampvormig isopropylacetaat corrosieve effecten op het hoornvlies ('corneal burns'), respectievelijk oogirritatie kan veroorzaken. De commissie is geen gegevens over sensibilisatie op het spoor gekomen.

In onderzoek met konijnen is niets gebleken van huidirritatie door isopropylacetaat, maar dat onderzoek voldeed niet aan de richtlijnen van de EU en de OECD. Voor muizen is een RD_{50} (de concentratie die 50% reductie van de ademhalingsfrequentie teweegbrengt) van ongeveer 18 g/m^3 (4300 ppm) gerapporteerd. Inzake letaliteit na eenmalige blootstelling zijn de volgende gegevens beschikbaar: LC_{50} (dodelijke concentratie voor 50% van de proefdieren) voor blootstelling van ratten gedurende 8 uur: 50 g/m^3; orale LD_{50} (dodelijke dosis voor 50% van de proefdieren) voor ratten en muizen: 6600 mg per kg lichaamsgewicht. Hieruit blijkt dat isopropylacetaat nauwelijks toxisch is bij blootstelling via uiteenlopende routes. In een niet-gevalideerd onderzoek bij muizen zijn, na blootstelling gedurende 4 uur aan concentraties vanaf ongeveer

6000 mg/m^3 (1400 ppm), veranderingen in gedragskenmerken waargenomen (kortere duur van de immobiliteit in de 'behaviour despair' zwemtest).

De commissie heeft geen gegevens gevonden over proefdieronderzoek naar effecten van herhaalde blootstelling (inbegrepen beïnvloeding van de reproductie).

Isopropylacetaat was negatief in tests met en zonder metabolische activatie in verscheidene *S. typhimurium*-stammen.

In *S. cerevisiae* veroorzaakte het geen puntmutaties of mitotische recombinaties, maar gaf wel een zwakke inductie van aneuploïdie, vermoedelijk door interferentie met de kernspoel.

7 Gezondheidskundige advieswaarde

De commissie vindt dat er te weinig wetenschappelijke gegevens zijn voor de afleiding van een gezondheidskundige advieswaarde.

Executive summary

1 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. It constitutes the first step in a three-step procedure that leads to legally-binding limit values.

In the present report, the committee discusses the consequences of occupational exposure to isopropyl acetate. The committee's conclusions are based on scientific publications prior to June 1995.

2 Occurrence, physical and chemical properties

Isopropyl acetate is a colourless liquid with a fruity odour. It is soluble in water and acetone and miscible with alcohol and ether. Its vapour is heavier than air (vapour pressure at 20 °C: 6.1 kPa), and can be ignited from a distance.

Isopropyl acetate occurs in natural products such as certain fruits. It has been found in certain food products as well.

Isopropyl acetate is used as a solvent for coatings, printing inks, cellulose derivatives, plastics, oils, and fats, as a chemical intermediate, and in the manufacture of perfumes and flavouring agents.

3 Monitoring

Methods for the determination of isopropyl acetate in workplace air have been described by the Netherlands Normalisation Institute and by NIOSH, and are based on gaschromatografic (GC-FID) analysis.

Methods for personal air sampling using diffusive samplers have also been reported.

4 Current limit values

The current occupational exposure limit is 950 mg/m^3 (250 ppm) in The Netherlands and the USA, and 840 mg/m^3 (200 ppm) in Germany and the UK.

5 Kinetics

No data were available on the kinetics of isopropyl acetate.

From data on other acetates, it can be expected that isopropyl acetate will be hydrolysed by carboxylic esterases to acetic acid and isopropanol in the liver, small intestine, and the respiratory tract. In blood, it may dissociate relatively slowly.

6 Effects

The human data on effects of exposure to isopropyl acetate are limited to old data concerning irritation. They indicate that liquid and vaporous isopropyl acetate may cause corneal burns and eye irritation, respectively. No data on sensitisation were found.

Isopropyl acetate was not irritating to the skin and eyes of rabbits, but was not tested according to EU- or OECD-guidelines. In mice, an RD_{50} *of approximately 18 g/m^3 (≈ 4300 ppm) has been reported. From lethality data following single exposure (8-h LC_{50} **rat: ≈ 50 g/m^3; oral LD_{50} ***rat, mouse: ≈ 6600 mg/kg), it can be seen that isopropyl acetate is hardly toxic via the various exposure routes. When mice were exposed to levels of approximately 6000 mg/m^3 (≈ 1400 ppm) and higher, for four hours, changes in a behavioural parameter in a non-validated test (i.e., decreased duration of immobility in the 'behavioural despair' swimming test) were observed.

No experimental animal studies were found regarding effects (including those on reproduction) following repeated exposures.

* RD_{50}, concentration associated with 50% decrease in the respiratory rate
** LC_{50}, lethal concentration for 50% of the exposed animals
*** LD_{50}, lethal dose for 50% of the exposed animals

Isopropyl acetate was negative when tested with and without a metabolic activation in several *S. typhimurium* strains. It did not cause point mutations or mitotic recombinations in *S. cerevisiae*, but was a weak inducer of aneuploidy probably because of interference with the spindle apparatus.

7 Recommended occupational exposure limit

The committee considers the available data insufficient to recommend an occupational exposure limit

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). This evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if sufficient data are not available, or if the toxic action cannot be evaluated using a threshold model. In the latter case, an exposure-response relationship is recommended for use in regulatory standard setting.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister on 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 official Occupational Exposure Limit.

1.2 Committee and method of work

This document is a co-production of the Swedish Criteria Group (SCG) and DECOS. It is a result of an agreement between both groups to prepare jointly criteria documents which can be used by the regulatory authorities in Sweden and in the Netherlands. The

draft document has been prepared by H. Stouten MSc, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, Zeist, The Netherlands, and was first reviewed by DECOS.

In May 1996 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. DECOS, further on to be denoted as the committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

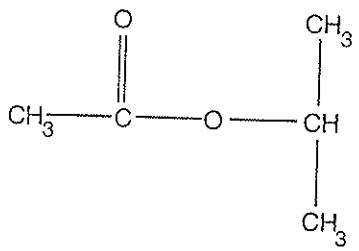
Starting point in searching literature on the health effects of exposure to isopropyl acetate was the review by Zaleski (Zal92). Unless otherwise indicated, data were derived from this document. Data considered to be critical were evaluated by reviewing the original publications. In addition, literature was retrieved from the on-line databases CA SEARCH, TOXLINE, and MEDLINE starting from 1977, 1965, and 1980, respectively. The final search has been carried out in February, 1996, and included Chem Abs 1996 vol 124/6 (960131/ED) and Medline 960125/UP. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO95, NLM95).

Chapter 2

Identity, properties, and monitoring

2.1 Identity

2.1.1 *Structure*



2.1.2 *Chemical names and synonyms/registry numbers*

name	: isopropyl acetate
CAS registry number	: 108-21-4
CA index name	: acetic acid, 1-methylethyl ester
	acetic acid, isopropyl ester
synonyms	: 2-propyl acetate
	sec-propyl acetate
	1-methyl ethyl acetate
	2-acetoxypropane
	isopropyl ethanoate
	paracetat

EINECS No	:	203-561-1
EEC No	:	607-024-00-6
EEC Labelling	:	R: 11
S: (2-)16-23-29-33		
EEC Classification	:	F; R 11
RTECS No	:	AI4930000

Physical and chemical properties*

Molecular formula	:	$C_5H_{10}O_2$
Molecular weight	:	102.13
Boiling point (101 kPa)	:	89 °C
Melting point (101 kPa)	:	-73.4 °C
Relative density (20 /4 °C)	:	0,87
Vapour density (air=1; 101 kPa)	:	3.5
Relative density of saturated vapour/air mixture (air=1; 20 °C)	:	1.2
Vapour pressure (101 kPa)	:	6.1 kPa (20 °C); 9.73 kPa (25 °C)
Percentage in saturated vapour/air mixture (101 kPa)	:	6
Flashpoint, closed cup	:	2 °C
open cup:	:	4 °C
Explosive limits, vol% in air	:	1.8-8%
Solubility in water, g/100 ml (20 °C)	:	3.1
Solubility in organic solvents	:	soluble in acetone; miscible with alcohol, ether
Physical form	:	colourless liquid
Odour	:	fruity
Odour detection threshold	:	1.9-140 mg/m^3
Odour recognition threshold	:	1.9-170 mg/m^3
Log $P_{octanol/water}$ (calculated)	:	1.3
Conversion factors (20 °C, 101 Kpa)	:	1 ppm = 4.22 mg/m^3 1 mg/m^3 = 0.24 ppm

Isopropyl acetate vapour is heavier than air, travels along surfaces, and can be ignited from a distance. Upon contact with water or moist air, isopropyl acetate decomposes

* data from: Bud89, Gem77, Lid94, Stu94, Zal92

into acetic acid and isopropanol*. It can react vigorously with oxidising agents (Stu94).

Imbriani *et al* (Imb85) have determined Ostwald partition coefficients for isopropyl acetate: the (human) blood/air coefficient was 36, the urine/air coefficient 40.

Isopropyl acetate is available in grades of 85-88%, 95%, or 95-99+% (NLM95).

2.2 Validated analytical methods

2.2.1 *Environmental monitoring*

NVN method 2948/2970 (NVvA92)

By this active personal sampling method of the Netherlands Normalisation Institute, the compound is adsorbed to Chromosorb 106, thermally desorbed, and analysed gas chromatographically using FID. The limit of detection is 20 ng per sample. The maximum sample size is 75 l for a sampling period of eight hours and 3 l for a period of fifteen minutes. The method is suitable in the concentration range 0.001-400 mg/m^3 for an eight-hour period and in the range 0.022-9999 mg/m^3 for a fifteen-minute period.

NIOSH method S50 (NVvA92)

This active personal air sampling method uses charcoal as adsorbents and carbon disulphide to desorb the compound. Analysis is by gas chromatography using FID. The limit of detection is 0.01 mg per sample. Maximum sample sizes are 9 or 3 l for an eight-hour and fifteen-minute sampling period, respectively. The method is suitable in the concentration ranges 3.7-9999 mg/m^3 for an eight-hour period and in the range 11-9999 mg/m^3 for a fifteen-minute period.

HSE has published a method in the MSDH series (Methods for the Determination of Hazardous Substances), viz, MDSH 70 - general methods for gases and vapours (HSE96).

The use of diffusive samplers in monitoring isopropyl acetate vapours in indoor/workplace air has been reported (Gen87, Gut92).

Finally, concentrations of organic solvents including acetic acid esters such as isopropyl acetate were quantitatively and quasi-continuously analysed in the waste air of a pharmaceutical production facility by means of IR spectrometry (Düb91).

* this is conflicting with other information which indicates that hydrolysis is likely to occur under basic conditions (pH>9) only (see Section 4.1.2)

2.2.2 *Biological monitoring*

Several methods to determine isopropanol and acetone, possible metabolites of isopropyl acetate, have been published (see e.g., Hea94).

No validated methods for biological monitoring of workers exposed to isopropyl acetate were found.

Chapter 3

Sources

3.1 Natural occurrence

Isopropyl acetate is reported to occur in natural products such as apples, bananas, black currants, grapes, melons, nectarines, pineapples, strawberries, honey, beans, and soybeans. In addition, it was found in food products such as honey, cheddar cheese, cocoa, beer, white and red wine, and plum brandy (Maa92).

3.2 Man-made sources

3.2.1 Production

Isopropyl acetate is prepared from catalysed reactions of anhydrous acetic acid and propylene, or of acetic acid and isopropanol (NLM95).

3.2.2 Uses

Isopropyl acetate is used as a solvent for coatings, printing inks, cellulose derivatives, plastics, oils, and fats, as a chemical intermediate, and in the manufacture of perfumes and flavouring agents (NLM95).

Chapter 4

Exposure

4.1 General population

4.1.1 *Air*

Although isopropyl acetate was detected in ambient air of The Netherlands, and described as one of the principal compounds emitted (Sme84), it was not included in a Dutch programme regarding industrial emissions into air (Ber93).

Isopropyl acetate has been measured in 1976-1977 near a waste disposal site in New Jersey, USA (estimated concentration: 6.5 $\mu g/m^3$) and in a industrialised region in West Virginia, USA (concentration not specified) (NLM95).

4.1.2 *Water*

If released to surface water, isopropyl acetate is expected to rapidly volatilise to the atmosphere; the half life for volatilisation from a model river was calculated to be approximately 6 h (NLM95).

Hydrolysis rate constants indicate that hydrolysis of isopropyl acetate in aquatic systems is not likely to occur except under basic conditions of pH>9 (NLM95).

In The Netherlands, isopropyl acetate was not listed among compounds that were monitored with respect to industrial emissions into surface waters (Ber93).

Isopropyl acetate was reported to be detected in US drinking water supplies (NLM95).

4.1.3 *Food*

Isopropyl acetate was present at an amount of 0.05 ppm in black currants and of 0.035 ppm in grapes (Maa92).

4.2 Working population

The use of isopropyl acetate in Dutch paint industry has been reported to amount to 200 tonnes in 1979 (Doo86). In Sweden, 25-49 tonnes were used in 1994 (Ric96).

In a survey carried out at 12 Dutch project locations with respect to exposure of maintenance and house painters to paint solvents, isopropyl acetate was detected in one particular solvent (spray painting a two-component polyurethane lacquer for several minutes) at a level of 22-28 mg/m^3 (≈ 6 ppm) (8-h TWA; personal air sampling) (Sch85). In a review on exposure levels of organic solvents at Dutch workplaces (measurements by the Directorate-General of Labour of the Ministry of Social Affairs and Employment), isopropyl acetate was mentioned once: when printing plastic foil, breathing zone air levels ranged between 2 and 125 mg/m^3 (0.5-30 ppm) (Doo86).

In a survey on levels of organic solvents used in eleven Spanish auto paint shops, isopropyl acetate was detected in four of them at levels varying from approximately 8 to 107 mg/m^3 (≈ 2-26 ppm) (personal air sampling) (DeM88).

In a sampling campaign carried out in 543 French workplaces between 1981 and 1985, isopropyl acetate was found to be present in 69 cases (total number of measurements: 2013). In 6% of them, levels exceeded the occupational exposure limit of 950 mg/m^3 (250 ppm) while in 85% levels were below 475 mg/m^3 (125 ppm); approximately half of these were less than 95 mg/m^3 (Ens88).

In a Belgian survey carried out in the mid 1980s, isopropyl acetate was present in six out of 94 personal air samples from 24 printing facilities, but not in 168 samples from painting, car repair, and other facilities (Veu87).

Data on occupational exposure levels in Sweden have not been found (Ric96).

Chapter 5

Kinetics

5.1 Absorption

The main route of entry into the body is via the lungs. Based on its physico-chemical properties, absorption of liquid isopropyl acetate through the skin can be expected. However, no quantitative data on skin absorption were found.

5.2 Distribution

No data were found.

5.3 Biotransformation

No data were found.

Like other acetates, isopropyl acetate will be hydrolysed by carboxylic esterases to acetic acid and its corresponding alcohol in the liver, the small intestine, and in the respiratory tract (Hea97; Rii90). This may already occur in the blood although *in vitro* experiments in which a number of acetates were incubated with human blood in airtight sealed vials for up to eight hours did not demonstrate hydrolytic cleavage of isopropyl and *t*-butyl acetate (Ghi84). However, in a separate *in vitro* experiment, *t*-butyl acetate dissociated slowly (when compared to the *n*-butyl isomer) in human and rat blood ($t_{1/2}$ ≈ 300 min vs ≈ 10 min) (Ess89). Based on the latter study, a relatively slow hydrolysis of isopropyl acetate in the blood may be expected.

The acetic acid is oxidised via the citric acid cycle to carbon dioxide and water. Isopropanol is metabolised mainly to acetone and carbon dioxide (Hea94, Hea97).

Since the hydrolysis is catalysed by the rather aspecific carboxylic esterases, interference may occur by other compounds while the metabolism of isopropanol can be retarded by preceding or concomitant ethanol consumption (Hea94, Rii90).

Both isopropanol and acetone can be formed endogenously (Hea94).

5.4 Elimination

No data were found.

As was reported for ethyl acetate (Rii90), isopropyl acetate may be excreted unchanged in exhaled air.

In rats and mice exposed to isopropanol by gavage, intravenous injection, or inhalation, exhalation of acetone and carbon dioxide was the major route of excretion (more than 80% of the absorbed dose). In workers occupationally exposed to isopropanol, 11-40% of the amount taken up was exhaled as acetone; acetone was found in the urine to a small extent only (Hea94).

5.5 Biological monitoring

No studies were found in which the relation between inhaled concentrations of isopropyl acetate and the excretion of the parent compound or metabolites have been investigated.

Physiological levels of isopropanol, a possible metabolite, may amount up to 0.1 mg/l in serum and urine; for acetone, these levels are 7 and 3.5 mg/l, respectively (Hea94).

5.6 Summary

There are no data on the kinetics of isopropyl acetate.

From a comparison with other acetates the committee deems it plausible that isopropyl acetate will be hydrolysed by carboxylic esterases to acetic acid and isopropanol in the liver, the small intestine, and the respiratory tract. In blood, it may dissociate relatively slowly. Excretion of isopropyl acetate and its metabolites may occur via the exhaled air and the urine.

Chapter 6

Effects

6.1 Observations in man

6.1.1 *Irritation and sensitisation*

The majority (not specified) of twelve male and female volunteers complained of irritation of the eyes when exposed to isopropyl acetate concentrations of approximately 850 mg/m^3 (200 ppm) for fifteen minutes. No nose or throat irritation was reported (Sil46)

Splashing may cause corneal burns which may heal promptly within 48 hours (McL46).

No reports on sensitisation were found.

6.1.2 *Toxicity due to experimental or occupational exposure*

No studies were found from which conclusions can be drawn concerning adverse effects in man due to experimental or occupational exposure.

6.2 Animal experiments

6.2.1 *Irritation and sensitisation*

Following application of 0.01 ml of the undiluted ester to the clipped skin of five albino rabbits, isopropyl acetate scored an injury grade of 1 (i.e., giving rise to 'the least visible capillary injection') on a scale from 1 to 10 (Smy54).

No studies on skin sensitisation in experimental animals were found.

When tested for irritation on the eyes of rabbits, it scored an injury grade of 2 on a scale from 1 to 10. It was not stated whether the eyes were rinsed with water after application of the test substance (Smy54).

With respect to the respiratory tract, the sensory irritation in the upper part was studied by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}). Using (probably ten male Swiss OF1) mice, the RD_{50} for isopropyl acetate was 17,783 mg/m^3 (4268 ppm) (Mul84; see also Bos92).

6.3 Toxicity due to acute exposure

Data on the toxicity following single exposure to isopropyl acetate are summarised in Table 1.

In an abstract from a paper from one of the former Soviet Republics, it was mentioned that acute inhalation and single oral (gavage) administration of isopropyl acetate to rats and mice resulted in rapid intoxication. Irritation, increased motor activity, interrupted respiration, narcosis, and death were observed within one to three days (Gus86).

Possible neurobehavioural effects following acute inhalation exposure were examined in mice (male Swiss OF1; n=10 per group) using the 'behavioural despair' swimming test. This bioassay is based on the finding that rodents that are forced to swim in a restricted space exhibit vigorous escape-directed activity during the first minute, then a transient period of swimming activity and immobility, and, after three minutes, a state of complete immobility. Exposure to 5798, 6073, 6769, 7929, and 8440 mg/m^3 (1374, 1439, 1604, 1879, 2000 ppm), for four hours, showed a dose-related decrease (statistically significant at 6073 mg/m^3 and higher) in the duration of immobility measured over a three-minute period. The ID_{50}, i.e., the concentration at which a 50% decrease in immobility occurs (compared to control values), was calculated to be 6773 mg/m^3 (1605 ppm; 95% CI: 1455-1641 ppm). De Ceaurriz *et al* suggested that the decrease in duration of immobility is caused by prolongation of escape-directed activity,

Table 1 Effects on experimental animals after single exposure to isopropyl acetate.

species	concentration/ dose	duration	route	effect	reference
rat	50.6 g/m³	8 h	inhalation	LC_{50}	Poz59
rat	27.9 g/m³	?	inhalation	LC_{50}	Gus86
rat	135.0 g/m³	4 h	inhalation	5/6 animals died	Smy54
rat	≈250 g/m³[a]	30 min	inhalation	no deaths	Smy54
rat	6750 mg/kg	-	oral	LD_{50}	Smy54
rat	10,900 mg/kg	-	oral (gavage)	LD_{50}	Gus86
rat	14,960 mg/kg	-	oral	LD_{50}	Poz59
mouse	37.0 g/m³	?	inhalation	LC_{50}	Gus86
mouse	6650 mg/kg	-	oral (gavage)	LD_{50}	Gus86
rabbit	6945 mg/kg	-	oral	LD_{50}	Mun72
rabbit	3064 mg/kg	-	oral	ND_{50}[b]	Mun72
rabbit	> 20 mL/kg	-	dermal	LD_{50}	Smy54

Note: In reviews (ACG91a, Bis94, Zal92), another rat oral LD_{50} was mentioned referring to Jen64. However, in this latter paper, no rat oral LD_{50} for isopropyl acetate was reported.

[a] Vapours were stated to be concentrated, probably saturated; in this case, listed concentration can be calculated; rats could tolerate this level without death for a maximum of 30 min.

[b] ND_{50}: the quantity that produced stupor and loss of voluntary movements on half of the number of the animals.

and that further investigations are required to explain the meaning of this increase in initial swimming activity (DeC83).

Isopropyl acetate was examined as a solvent control agent in an experiment to test whether methyl *t*-butyl ether, a contact dissolution agent for gallstones (via a percutaneous transhepatic catheter into the gallbladder), might cause serious tissue injury if accidently infused outside the gallbladder. A single injection of 0.2 mL/kg bw (≈ 1750 mg/kg) into the inferior *vena cava* or a peripheral (tail) vene, or into the intrahepatic parenchyma of ether-anaesthetised rats (male; Sprague-Dawley; n=6, 5, and 5, respectively) resulted in lung injury and death of all treated animals. Intrahepatic injection induced liver injury in 3/5 animals. Injection of a similar amount ip caused lung injury in 1/5 rats only (Aki92).

6.3.1 *Toxicity due to short-term exposure*

No short-term toxicity studies on isopropyl acetate were found.

6.3.2 *Toxicity due to long-term exposure and carcinogenicity*

No long-term toxicity or carcinogenicity studies on isopropyl acetate were found.

6.3.3 *Genotoxicity*

Isopropyl acetate (purity: > 99%) was negative when tested in *S. typhimurium* strains TA100, TA1535, TA1537, TA97, and TA98 at concentrations of 100-10,000 µg/plate with and without metabolic activation (i.e., 10 and/or 30% S9 fractions of induced livers from male rats and hamsters) (Zei92).

Isopropyl acetate (concentration in the medium: 0.74-1.23%) was a weak inducer of aneuploidy in the yeast *S. cerevisiae* (diploid strain D61.M), but it did not cause mitotic recombination or point mutations. The induction of aneuploidy was not due to interactions with DNA, but due to interference with the spindle apparatus. The effect was most pronounced using a treatment protocol in which growing cells were exposed during a growth period of four hours at 28 °C followed by incubation in ice (Zim85). Under similar conditions, isopropyl acetate potentiated the effects of low concentrations of propionitrile (Zim89).

6.3.4 *Reproduction toxicology*

The Commission of the European Communities has reviewed the reproduction toxicity of a number of compounds of industrial interest including isopropyl acetate. As to isopropyl acetate, no relevant data could be found (Sul93).

6.4 Summary

The human data on effects of exposure to isopropyl acetate are limited to old data concerning irritation. They indicate, according to the committee, that liquid and vaporous isopropyl acetate may cause corneal burns and eye irritation, respectively.

Isopropyl acetate was not irritating to the skin and eyes of rabbits, but was not tested according to EU- or OECD-guidelines. In mice, an RD_{50} of approximately 18 g/m^3 (≈ 4300 ppm) has been reported. From lethality data following single exposure, the committee concludes that isopropyl acetate is hardly toxic via the various exposure routes. When mice were exposed to levels of approximately 6000 mg/m^3 (≈ 1400 ppm) and higher, for four hours, changes in a behavioural parameter in a non-validated test were observed.

No experimental animal studies were found regarding effects (including those on reproduction) following repeated exposures.

Isopropyl acetate was negative when tested with and without metabolic activation in several *S. typhimurium* strains. It did not cause point mutations or mitotic recombinations in *S. cerevisiae*, but was a weak inducer of aneuploidy probably because of interference with the spindle apparatus functioning.

Chapter 7

Existing guidelines, standards, and evaluations

7.1 General population

No data on guidelines concerning the general population were found.

7.2 Working population

7.2.1 *Occupational exposure limits*

Occupational exposure limits in the Netherlands and in some other countries are presented in Table 2.

ACGIH has based its threshold limit values on rather old acute toxicity data and on comparison with other alkyl acetates. It was stated that the irritative and narcotic potential of these esters increases as a function of molecular weight and volatility. Since isopropyl acetate was somewhat less toxic than n-propyl acetate, slightly higher levels were recommended. These levels should minimise potential ocular and upper respiratory tract irritation in humans resulting from exposure to isopropyl acetate (date of review: 1992) (ACG91a, ACG91b).

7.2.2 *Biological limit values*

No biological limit values have been established by ACGIH or DFG.

Table 2 Occupational exposure standards in various countries.

country - organisation	occupational exposure limit		averaging time	type of exposure limit	note[a]	lit ref[b]	year of adoption[c]
	ppm	mg/m^3					
The Netherlands							
- Ministry	250	950	8 h	regulatory limit		SZW96	unknown
Germany							
- AGS	200	840	8 h	MAK		DFG96	unknown
- DFG MAC-kom.	400	1680	5-min ceiling[d]				
Great-Britain							
- HSE	200	840	15 min	OES		HSE96	unknown
Sweden							
Denmark[e]	200	840	8 h			Arb92	unknown
USA							
- ACGIH	250	1040	8 h	TLV		ACG96	1976
	310	1290	15 min				
- OSHA	250		8 h	PEL		ACG91a	unknown
	310		15 min				
- NIOSH	no limit					ACG91a	
European Union							
- SCOEL							

[a] S = skin notation; which mean that skin absorption may contribute considerably to body burden. sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Year that this limit was officially adopted or established.

[d] Limited to maximal eight times per shift.

[e] Intended to be changed to 150 ppm.

Chapter 8

Hazard assessment

8.1 Assessment of health hazard

Apart from two old studies reporting effects on the eyes from contact with liquid or vapour, no toxicity data in humans due to exposure to isopropyl acetate were available to the committee.

Animal data were limited to the results from single exposure experiments. Isopropyl acetate was not irritating to the eyes and skin of rabbits, and showed little toxicity (parameter: lethality) via the inhalatory, oral, or dermal route. Exposure to approximately 6000 mg/m^3 (≈ 1400 ppm) for four hours caused some impairment in a non-validated behavioural test in mice. No data on sensitisation were found.

Isopropyl acetate was negative when tested with and without metabolic activation in *S. typhimurium*, nor did it cause point mutations or mitotic recombinations in *S. cerevisiae*. It was a weak inducer of aneuploidy probably due to interference with the spindle apparatus functioning.

There were no data on toxicokinetics.

The committee deems the available data to be insufficient to recommend a health-based occupational exposure limit.

Since there were no data on kinetics, and since some information from *in vitro* experiments indicates that isopropyl acetate may dissociate relatively slowly into isopropanol and acetic acid, the committee considers it unjustifiable to use the toxicological data

base of isopropanol to derive an health-based occupational exposure limit for isopropyl acetate.

8.2 Groups at extra risk

The committee could not identify groups at extra risk.

8.3 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards considered the available toxicological data base to poor to justify the recommendation of a health-based occupational exposure limit for isopropyl acetate.

Chapter 9

Recommendations for research

In order to allow a proper evaluation of the toxicity of isopropyl acetate, studies on inhalatory kinetics, and on subchronic and reproduction toxicity are recommended. In addition, an *in vitro* gene mutation and a chromosome aberration test in mammalian cells should be conducted.

Rijswijk, 4 September 1997,
On behalf of the committee,

Dr CA Bouwman,
scientific secretary

Professor dr VJ Feron,
chairman

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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 committee

- VJ Feron, *chairman*
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  epidemiologist; Agricultural University, Wageningen
- PTh Henderson
  professor of toxicology; University Limburg, Maastricht
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- G de Mik
  toxicologist; National Institute of Public Health and the Environment, Bilthoven
- J Molier-Bloot
  occupational physician; Academic Medical Centre (AMC), Amsterdam
- PC Noordam, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, Rijswijk

- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol
- GMH Swaen
  epidemiologist; University Limburg, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- AAE Wibowo
  toxicologist; Coronel Laboratory, Amsterdam
- F de Wit
  occupational physician; Labour Inspectorate, Deventer
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, Rijswijk
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Rijswijk

The first draft of the present advisory report was prepared by H. Stouten, MSc, from the TNO Nutrition and Food Research Institute, Department of Occupational Toxicology, Zeist, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance was provided by E Vandenbussche-Parméus.
Lay-out: J van Kan.

Annex C

Comments on the public review draft

A draft of the present report was released in 1996 for public review. The following organisations and persons have commented on the draft document:

- Ms T Stewart
  Health and Safety Executive
- dr TB Adams
  Flavour and Extract Manufacturers' Association of the United States
  by Ir H Vrijhof, ECETOC

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
SCOEL	Scientific Committee on Occupational Exposure limits
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	
Bisphenol A	1995/05WGD
Butanol (1,2- and t-)	1996/02WGD
Cadmium and inorganic cadmium compounds	1994/10
Calculating cancer risk	1995/04WGD
Carbon disulphide	1995/06WGD
Chlorine dioxide	1994/08
1,2-Dichloroethane	1995/07WGD
1,2-Ethanediamine	1997/01WGD
Ethyleneglycol ethers	1996/03WGD
Formamide and dimethylformamide	1996/01WGD
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1995/08WGD
Man made mineral fibers	1997/03WGD
Methyl Methacrylate	1995/02WGD
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/09
Methyl-t-butylether	1994/11
Methyl chloride	1994/23
Phenol	1995/01WGD
Propanol (1- and 2-)	1996/04WGD
Propylene oxide	1994/24
Thrichloroethane (-1,1,1)	1997/02WGD
Trichloropropane (1,2,3-)	1995/03WGD
	1994/25

The following documents, that were published before 1994, can be ordered from the Sdu Uitgeverij Den Haag.

Acetaldehyde	RA 6/92
Acrylaten	RA 13/87
Aflatoxine B1, B2, G1 en G2	RA 6/87
Allylglycidylether	RA 1/92
Amyl acetate	RA 4/90
Aniline	RA 2/89
Anorganisch Lood	RA 2/80
Anorganische Kwikzouten	RA 3/82
Arc welding fume particles not containing chromium and nikkel	RA 1/93
Arseenverbindingen (anorganische)	RA 2/84
Asbest	RA 1/84
Asbest, Evaluatie van risico op kanker bij beroepshalve blootstelling aan (aanvullend op RA 1/84)	RA 9/89
Benzeen	RA 5/89
Beryllium and beryllium compounds	RA 4/88
Blootstelling, Gezondheidskundige aspecten van het begrip en van het meten/schatten ervan	RA 8/90
Butadiene (1,3-)	RA 5/90
Cadmium	RA 5/80
Caprolactam	RA 4/84
Carbon monoxide	RA 7/92
Carbonylfluoride and PTFE pyrolysis products	RA 3/88
Carcinogene stoffen	RA 3/80
Chloor	RA 6/80
Chloroform	RA 7/87
ß-Chloroprene	RA 4/93
Chroom en chroomverbindingen	RA 6/85
Cyclohexane	RA 15/90
Cyclohexanol	RA 3/90
Cyclohexanone	RA 9/93
Dibroomethaan	RA 5/87
Dichloorethaan (1,1-)	RA 8/87
Diisocyanates	RA 3/91
Dimethyl- en diethylsulfaat	RA 12/90
Dimethylamine	RA 10/90
Dimethylbutane (2,2- & 2,3-)	RA 7/93
Dimethylhydrazine	RA 2/87
Dinitro-*ortho*-cresol (4,6-)	RA 4/87
Dioxaan (1,4-)	RA 1/87
Epichloorhydrine	RA 1/86
Ethylacetate	RA 10/91
Ethylacrylate	RA 6/90
Ethyl Methanesulphonate (EMS)	RA 4/89
Ethylamine	RA 7/90

Ethylbenzene	
Ethyleenoxide	RA 9/91
Fenylhydrazine	RA 6/89
Fluorcarbons (except FC11)	RA 2/87
Fluorine compounds (inorganic)	RA 15/87
Fluorine	RA 1/89
Formaldehyde	RA 1/89
Fosfine	RA 3/87
Fijn hinderlijk stof; gezondheidskundige aspecten van bijlage 3 bij de Nationale MAC-lijst 1989	RA 1/80
Gasoline	RA 9/90
Heptaan (n-)	RA 3/92
Heptane (n-)	RA 1/81
Hexaan (n-)	RA 6/93
Hexachlorobenzene	RA 11/87
Hexanone (2-)	RA 2/88
Hydrazine	RA 2/90
Hydrogenfluoride	RA 2/87
Hydroxyethylhydrazine	RA 1/89
Isopropylglycidylether	RA 12/87
Isopropoxyethanol (2-)	RA 1/92
Koolmonoxide (Carbon monoxide)	RA 2/87
Kwikalkylverbindingen - Korte keten	RA 2/79 (7/92)
Kwikverbindingen (Organische)	RA 5/82
Lachgas (Nitrous oxide)	RA 4/82
Lasrook (Arc welding fume.....nickel)	RA 2/85 (2/92)
Mangaan	RA 1/93
Metallisch Kwik	RA 1/82
1-Methoxypropanol-2	RA 5/81
2-Methoxypropanol-1	RA 5/93
1-Methoxypropylacetate-2	RA 5/93
2-Methoxypropylacetate-1	RA 5/93
Methylacrylate	RA 5/93
Methyleenchloride (Methylene chloride)	RA 1/90
Methyl ethyl ketone	RA 1/83 (8/92)
Methyl isobutyl ketone	RA 16/90
Methyl Methanesulphonate (MMS)	RA 4/91
Methylbromine	RA 4/89
Methylpentane (2- & 3-)	RA 13/90
Monochloorethaan	RA 7/93
Monoketones (7/8 carbon chain aliphatic)	RA 2/82
Nikkel en nikkelverbindingen	RA 14/90
Nitropropaan (2-)	RA 3/85
Nitrous oxide	RA 1/85
Ozone	RA 2/92
para-Dichloorbenzeen	RA 4/92
Pentaan	RA 1/88
Phthalate esters	RA 2/81
	RA 8/93

Phthalic anhydride	RA 3/89
Piperazine	RA 7/91
Polyvinyl chloride (PVC) dust	RA 2/93
Propoxyethanol (2-)	RA 12/87
Propoxyethylacetate (2-)	RA 12/87
Pyridine	RA 3/93
Selenium en -verbindingen	RA 7/89
Silicon dioxide, crystalline forms of	RA 5/92
Stikstofdioxide (Nitrogen dioxide)	RA 5/85
Styreen	RA 8/89
Talc dusts	RA 6/91
Tetrahydrofuran	RA 1/91
Thiourea	RA 11/90
Tolueen diisocyanaat	RA 4/80
Tolueen	RA 2/91
Trichloorethaan (1, 1, 1-)	RA 3/81
Trichloorethyleen	RA 3/83
Trichlorofluoromethane	RA 14/87
Triethylamine	RA 2/83
Trimethylamine	RA 9/87
Vanadium metaal en anorganische verbindingen	RA 10/87
Wood dust	RA 8/91
Xylene	RA 5/91
Zwaveldioxide (sulphur dioxide)	RA 4/85