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Ministry of Social Affairs and Employment

Health-based recommended occupational exposure limit for Cyclohexanone

Dutch expert committee on occupational standards (met Nederlandstalige samenvatting)

RA 9/93

Labour Inspectorate

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This is a report of the Dutch Expert Committee on occupational standards (DECOS).
The draft-document has been prepared by dr. A.A.E. Wibowo.

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NEDERLANDSTALIGE SAMENVATTING

CYCLOHEXANON

1. Fysische en chemische eigenschappen

Cyclohexanon is een kleurloze vloeistof met een typerende geur van pepermunt en aceton. Het is mengbaar met de meeste organische oplosmiddelen, oplosbaar in ethanol, diethylether, benzeen, chloroform. Het is matig oplosbaar in water. Kookpunt: 155,65°C. Synoniemen zijn: ketohexamethyleen, pimelic keton, cyclohexyl keton. Conversiefactor: 1 ppm = 4,08 mg/m^3.

2. Monitoring

Voor monitoring van de lucht op de werkplek wordt verwezen naar de NIOSH-methode. De spreiding bedraagt tussen 100 en 400 mg/m^3 en de precisie 0,062. Voor biologische monitoring van beroepsmatig blootgestelde werknemers wordt het meten van metabolieten van cyclohexanon (cyclohexanol en/of cyclohexanediol) in de urine voorgesteld.

3. Grenswaarden

De huidige MAC-waarde voor cyclohexanon in Nederland is 200 mg/m^3 (50 ppm), tgg-8u. Deze waarde geldt ook in Duitsland. In de Verenigde Staten (ACGIH, NIOSH en OSHA), Verenigd Koninkrijk en Zweden zijn de grenswaarden lager, namelijk 100 mg/m^3 (25 ppm), tgg-8u. Voor kortdurende blootstellingslimieten heeft Zweden een grenswaarde van 200 mg/m^3 (50 ppm) en het Verenigd Koninkrijk 400 mg/m^3 (100 ppm).

4. Toxicokinetiek

De meest gebruikelijke opnameroutes op de werkplek zijn: via inhalatie van de damp of aerosolen en via direct contact van de vloeistof met de huid. Er zijn geen gegevens over de retentie in de longen. Er is wel een sterke correlatie tussen de concentratie van cyclohexanon in de ademzone van werknemers en het gehalte van cyclohexanol in de urine. Uit dierexperimentele gegevens blijkt dat cyclohexanon via de huid wordt opgenomen; de opname via de huid wordt ongeveer 10x lager geschat dan opname via de orale route. Er zijn geen gegevens bekend over de distributie van cyclohexanon of zijn metabolieten bij de mens. De volgende biotransformatie-wegen worden voor cyclohexanon bij de mens gesuggereerd: cyclohexanon wordt met de hulp van alcohol dehydrogenase tot cyclohexanol omgevormd. Dit wordt verder via microsomale mixed-function oxidase tot 1,2-, 1,3- en 1,4-cyclohexanediol geoxideerd. Andere mogelijkheid is via conjugatie van cyclohexanol met glucuronide tot cyclohexylglucuronide. Uitscheiding vindt plaats via urine en gal/faeces. Biologische monitoring kan toegepast worden door het meten van de concentratie van cyclohexanol in de urine.

5. Effecten

Cyclohexanon damp veroorzaakt irritatie van de ogen, neus en keel bij concentraties van 300 mg/m^3. Door proefpersonen werd een concentratie van 100 mg/m^3 aanvaardbaar gevonden.
Het kritisch orgaan bij acute blootstelling is het centraal zenuwstelsel. Bij de rat werd afwijkend gedrag gevonden bij concentraties van 750-2350 mg/m^3 gedurende 4 uur.
Het centraal zenuwstelsel is eveneens het kritisch orgaan bij langdurende blootstelling. De niet-nadelig-effect concentratie bij konijnen wordt geschat op 2450 mg/m^3, 6 u/d, 5 d/w voor 10 weken. Cyclohexanon heeft geen effect op het perifere zenuwstelsel. Effecten op de lever worden ook gerapporteerd. Een toename van het absolute en relatieve levergewicht werd gevonden bij honden na i.v. injecties met doseringen van 284 mg/kg/d gedurende 18-21 dagen. Uit pathologisch onderzoek bleek depletie van glycogeen, infiltratie van cellen rondom de veneuze bloedvaten van de lever, depositie van hemosiderine en extramedulaire hematopoise. Bij doseringen tussen 142-284 mg/kg/d i.v. bij honden werden afwijkingen in de bloedvormende organen gevonden.
In een studie bij ratten en muizen met langdurende cyclohexanon toediening via drinkwater werden geen aanwijzingen voor carcinogeniteit gevonden. Wel werd een daling van het lichaamsgewicht bij hoge concentraties gevonden. De minimale nadelige concentratie wordt geschat op 3300 ppm cyclohexanon in drinkwater voor de rat, wat overeenkomt met een dosis van 500 mg/kg/d gedurende 2 jaar. Er zijn geen aanwijzingen gevonden voor mutagene activiteit van cyclohexanon. Er zijn ook geen aanwijzingen voor effecten op de reproductie bij doseringen beneden de maternale toxische dosis. Voor de laatste wordt een niet-nadelig-effect concentratie geschat van 2650 mg/m^3 cyclohexanon in inademingslucht gedurende 12 gestationele dagen in ratten en muizen. In een twee-generatie-studie met ratten werd bij een concentratie van 5710 mg/m^3, 6 u/d, 5 d/w, een vermindering van het maternale lichaamsgewicht, verminderde mannelijke fertiliteit, overlevingskansen en lichaamsgewicht van het nageslacht gevonden. De niet-nadelig-effect concentratie wordt geschat op 2040-4080 mg/m^3. Er zijn geen epidemiologische gegevens beschikbaar over effecten op de gezondheid van werknemers blootgesteld aan cyclohexanon.

6. Evaluatie en advies

De Werkgroep van Deskundigen gaat uit van een vrijwilligersonderzoek waar bij expositie aan 300 mg/m^3 cyclohexanon, klachten van irritatie van ogen, neus en keel voorkomen. Bij 100 mg/m^3 komen deze klachten niet meer voor. Met inachtneming van een veiligheidsfactor van twee, adviseert de WGD een gezondheidkundige waarde van 50 mg/m^3 cyclohexanon (12,5 ppm), TWA-15 min, met een huidnotatie.

1. INTRODUCTION

This document has been prepared at the request of the Dutch Directorate-General of Labour.

For *background material* the following papers are used:

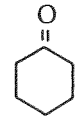
IARC: Cyclohexanone. IARC monographs on the evaluation of carcinogenic risks to humans. Some organic solvents, resins monomers and related compounds, pigments and occupational exposures in paint manufacture and painting, Volume 47, WHO/IARC, 1989 pages 157-168.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, MONITORING

2.1. IDENTITY

2.1.1. Structure

$C_6H_{10}O$



2.1.2. Chemical names and synonyms/registry numbers

Cyclohexanone

Synonyms : Ketohexamethylene
Pimelic ketone
Pimelin ketone
Cyclohexyl ketone (IUPAC systematic name)

CAS Reg. No. 108-94-1

2.2. PHYSICAL AND CHEMICAL PROPERTIES

Chemical formulae	: $C_6H_{10}O$
Molecular weight	: 98.14
Boiling point (° C) at 1 bar	: 155.65
Melting point (° C)	: -16.4
Density (at 20° C/4° C)	: 0.948
Solubility	: Miscible with most organic solvents. Soluble in ethanol, diethylether, benzene, chloroform and other common organic solvents. Soluble in water (150 g/l at 10° C, 50 g/l at 30° C)
Volatility (at 25° C)	: vapour pressure 5.2 mm Hg
Refractive index (at 20° C)	: 1.4507
Flash point (° C)	: 44
Conversion factor	: 1 ppm = 4.08 mg/m^3
(25° C, 760 mm Hg)	: 1 mg/m^3 = 0.25 ppm

Cyclohexanone is a colourless liquid with peppermint and acetone odour. Cyclohexanone is available in various grades of purity (98 % min, > 99.8 %). Impurities reported include formic acid (up to 0.05 %) and water (up to 0.2 %).

2.3. ANALYTICAL METHODS

2.3.1. Environmental monitoring

The NIOSH (1974) recommended the following method: A known volume of air is drawn through a charcoal tube to trap the organic vapours present. The charcoal in the tube is transferred to a small, stoppered sample container and desorbed with carbon disulphide. An aliquot of the desorbed sample is then injected into a gas chromatograph (equiped with flame-ionisation detector). The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

Range : 100-400 mg/m^3

Precision (CV_T) : 0.062

An electrometric or colorimetric titration method, which can be used when no other carbonyl compound is present, is based on the reaction of cyclohexanone with hydroxylamine hydrochloride to form the oxime and hydrogen chloride (IARC, 1989).

2.3.2. Biological monitoring

The determination of one of the metabolites of cyclohexanone in the urine can be used for biological monitoring (see chapter 6.4).

Determination of cyclohexanol in urine

In order to estimate the internal exposure the total level of cyclohexanol in urine has to be determined. This metabolite exists in urine as free compound or conjugated as glucuronide. To measure the total level, the cyclohexanol conjugates have to be transformed to free cyclohexanol by acid hydrolysis and subsequently analyzed by gas chromatography (Ong et al. 1991). For the GC conditions see referred paper. The relation between peak height and concentration for cyclo-

hexanol from 1 to 35 mg/l is linear with a typical regression equation of $y = 0.24x + 0.09$ and a correlation coefficient (r) of 0.99. The variations of the linearity and slope of the calibration graph for between-day analyses are less than 0.9 and 4 % respectively. For standardisation against variations in diureses, correction with the creatinine level in urine is proposed.

Determination of cyclohexanediol in urine

Another method for biological monitoring is determination of cyclohexanediol in urine. There are three methods available (Mills and Walker, 1990):

(a) urine, acidified to pH 1.0 and extracted with ethylacetate, is analyzed by thin-layer chromatography on silica gel with benzene/acetic acid/water (70/29/1 by vol) for development, and naphthoresorcinol as staining agent.

(b) 1 ml of urine is mixed with an equal volume of 5 mol/l hydrochloric acid and heated for 1 h at 100° C. Split samples of hydrolysed and nonhydrolized urine are extracted with ethyl acetate and diethyl ether, derivatized with BSTFA (bis-trimethylsilyl-trifluoroacetamide), and analyzed for cyclohexanediol by GC.

(c) urine acidified to pH 5.0 is incubated with ß-glucuronidase at 37° C overnight. Split samples of hydrolyzed and nonhydrolyzed urine are extracted and analyzed for cyclohexanediol and cyclohexanol.

3. SOURCES OF EXPOSURE

3.1. NATURAL OCCURRENCE

Cyclohexanone is not known to occur as a natural product.

3.2. MAN-MADE SOURCES

3.2.1. Production

Cyclohexanone production and consumption are determined by the demand for raw materials for nylon. Other uses are minor and have little effect on overall production (IARC, 1989).

Cyclohexanone is produced commercially in several ways. One widely used process yields cyclohexanol and cyclohexanone by the catalytic oxidation of cyclohexane. Another important and very efficient process is based on the hydrogenation of phenol.

The amount of cyclohexanone produced in the Netherlands is not known. The US International Trade Commission reported production of approximately 360 000 tonnes each year in 1984 and 1985 and 404 000 tonnes in 1986 in the US.

3.2.2. Uses

The following uses of cyclohexanone are reported:

- Cyclohexanone is used predominantly for the synthesis of raw materials used in the production of nylon.
- It is used as chemical intermediate, e.g. as an additive or as a high-boiling, slow-drying solvent.
- It is used as a solvent in insecticides, wood stains, paint and varnish removers, spot removers, cellulosics and natural and synthetic resins and lacquers.

- As additive, cyclohexanone is used in detergents, degreasing of metals (e.g. nickel sheets), mould release agent for paints or varnishes, leveling agent in dying and delustering silk, and lube oil additive, especially for aircraft piston-type engine.
- Cyclohexanone is also used as monomer in the synthesis of cyclohexanone resins, polyvinyl chloride and its copolymers, and methacrylate ester polymers.

4. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

4.1. ENVIRONMENTAL LEVELS

4.1.1. Water and food

There are no data available on the levels of cyclohexanone in food and water. Since it is not a natural product the only possible existence is by contamination, e.g. in plastic-wrapped food or plastic bottled drinking water. Mills and Walker (1990) claimed to find cyclohexanone in infusion fluids used for newborn babies. They found that both 100 g/l dextrose and intravenous feeding mixture contained cyclohexanone before being introduced into the administration set. In addition, substantial amounts of cyclohexanone were leached from the infusion system when both water and parenteral feeding solution were pumped through. The burette, rather than the filter, was the main source of the compound.

4.1.2. Air (Occupational)

Few data are available on ambient air concentrations of cyclohexanone. Its presence was reported in the air of one house near an offset printing office in the Netherlands, but the concentration was not given (Verhoeff et al. 1987).

Samimi (1982) carried out an environmental monitoring in a screen printing plant in the U.S. Air samples were collected from both workers breathing zone and various workplace areas of the plant. The following results were attained (in mg/m^3):

Job classification	Mean TWA levels of cyclohexanone	
	Breathing zone levels	Workplace levels
Printing press	114	95
Automatic dryer*	45	55
Manual drying**	73	73
Paint mixing	35	43
Screen wash	24	14
General air	n.d.	11

n.d. = not determined
* near the conveyer belt where dried printed sheets emerged.
** where wet printed sheets were manually hang-dried in the general plant's atmosphere

Ong et al. (1991) performed environmental monitoring in the breathing zone of 27 workers employed in a videotape manufacturing plant in Singapore. They used a 3 M Organic solvent dosimeter throughout the whole workshift of 8 hours. The levels found ranged from 2 to about 30 ppm.

4.2. HUMAN EXPOSURE

4.2.1. General population

Mills and Walker (1990) investigated the urinary excretion of organic acids of 278 newborn babies in a special care unit of a hospital in Southampton, UK. In 101 of 584 urine samples analyzed, they found isomers of cyclohexanediol. The babies received normal clinical care, those who were too sick for oral feeding received intravenous fluids. During the first of three days this comprised of dextrose and electrolytes. As the clinical condition improved, oral milk was introduced and the volume of intravenous fluid was reduced progressively during the first week. It was strongly suspected that the probable source of cyclohexanediol was the solvent cyclohexanone, which was found as a contaminant of intravenous dextrose and the parenteral feeding solution, and was also leached into the infusion fluids from the administration set.

4.2.2. Occupational population

A list of occupations in which exposure may occur includes:

Plastic makers

Resin makers

Paint remover workers

Disinfectant workers

PVC-production workers

Metal degreasing workers

Silk workers

Video-tape production workers.

Pesticide formulators

5 GUIDELINES AND STANDARDS

5.1. GENERAL POPULATION

There is no standard for the general population.

5.2. OCCUPATIONAL POPULATION

Country (year)	Levels in mg/m^3 (ppm)	Description
The Netherlands (1989)	200 (50)	TWA-8 h
The United States of America		
ACGIH (1991)	100 (25)	TWA skin notation
OSHA (1990)	100 (25)	TWA skin notation
NIOSH (1990)	100 (25)	TWA skin notation
Fed Rep.Germany (1991)	200 (50)	TWA
Sweden (1991)	100 (25)	TWA-8 h
	200 (50)	Short-term skin notation
United Kingdom (1990)	100 (25)	TWA-8 h
	400 (100)	short-term

6. TOXICOKINETICS

6.1. ABSORBTION

The most probable method of uptake of cyclohexanone in the work environment is by inhalation of the vapour or through skin contact with the liquid phase. In specific instances, it may also be absorbed through the gastro-intestinal tract.

There are no data on the quantity of retention in the lungs; it is estimated to be high, due to its solubility. There is a very high correlation between the level of cyclohexanone in the breathing zone of workers and the level of cyclohexanol, its metabolite, in their urine (see Chapter 6.4).

Animal data indicate that cyclohexanone in liquid phase may also be absorbed through the skin as well as through the gastro-intestinal tract. The range of lethal dose in rabbits by oral administration was 1.6-1.9 g/kg b.w., and by cutaneous administration 10.2-23.0 g/kg b.w. (Treon et al. 1943 A). This may mean that absorption through the skin is about a factor 10 less than that through the oral route. No human data are available.

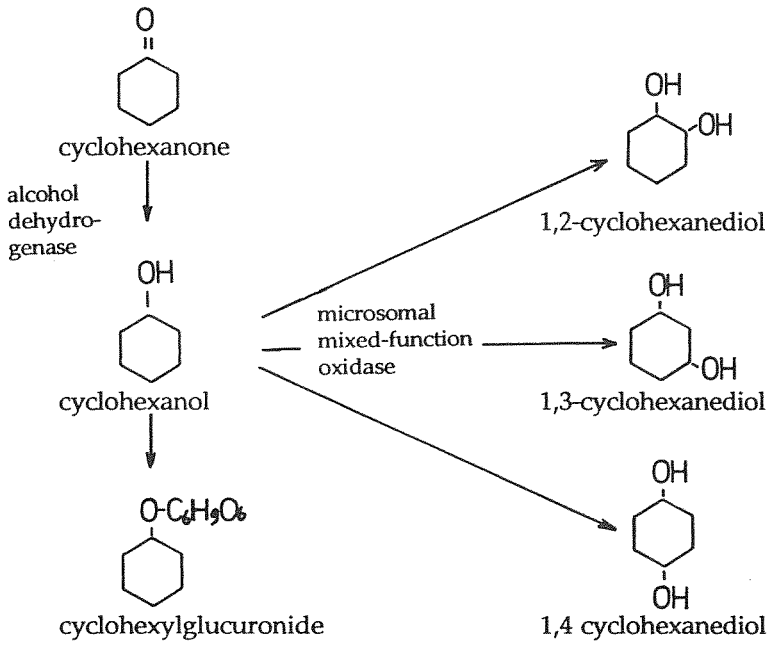
6.2. DISTRIBUTION AND BIOTRANSFORMATION

No quantitative data are available on the distribution of cyclohexanone in human.

Ong et al. (1991) found a significant relationship between the levels of cyclohexanone in the breathing zone of workers and the levels of cyclohexanol in the urine of these workers. Mills and Walker (1990) found isomers of cyclohexanediol in the urine of newborn babies fed with parenteral feeding contaminated with cyclohexanone. In a case of attempted suicide by drinking a mixture of solvents Sakata et al. (1989) reported that one of the compounds ingested was cyclohexanone (39 %). They found that the concentrations of cyclohexanone and cyclohexanol in urine at the first sampling point (12 hours after ingestion) were 33 and 51 µg/ml respectively, which decreased gradually and they were still detectable until 25 hours after ingestion. Cyclohexanol glucuronide in urine at the first sampling point

showed the highest value of 440 µg/ml and it was still detectable until 47 hours after ingestion.

From these data the following biochemical pathway of cyclohexanone is proposed in humans:



Observations in animals support this sequence. Rabbits (Elliot et al. 1959) administered by oral intubation, dogs (Martis et al. 1980, Koeferl et al. 1981) administered by intravenous injection and rats (Greener et al. 1982) also administered by intravenous injection with cyclohexanone showed reduction to cyclohexanol, which was excreted as the glucuronide conjugate. This was apparently the main metabolite of cyclohexanone.

When rabbits were fed 270 mg/kg cyclohexanol orally, 60 % was excreted as cyclohexanol-glucuronide conjugate and 6 % as the glucuronide conjugate of trans-1,2-cyclohexanediol (Elliot et al. 1959). Thus, an enzyme pathway exists in vivo by which cyclohexanone could be converted through cyclohexanol to trans-1,2-cyclohexanediol. Greener et al. (1982) administered cyclohexanone i.v. for 28 consecutive days to Wistar and Gunn rats in two doses of 50 and 100 mg/kg. The amount of the dose excreted in the urine as glucuronides of cyclohexanol in Wistar

rats ranged from 15 to 20 % for the low dose group and 19 to 29 % for the high dose group. Urinary excretion of glucuronides of cyclohexanol in Gunn rats accounted for 17-25 % and 24-34 % of the administered dose for the low and high dose groups, respectively. At 24 h after i.v. administration of cyclohexanone, there were no detectable concentrations of cyclohexanone and/or its metabolite cyclohexanol in the plasma. These substances were thus cleared from the blood in less than 24 hours.

In dogs administered intravenously with a dose of 284 mg/kg cyclohexanone for 18 or 21 days showed that the distribution half-life, biological half-life and clearance values for cyclohexanone were 7 min, 81 min and 27 ml/kg/min, respectively (Martis et al. 1980). Between 74 % and 100 % of the administered dose of cyclohexanone was converted to cyclohexanol and approximately 60 % of the dose was excreted in the urine as the glucuronide conjugate of cyclohexanol. The apparent elimination half-life of the metabolite was 99 min.

6.3. EXCRETION

As mentioned in the previous chapter, the main excretion pathway is through the urine as the glucuronide conjugate of cyclohexanol. Urinary excretion of unconjugated cyclohexanone and cyclohexanol accounted for less than 1 % of the administered dose (Koeferl et al. 1981). Other possible excretion pathway is through the bile, and consequently in the faeces (Greener et al. 1982).

6.4. BIOLOGICAL MONITORING

A good correlation exists between the levels of cyclohexanone in the breathing zone of workers and the concentrations of cyclohexanol in the urine.

Ong et al. (1991) performed a study on 27 workers from a video tape manufacturing plant in Singapore. These workers were exposed to cyclohexanone with time-weighted average concentrations from 2 to 30 ppm (8 - 122 mg/m^3). All urine specimens were collected at the end of their workshift. Urinary samples for recovery analyses were obtained from the medical and technical staff of the University Hospital. The level of cyclohexanol in urine was determined by GC after hydrolysation of the conjugates and expressed after correction for creatinine in

urine level. Environmental exposure to cyclohexanone at the workplace was monitored by using 3 M organic solvent dosimeter throughout the whole workshift of 8 hours. The passive dosimeters were attached to the breathing zone of the workers before they entered the plant. Analysis of cyclohexanone in the dosimeter was usually carried out within one week. The results of the study showed *a linear relationship between the urinary cyclohexanol concentrations when plotted against the corresponding environmental cyclohexanone levels. The linear equation was y = 0.44x + 2,58 and the correlation coefficient was 0.88.* (x = the level of cyclohexanone in air, in ppm; y = the concentration of cyclohexanol in urine, in mg/g creatinine) see *Figure 1.*

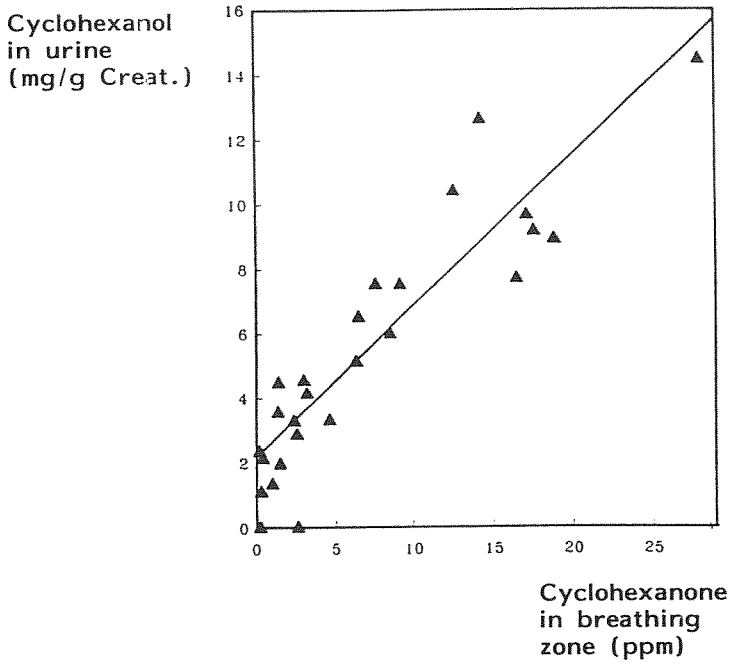


Figure 1. The relationship between cyclohexanone in the environment and urinary cyclohexanol, found in 27 workers employed in a video tape manufacturing plant (Ong et al. 1991).

Another metabolite of cyclohexanone is cyclohexanediol, which is also excreted in the urine. Although this method has not been applied yet to workers population it

is of interest to report that Mills and Walker (1990) found isomers of cyclohexanediol in the urine of newborn babies who were fed with intravenous feeding which was contaminated with cyclohexanone. Trans-1,2-cyclohexanediol was always the most abundant isomer; the highest concentration of cyclohexanediol was 30 mmol/mol creatinine.

6.5. SUMMARY

The most probable route of exposure to cyclohexanone in work environment is by inhalation of its vapour or through skin contact with its liquid phase. The biotransformation pathway of cyclohexanone goes through several steps, the first being reduction into cyclohexanol by the enzyme alcohol dehydrogenase. Most of this metabolite is found in the urine, conjugated to glucuronide. A small part of cyclohexanol is further metabolized into several isomers of cyclohexanediol, the most abundant being the metabolite trans-1,2-cyclohexanediol. These metabolites are also found in urine conjugated to glucuronide.

The excretion pathway of the metabolites is by urine, although elimination through bile and faeces may also be considered to take place. Biological monitoring of workers occupationally exposed to cyclohexanone can be performed by determination of the level of cyclohexanol in urine. A good relationship was found between the levels of this metabolite and the concentrations of cyclohexanone in the breathing zone of workers.

7. EFFECTS

7.1. ANIMAL EXPERIMENTS

7.1.1. Irritation and sensitization

Gupta et al. (1979) performed a *dermal irritation test* by placing several concentrations of cyclohexanone in cotton seed oil on the shaved backs of male rabbits and covering these with an occlusive patch for 24 h. Each site was examined daily for 7 days and the irritation evaluated. The results showed that topical application of 12.4 to 99 % cyclohexanone produced a concentration dependent irritation, whose intensity and duration was related to the concentration. The low concentration (12.4 %) produced a minimally detectable response which disappeared within 24 hours. The undiluted cyclohexanone (99+ %) produced the most severe response which did not totally disappear after 6 days. An *intradermal irritation test* showed the same response at levels between 4 and 31.1 %; the threshold irritation concentration was found to be 12.8 % cyclohexanone. An *opthalmic irritation test* was also performed on rabbits. The test showed that cyclohexanone at levels of 2.5 % or less in cotton seed oil were not irritating. A concentration dependent irritation was observed with concentrations of 5 to 40 %.

Bruze et al. (1988) performed *sensitization studies* in Guinea pigs using two cyclohexanone resin batches and cyclohexanone. The two batches of cyclohexanone resin showed to have sensitizing potential, on the other hand cyclohexanone itself did not reveal any allergenic potential. It should be noted that cyclohexanone resin is not a chemically defined compound but consists of the main raw material, cyclohexanone and several other substances formed when the resin is manufactured.

7.1.2. Acute toxicity

Gupta et al. (1979) performed acute toxicity studies by administering cyclohexanone as a single dose, either per oral or intraperitoneal, to groups of animals.

The animals were observed for 7 days for evidence of toxicity and post-mortem examinations were conducted. The following results were attained for LD50 (g/kg):

species	sex	number/group	route	LD50 (g/kg)
mice	M	10	ip	1.23
	M	10	po	2.07
	F	10	po	2.11
rat	M	4	ip	1.13
	M	4	po	1.80
	F	4	po	1.80
rabbit	M	3	ip	1.54
Guinea pigs	M	3	ip	0.93

Note: ip = intra peritoneal; po = per oral

Post mortem examination of animals dying from cyclohexanone revealed peritoneal and intestinal congestion, suggesting an irritant effect of the compound.

The acute lethality of cyclohexanone was determined by estimating the LT50 (the duration of inhalation exposure to saturated vapour which would kill 50 % of the exposed animals). For mice the investigators found a LT50 of 100 min. During exposure the animals exhibited *signs of irritation, laboured respiration and CNS depression*, sometimes followed by death. Gross postmortem examination showed general vascular congestion and haemorrhage of the lungs. Histological examination revealed *lung edema*. Those sacrificed 7 days after exposure showed hyperplasia of the spleen. Sections of the brain, heart, liver, adrenals and gonads were found to be within normal limits.

To study cellular toxicity, in vitro experiments were performed by the investigators. It was found that cyclohexanone was cytotoxic to mouse fibroblast cells in culture and produced negative inotropic effect upon the isolated perfused rabbit heart.

The target organ in acute exposure seems to be the central nervous system. Treon et al. (1943 A) reported that rapid narcosis without convulsions occurred in rabbits after receiving a single dose of cyclohexanone by stomach tubing at doses of 1600-1900 mg/kg. Also in exposure by inhalation, cyclohexanone may influence the central nervous system. De Ceaurriz et al. (1983) performed an experiment in which mice were exposed to various concentrations of cyclohexanone or other aliphatic or

aromatic solvents during a four hour period. After exposure the animals were investigated on the duration of immobility shown in a "behavioral despair" swimming test, by determining the ID50 (the atmospheric level responsible for a 50 % reduction in duration of immobility). The exposed animals showed a dose-dependent decrease of the duration of immobility when exposed to levels from 184 to 577 ppm (750-2350 mg/m^3) cyclohexanone, and an ID50 of 308 ppm (1260 mg/m^3).

Recently Holland et al. (1990) studied the mechanisms behind the influence of cyclohexanone on the central nervous system by testing the ability of the compound to produce seizures or to inhibit seizures induced by pentylenetetrazol and maximal electroshock in mice. It was found that cyclohexanol given at a dose of 0.01 ml/g body weight i.p. prevented both drug- and maximal shock-induced seizures. These results suggest that cyclohexanol acts at the picrotoxin receptor to increase or decrease neuronal activity. This means that cyclohexanone have mechanisms of action similar to those of the neuroactive γ-thiobutyrolactones.

7.1.3. Short-term toxicity

Similar to acute exposure, the target organ in short-term exposure to cyclohexanone is the ***central nervous system***.

Koeferl et al. (1981) exposed male dogs by intravenous administration of cyclohexanone at a dose of 284 mg/kg/d for 18-21 days. The signs of toxicity observed included vocalization, lacrimation, scleral vasodilation, mydriasis, salivation, urination, defecation, restlessness, stupor, ataxia, occasional convulsive movements, hyperpnoea and/or dyspnea. The severity of the responses correlated well with the maximal plasma concentrations of cyclohexanone attained, which ranged from 80 to 320 µg/ml.

There were some reports of effects on ***the liver*** after short-term exposure. Treon et al. (1943 B) reported that rabbits exposed to 190 ppm (775 mg/m^3) cyclohexanone repeatedly showed "barely demonstrable degenerative changes in the liver". They did not make any report on the animals exposed to higher doses. An increase of the absolute and relative liver weights in dogs was reported by Koeferl et al. (1981). The animals were administered by intravenous injection at a dose of 284

mg/kg/day for 18-21 days as a 6 % solution at 75 ml/min. On pathologic examination of the liver they found glycogen depletion, plasma cell infiltrates around the hepatic veins, hemosiderin deposits and extramedullary haematopoiesis. Gupta et al. (1979) performed a pentobarbital sleeping time experiment on ten male mice per group injected with 0.1, 0.2 or 0.5 of the acute LD50 (i.p.) of cyclohexanone daily for three consecutive days. 24 Hours after the last injection each mouse received 50 mg/kg pentobarbital sodium. It was found that pretreatment with cyclohexanone did not alter the sleeping time of the mice. This means that the compound did not influence the hepatic microsomal enzyme function responsible for pentobarbital metabolism. The activity of these enzymes was also not affected by cyclohexanone in beagle dogs (Martis et al. 1980).

At high doses cyclohexanone may have an effect on the ***blood forming organs***. Dogs receiving intravenous doses of 142 or 284 mg/kg/d, 5 d/w for 21 days showed erythroid hyperplasia as evidenced by increased haematocrit, erythroid ratios less than unity and nucleated red blood cells in peripheral blood. The bone marrow changes were accompanied by extramedullary haematopoiesis in the spleen (Koeferl et al. 1976). In a following study (Koeferl et al. 1981) on dogs administered i.v. with cyclohexanone at a dose of 284 mg/kg for 18-21 days they found haemolysis and secondary responses, e.g. bone marrow hyperplasia and extramedullary haematopoiesis. The doses given were very high, the highest dose is estimated to be equivalent to a level of 3000 mg/m^3 cyclohexanone in air (minute volume of 2 l and body weight of 10 kg).

A matter of contradiction is the influence of cyclohexanone on the ***induction of cataract***. The first account was reported by Rengstorff et al. (1972). Their experiment showed that small, multiple doses of cyclohexanone administered either cutaneously or subcutaneously on the backs of guinea pigs over a period of 3 to 8 weeks caused cataracts in 29 out of 120 animals. They consisted of subcapsular focal or extensive vacuolated areas extending from the periphery towards the center of the lens. The histological appearance of the lenses was similar to that of senile cataract and some forms of diabetic cataract. These findings had been contradicted by Greener et al. (1982). In their experiments on two different species of rats exposed

to cyclohexanone by intravenous injection of 50 or 100 mg/kg/d for 28 consecutive days showed no treatment-related structural lesions on ophthalmologic examinations. On the other hand it should be mentioned that an increase in optical density of lenses was observed among some of both species of rats, across all control and treatment groups. In 1984 again Greener and Youkilis studied the cataract potential of cyclohexanone, this time on guinea pigs and rabbits. Two methods of administration were used, the animals were either administered intravenously with doses of 0.5 or 5.0 mg/kg three times a week for three consecutive weeks, or by application on the skin (0.5 ml) with the same period of treatment. Ophthalmic examinations performed monthly for 6 months for treated animals and 7 months for untreated animals revealed the presence of anterior subcapsular vacuoles in guinea pigs in all groups. There was no difference in the incidence and severity of the lesions among treatment groups. No lenticular alterations were noted in any of the rabbits treated with cyclohexanone. The same experience was reported by Mayhew (1984). In his experiment, guinea pigs and rats were administered with cyclohexanone dermally (0.5 ml) on clipped backs three times per week, for 3 weeks in guinea pigs and for 3 or 13 weeks in rats. In the guinea pigs, changes were noted in the eyes which were identical in the control group, the exposed group and the positive control group. No treatment-related ophthalmoscopic changes were noted on the rats. It may be concluded that these alterations are apparently an inherent characteristic of the guinea pigs used in this kind of experiment, making this species unsuitable as model for the assessment of cataractogenic potential of an agent.

7.1.4. Long-term toxicity/carcinogenicity

There are only very few data on long-term exposure experiments. The National Cancer Institute of the US sponsored a 2-year long-term toxicity assay of cyclohexanone in rats and mice by administering cyclohexanone in drinking water (Lijinsky and Kovatch, 1986). Two concentrations were given to rats, 6500 or 3300 ppm (wt/vol). Male mice received 13000 or 6500 ppm, while female mice were given three concentrations 25000, 13000 or 6500 ppm. Survival and weight gain during the experiment were similar to those of the controls at the lowest cyclohexanone dose in both sexes of both species, but *the weight gain was depressed at all*

of the higher doses. Male rats receiving 3300 ppm cyclohexanone had a 13 % incidence of adrenal cortex adenomas compared with an incidence of 2 % in controls; the incidence of this neoplasm did not increase in the male rats receiving 6500 ppm or in the female rats given either doses. The mice had a statistically significant increased incidence of lymphomas-leukemias among the females given 6500 ppm, but not among groups given higher doses of cyclohexanone. Male mice given 6500 ppm cyclohexanone showed an increased incidence of hepatocellular adenomas and carcinomas, 50 % versus 32.5 % in controls, but the incidence of these neoplasms was only 37 % in male mice given 13000 ppm cyclohexanone. It can be concluded that there is inadequate evidence for carcinogenic activity of cyclohexanone. Of interest in this experiment is the depressed body weight gain found at the higher doses. When we use this variable as a parameter for the health of these animals, then it may be concluded that the *MOAEL for the rat is about 3300 ppm cyclohexanone in water, or may be extrapolated as a dose of 500 mg/kg b.w./day* (the authors estimated that consumption of 6500 ppm cyclohexanone in drinking water is equivalent to a dose of 1g/kg b.w./day). In the mice the same effect was found but less vulnerable.

Treon et al. (1943 B) exposed rabbits by inhalation to various concentrations of cyclohexanone, 6 h/d, 5 d/w, 50 times. They found signs of lethargy at a level of 1400 ppm (5700 mg/m^3) after 10 weeks and signs of narcosis at a level of 3000 ppm (12240 mg/m^3) after 3 weeks. Although haematologic variables were examined every week, no anomalies were reported at the levels given. No effects on the central nervous system were noted at the levels of 190-600 ppm (775-2450 mg/m^3), although some signs of irritation occurred at the higher concentrations. This means an *NOAEL of about 600 ppm (2450 mg/m^3)*.

Cyclohexanone does not affect the ***peripheral nervous system***, according to Perbellini et al (1981). This conclusion is based on their experiment in which rats received i.p. injection twice daily with each containing 200 mg/kg of cyclohexanone for periods up to 13 weeks. The electrophysiological and neuropathological studies (including the motor conduction and sensory conduction velocities, distal motor latency and sensory potential amplitude) during and after the treatment failed to detect any damages of the peripheral nervous system.

7.1.5. Mutagenicity

The following informations were attained from the IARC (1989):

- Cyclohexanone was not mutagenic to four strains of Salmonella typhimurium (TA 1535, TA 1537, TA 98 and TA 100) in the presence or absence of an exogenous metabolic system in a plate incorporation assay.
- Exposure of Chinese hamster ovary cells to cyclohexanone just as they were entering the S-phase induced sister-chromatid exchange and gene mutation in the absence, but not in the presence of an exogenous metabolic system. Under these conditions no chromosomal aberrations were induced in the presence or absence of an exogenous metabolic system.
- Cyclohexanone at 10^{-2}, 10^{-3} and 10^{-4} M induced chromosomal aberrations in cultured leucocytes. It also induced an increase in the frequency of chromosomal damage in human lymphocytes both in terms of ploidy and structural changes.
- Chromosomal abnormalities were induced in bone-marrow cells of male rats 6, 24 and 48 hours after subcutaneous injections of three doses, each of 0.1, 0.5 and 1.0 g/kg b.w. cyclohexanone. Abnormalities increased with dose and decreased with time, and consisted of chromatid gaps, breaks, centric fusions, centromeric attenuation, chromatid exchanges and polyploidy.

In 1980, the NIOSH sponsored a mutagenic screening study on cyclohexanone (McGregor 1980). The following results were attained:

- An unscheduled DNA synthesis (UDS) assay in human diploid fibroblasts was performed with exposures of 3 h duration and concentrations up to 9.48 mg/ml of culture medium. There was no increase in UDS in cells treated with cyclohexanone.
- A dominant lethal test in male rats with exposure to atmosphere containing 50 ppm or 400 ppm cyclohexanone for 7 h/d for 5 consecutive days showed no effect on the pregnancy frequency, numbers of corpora lutea or implantations or the frequency of early deaths.
- Sperm abnormality test in male mice was preformed using the same exposure conditions as in the previous experiment. Sperm frequency was not affected.

- A cytogenetic test in male and female rat bone marrow cells was performed using the same exposure conditions as in the previous two experiments or a single exposure of 7 hours duration followed by sampling after 6 h, 24 h and 48 h. The results showed that the frequencies of chromosomal aberrations were not increased significantly.
- A sex-linked recessive lethal (SLRL) test on Drosophila melanogaster with exposure to atmospheres of 50 ppm for 7 hours or 400 ppm for 40 min was executed. The results showed no increase on the SLRL frequency.

Massond et al. (1986) studied the genotoxicity of cyclohexanone through forward mutation assay using Bacillus subtilis. The results showed severe effects on B. subtilis survivals. Mutants obtained were requiring different amino acids, and the leucine requiring mutants had the maximum percentage of all. The Ames backward mutation test was held on the histidine-requiring S. Typhimurium TA 1535, TA 1537, TA 1538, TA 98 and TA 100. TA 98 showed the greatest response in producing a large number of revertants. It should be noted that these informations were attained from an abstract and no informations were given on the test conditions.

From above mentioned data it may be concluded that there is *limited evidence on the mutagenicity of cyclohexanone.*

7.1.5. Reproduction toxicology

There are many studies to investigate the influence of exposure to cyclohexanone on the reproduction. A summary is presented in *Table 1.*

In general it may be concluded that there is *no adverse effect on the reproduction* when the animals were given cyclohexanone at doses which were below the maternal toxic levels.

Of interest for the health assessment of exposure to cyclohexanon in occupational situation are the animal experiments in which exposure takes place by inhalation. The experiments performed by Homan and Schroeder (1984) on pregnant rats and

mice showed that exposure to levels of 300 to 1400 ppm (1220-5710 mg/m^3) cyclohexanone by inhalation 6 h/d, gestional days 6-19 in rats or days 6-17 in mice, showed no adverse effect on the reproduction. But at the highest dose there is reduction of the maternal body weight in rats and mice, which may be classified as an undesirable effect. In addition to that, the fetal weight in rats and the number of corpora lutea and live fetuses in mice were reduced. This means that the *NOAEL is about 650 ppm (2650 mg/m^3) cyclohexanone*. This is further confirmed by two other independent animal experiments. In 1986, the American Biogenic Corporation conducted a two-generation reproduction study in rats. At an exposure level of 1400 ppm cyclohexanone, 6 h/d, 5 d/w, reduction of maternal body weight occurred as well as reduced male fertility, reduced progeny survival and progeny body weight. During the first exposures at levels of 1000 ppm of the first generation, clinical reactions such as lacrimation, ataxia and irregular breathing were found. No adverse effect on the reproduction as well as general toxicity were found at exposure levels of 500 ppm (2040 mg/m^3). This means that *the NOAEL should lie between 500 and 1000 ppm (2040 and 4080 mg/m^3, respectively)*. Another experiment was conducted by Samimi et al. (1989). Pregnant rats were exposed to 100, 250 and 500 ppm (408, 1020 and 2040 mg/m^3 respectively). No treatment related effects were found and no malformations on the external and soft tissues and the skelet were detected in the fetus. This means that the *NOAEL should be around or above 500 ppm (2040 mg/m^3)*.

When we summarize abovementioned data, then we can conclude that the NOAEL of 650 ppm (2650 mg/m^3) in rats and mice is confirmed by three independent experiments.

Table 1. A summary of animal studies performed to investigate the influence of cyclohexanone on the reproduction

Authors (year)	Species of animal	Level of exposure	Method and results of study	Comments
Gondry (1972)	male and female mice	1 % in food continuously for one generation (~ 2000 mg/kg/d)	Inhibits very slightly the growth of first-generation males, but more that of females. On the other hand the second generation was normal.	Low viability on the control and treated animals.
Hall et al. (1974)	female mice	50 mg/kg/d i.p. for 28 d	Housed with untreated males during treatment. No adverse effect on the litters.	
Chernoff and Kavlock (1983, cit.IARC)	pregnant mice	800 mg/kg/d oral day 8-12 of gestation	No treatment-related maternal or developmental effect was observed.	
Homan and Schroeder (1984)	pregnant rats	300, 650 and 1400 ppm by inhalation, day 6-19 of gestation	Maternal and fetal body weight significantly reduced at 1400 ppm. No effects on preimplantation loss, number of resorptions or dead or live fetuses per litter. No malformations.	Based on these informations the likely *NOAEL based on body weight is estimated at 650 ppm (2650 mg/m^3).*
	pregnant mice	1400 ppm by inhalation, day 6-17 of gestation	Maternal body weight was reduced. The number of corpora lutea and live fetuses were reduced. No significant increase of external malformations.	Visceral and skeletal examinations had not been completed.
Gray and Kavlock (1984)	pregnant mice	800 mg/kg/d oral day 8-12 of gestation	Extended observation for 250 days after treatment, on body and organ weights of the neonatus. No treatment-related effects were found.	Continuation of the experiment from Chernoff and Kavlock (1983)

Seidenberg et al. (1986)	pregnant mice	2200 mg/kg/d gavage day 8-12 of gestation	Lower neonatal body weight on day of birth and 2 days postpartum. No developmental toxicities were found.	The dose given was expected to be slightly toxic to the pregnant mice (body weight reduction).
American Biogenic Corporation (1986)	male and female rats	250, 500 and 1000 ppm (F_0) and 250, 500 and 1400 ppm (F_1), by inhalation 6 h/d, 5 d/w	Two-generation reproduction study. At 250, 500 (both generations) and 1000 ppm (first generation) induced no adverse effects. At 1400 ppm resulted in male body weight depressions, *reduced male fertility*, reduced progeny survival and progeny body weight depressions.	Based on this study it may be concluded that *the NOAEL lies between 500-1000 ppm (240-4080 mg/m^3).*
Samimi et al. (1989)	pregnant rats	100, 250 and 500 ppm, by inhalation 7 h/d, day 5-20 of gestation	No treatment-related effects on fetal weight, resorption sites, fetal death, sex-ratio. No malformations on the external and soft tissues and on the skelet.	This experiment confirms previous experiments that *at 500 ppm (2040 mg/m^3) no adverse effect is noted* on the reproduction.

7.2. OBSERVATIONS IN MAN

There is almost no information on the effects of occupational exposure to cyclohexanone on the health of workers. Until to date no epidemiological studies have been conducted.

In 1943 Nelson et al. studied the sensory response of industrial solvent vapours on human volunteers. An average number of ten persons, of both sexes, were exposed to a given concentration of solvent vapour for a period of 3 to 5 minutes. For exposure to cyclohexanone it was found that the highest concentration which the majority of the subjects agreed acceptable for an 8-hour exposure was 25 ppm (100 mg/m^3). The concentration in which the majority complained of irritation for the eyes as well as for the nose and throat was 75 ppm (300 mg/m^3) .

Bruze et al. (1988) reported cases of 5 patients with allergic contact dermatitis caused by various paints. Patch testing revealed contact allergy to the relevant paint, and additional testing with the ingredients showed a cyclohexanone resin to be the sensitizer in all patients. Cyclohexanone resin is not a chemically defined compound but consists of the main raw material, cyclohexanone, and several other substances formed when the resin is manufactured. No attempts have been made to identify the sensitizers responsible for contact allergy to cyclohexanone resin, but they are probably to be found among the monomers and dimers formed when cyclohexanone is condensed in the production of the cyclohexanone resin.

Sakata et al. (1989) reported a case of attempted suicide in which the patient came to a coma after drinking a liquid cement for PVC resin, containing acetone, MEK, cyclohexanone and PVC. Although cyclohexanone made up the largest component in the solvent, the blood level was extremely low and a large amount of cyclohexanol was detected in blood and urine.

7.3. SUMMARY

- Animal data showed that cyclohexanone induced concentration dependent irritation to the skin and eyes. Cyclohexanone itself had no allergenic potential, but cyclohexanone resin induced sensitization on the skin of guinea pigs.

- Human volunteer studies showed that at the level of 75 ppm (300 mg/m^3) the majority complained of irritation of the eyes, the nose and throat. At 25 ppm (100 mg/m^3) it was agreed to be acceptable for most of them. Cases of allergic contact dermatitis has been reported on people working with paints, probably caused by cyclohexanone resin.

- The oral LD50 for rats is 1800 mg/kg b.w., and for mice 2100 mg/kg b.w. During exposure to lethal concentrations of cyclohexanone the animals showed signs of irritation, laboured respiration and CNS depression. Histological examination revealed lung edema.

- The *critical organ in acute exposure* seems to be the *central nervous system*. An increase in immobility was observed in rats in a "behavioral despair" swimming test when exposed to 184-577 ppm (750-2350 mg/m^3) during a 4 hour period. A study on the mechanisms revealed that cyclohexanone probably acts on the picrotoxin receptor to increase or decrease neuronal activity.

- *Long-term* toxicity studies also showed the *central nervous system* to be the target organ. For rabbits a *NOAEL of about 600 ppm (2450 mg/m^3), 6 h/d, 5 d/w for 10 weeks* can be established. Lethargy occurred when they were exposed to higher levels. On the other hand, cyclohexanone appears not to affect the peripheral nervous system.

- There were some reports of effects on *the liver* after short-term exposure to cyclohexanone. An increase of absolute and relative liver weights was found in dogs after i.v. injections of a dose of 284 mg/kg/d for 18-21 days. Pathologic examination revealed glycogen depletion, plasma cell infiltrates around the hepatic veins, hemosiderin deposits and extra-medullary haematopoiesis. An experiment with mice showed that pretreatment with cyclohexanone did not influence the pentobarbital-induced sleeping time.

- At high doses cyclohexanone may influence the *blood forming organs* and peripheral red blood cells. These effects were found in dogs administered i.v. 142-284 mg/kg/d, 5 d/w for 21 days. Bone marrow hyperplasia and extramedullary haematopoiesis were observed.

- The induction of *cataract* by cyclohexanon when administered to guinea pigs may be an artifact. This kind of effect seems to be an inherent characteristic of guinea pigs, but not of rats and rabbits.

- One *long-term* animal study in rats and mice in which cyclohexanone was administered through drinking water, inadequate evidence for carcinogenic activity is found. Of interest is the depressed body weight gain found in animals exposed to high doses. Using this variable it may be concluded that the *MOAEL for the rat is about 3300 ppm cyclohexanone in drinking water, what corresponds to a dose of 500 mg/kg b.w./d. during two years*

- For the *genotoxicity and clastogenicity* experiments performed on cyclohexanone it may be concluded that there is limited evidence of the mutagenicity.

- In general it may be concluded that there is no evidence of an adverse effect on *the reproduction* when experimental animals were given doses which were below the maternal toxic levels.

  Of interest in these experiments were those in which the animals were given cyclohexanone by inhalation. Pregnant rats and mice exposed to 300-1400 ppm (1120-5710 mg/m^3) cyclohexanone showed reduction of maternal body weight at the higher doses. In addition to that, the fetal weight in rats and the number of corpora lutea and live fetuses in mice were also reduced. It may be concluded that the *NOAEL is about 650 ppm (2650 mg/m^3) cyclohexanone, for 12 gestational days.*

  In a two-generation study of rats, exposure to 1400 ppm (5710 mg/m^3), 6 h/d, 5 d/w, also reduced maternal body weights were found as well as reduced male fertility, progeny survival and progeny body weight. From this study the *NOAEL is estimated to lie between 500-1000 ppm (2040-4080 mg/m^3) cyclohexanone.*

  These above mentioned assessments have been confirmed in another study of pregnant rats given levels of 100, 250 and 500 ppm (408, 1020 and 2040 mg/m^3,

respectively) cyclohexanone. No treatment-related effects and no malformations in the fetus were found. This means that ***the NOAEL should be around or above 500 ppm*** (2040 mg/m^3) ***cyclohexanone for 15 gestational days.***

- Until to date no epidemiological study on the effects of cyclohexanone on the health of workers has been reported.

8. PREVIOUS EVALUATION BY (INTER)NATIONAL BODIES

In ***the United States***, the ACGIH recommended a TLV-TWA of 25 ppm (100 mg/m^3) for cyclohexanone with a skin-notation in 1987. This standard is based on experimental data from Treon et al. (1943) and Nelson et al. (1943), who stated that a level of 190 ppm in rabbits is very little above the maximal safe level for these animals, and in humans 50 ppm is not tolerated and at 25 ppm was not objectionable for most subjects during 3-5 min exposure. They agreed that prolonged exposure to rabbits may induce liver and kidney damage. The Committee of the ACGIH also recommends the deletion of the STEL until additional toxicological data and industrial hygiene experience become available. In 1985, the STEL was placed in the Notice of Intended Changes.

In ***Germany*** the DFG recommended a MAK level of 50 ppm (200 mg/m^3) cyclohexanone in 1971. This concentration is based almost on the same grounds as that of the ACGIH, only with the following note: "Der derzeitige MAK-wert von 50 ppm wurde auf Grund der angeblichen Reizwirkung höherer Konzentrationen angesetzt. 50 ppm bietet somit einen genügenden Sicherheitsspielraum".

Sweden uses occupational standards of 25 ppm (100 mg/m^3) for TWA-8 h and 50 ppm (200 mg/m^3) for short-term exposure, with a skin notation in 1990. No scientific criteria document is available for the health assessment (Lundberg et al. 1991).

No scientific criteria document existed for the occupational standards from the Netherlands and the United Kingdom.

9. EVALUATION OF HUMAN HEALTH RISKS

9.1. GROUPS AT EXTRA RISKS

Based on literature data there are no indications of groups at extra risk in exposure to cyclohexanone exclusively.

It should be pointed out that for exposure to *cyclohexanone resin*, some reports of allergic contact dermatitis had been published. Workers who have shown allergic symptoms to the resin should therefore be classified as group at extra risk.

9.2. ASSESSMENT OF HEALTH RISKS

Cyclohexanone is a volatile colourless liquid with a peppermint and acetone odour. The most probable method of exposure to cyclohexanone in work environment is by inhalation of its vapour or through skin contact with its liquid phase. After absorption, cyclohexanone is metabolized into cyclohexanol and isomers of cyclohexanediol. Biological monitoring is possible by determining the metabolite levels in urine.

There is one important drawback in the health-assessment of exposure to cyclohexanone. Until to date, no epidemiological study on the effects of cyclohexanone on workers occupationally exposed to this compound has been reported. This leaves health-assessment from animal data exclusively.

The first objective in a health-assessment of exposure to an agent is to determine the target organs. For cyclohexanone it depends on the exposure duration. In *acute exposure* the target organs are the mucous membranes of the upper respiratory tract and the central nervous system. At 75 ppm (300 mg/m^3) for a few minutes irritation of the nose, throat and eyes have been reported in human volunteers. In rats behavioral aberrations occurred at levels of 184-577 ppm (750-2350 mg/m^3) during 4 hours period, although the extrapolation into human behaviour is difficult to make.

In *short-term exposure* the target organ is the central nervous system, although aberrations of the liver and the blood forming organs as well as peripheral red blood

cells may also occur but at much higher levels of exposure. Based on the CNS effects a NOAEL of about 600 ppm (2450 mg/m^3), 6 h/d, 5 d/w, 10 weeks is found. However, it should be pointed out that the experiment was performed with a very small number of animals (four rabbits each, Treon et al. (1943!). The results should be treated with caution.

One *long-term exposure* experiment with rats and mice given cyclohexanone by drinking water showed that the evidence for carcinogenicity is marginal. Of interest in this experiment is the depressed weight gain found in animals exposed to the higher doses. It may be concluded that, based on this variable, the *MOAEL for the rat is about 500 mg/kg/d for 2-years*. When extrapolated to a dose for humans and by using a safety factor of 10, this level is equivalent to a level of *350 mg/m^3 (88 ppm) cyclohexanone in inhaled air during 8 hours exposure per day.* There is inadequate evidence that cyclohexanone is mutagenic, on the other hand some evidence exists for clastogenicity.

There are three experiments performed to study the influence of cyclohexanone, administered by inhalation, on reproduction. It may be concluded that there are no adverse effects when the pregnant animals are given doses below the maternal toxic levels. Surprisingly all these independent experiments give the same conclusion, namely that the *NOAEL should be about 500-650 ppm (2040-2650 mg/m^3) cyclohexanone* when given during pregnancy. At higher levels of exposure, reduction of maternal and fetal body weight occurred as well of the number of corpora lutea and live fetuses.

Human volunteer studies showed that exposure at the level of 300 mg/m^3 the majority complained of irritation of the eyes, nose and throat and at 100 mg/m^3 it was agreed to be acceptable for most of them. The DECOS expresses more significance on the local effects as found acceptable at 100 mg/m^3, as the ***starting point***, than that of the systemic effects as found in the animal data, since the former occurred at lower levels. Based on this notation and using a safety factor of two, the DECOS recommends ***a health-based occupational exposure limit of 50 mg/m^3 (12.5 ppm) for cyclohexanone.***

A skin notation is proposed since absorption through the skin is estimated at ten percent from that through the oral route.

9.3. RECOMMENDED OCCUPATIONAL EXPOSURE LIMIT

Health-Based Occupational Exposure Limit of cyclohexanone of 50 mg/m^3 (12.5 ppm) TWA-15 minutes with skin notation.

10. RECOMMENDATIONS FOR RESEARCH

- Epidemiological studies on workers occupationally exposed to cyclohexanone are very much needed to confirm the existing animal data. Environmental monitoring programs should be set up in specific occupations to give insight on levels of exposure.

- Biological monitoring studies are also recommended to investigate the relationship between cyclohexanol and the other metabolites of cyclohexanone, the cyclohexanediols.

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Members of the Dutch Expert Committee on Occupational Standards (DECOS)

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RAPPORTEN VAN DE WERKGROEP VAN DESKUNDIGEN
(op alfabetische volgorde)

	RA
Acetaldehyde	6/92
Acrylaten	13/87
Aflatoxine B1, B2, G1 en G2	6/87
Allylglycidylether	1/92
Amyl acetate	4/90
Aniline	2/89
Anorganisch Lood	2/80
Anorganische Kwikzouten	3/82
Arc welding fume particles not containing chromium and nickel	1/93
Arseenverbindingen (Anorganische)	2/84
Asbest	1/84
Asbest, Evaluatie van risico op kanker bij beroepshalve blootstelling aan (aanvullend op RA 1/84)	9/89
Benzeen	5/89
Beryllium and Beryllium compounds	4/88
Blootstelling, Gezondheidskundige aspecten van het begrip en van het meten/schatten ervan	8/90
Butadiene(1,3-)	5/90
Cadmium	5/80
Caprolactam	4/84
Carbon disulphide	9/92
Carbon monoxide	7/92
Carbonylfluoride and PTFE Pyrolysis products	3/88
Carcinogene stoffen	3/80
Chloor	6/80
Chloroform	7/87
ß-Chloroprene	4/93
Chroom en chroomverbindingen	6/85
Cyclohexane	15/90
Cyclohexanol	3/90
Cyclohexanone	9/93
Dibroomethaan	5/87
Dichloorethaan (1,1-)	8/87
Diisocyanates	3/91
Dimethyl- en diethylsulfaat	12/90
Dimethylamine	10/90
Dimethylbutane (2,2- & 2,3-)	7/93
Dimethylhydrazine	2/87
Dinitro-ortho-cresol (4,6-)	4/87
Dioxaan (1,4-)	1/87
Epichloorhydrine	1/86
Ethyl acrylate	6/90
Ethyl acetate	10/91
Ethyl Methanesulphonate (EMS)	4/89
Ethyl amine	7/90
Ethylbenzene	9/91
Ethyleenoxide	6/89
Fenylhydrazine	2/87
Fluorcarbons(except FC11)	15/87
Fluorine compounds(inorganic)	1/89
Fluorine	1/89

Formaldehyde	3/87	
Fosfine	1/80	
Fijn hinderlijk stof; gezondheidskundige aspecten van bijlage 3 bij de Nationale MAC-lijst 1989	9/90	
Gasoline	3/92	
Heptaan (n-)	1/81	
Heptane (n-)	6/93	
Hexaan (n-)	11/87	
Hexachlorobenzene	2/88	
Hexanone (2-)	2/90	
Hydrazine	2/87	
Hydrogenfluorine	1/89	
Hydroxyethylhydrazine	2/87	
Isopropylglycidylether	1/92	
Isopropoxyethanol (2-)	12/87	
Koolmonoxide (Carbon monoxide)	2/79	(7/92)
Kwikalkylverbindingen - Korte keten	5/82	
Kwikverbindingen (Organische)	4/82	
Lachgas (Nitrous oxide)	2/85	(2/92)
Lasrook (Arc welding fume....nickel)	1/93	
Mangaan	1/82	
Metallisch Kwik	5/81	
1-Methoxypropanol-2	5/93	
2-Methoxypropanol-1	5/93	
1-Methoxypropylacetate-2	5/93	
2-Methoxypropylacetate-1	5/93	
Methyl acrylate	1/90	
Methyleenchloride (Methylene chloride)	1/83	(8/92)
Methyl ethyl ketone	16/90	
Methyl isobutyl ketone	4/91	
Methyl Methanesulphonate (MMS)	4/89	
Methylbromide	13/90	
Methylpentane (2- & 3-)	7/93	
Monochloorethaan	2/82	
Monoketones (7/8 Carbon chain Aliphatic)	14/90	
Nikkel en nikkelverbindingen	3/85	
Nitropropaan (2-)	1/85	
Nitrous oxide	2/92	
Ozone	4/92	
Para-Dichloorbenzeen	1/88	
Pentaan	2/81	
Phthalate esters	8/93	
Phthalic anhydride	3/89	
Piperazine	7/91	
Polyvinyl chloride (PVC) dust	2/93	
Propoxyethanol (2-)	12/87	
Propoxyethylacetate (2-)	12/87	
Pyridine	3/93	
Selenium en verbindingen	7/89	
Silicon dioxide, Crystalline forms of	5/92	
Stikstofdioxide	5/85	
Styreen	8/89	
Talc dusts	6/91	
Tetrahydrofuran	1/91	
Thiourea	11/90	

Tolueen Diisocyanaat	4/80
Tolueen	2/91
Trichloorethaan(1,1,1-)	3/81
Trichloorethyleen	3/83
Trichlorofluoromethane	14/87
Triethylamine	2/83
Trimethylamine	9/87
Vanadium metaal en anorganische verbingingen	10/87
Wood dust	8/91
Xylene	5/91
Zwaveldioxide	4/85

PUBLIKATIES ARBEIDSINSPECTIE

Publikatiebladen

CODE		PRIJS
P 1	Inhoud verbandtrommels Middelen voor de Eerste hulp bij ongevallen op het werk Vijfde druk 1993	f 7,50
P 41	Zittend en staand werk, ergonomische aspecten Vierde druk 1993	f 16,-
P 77	Het tegengaan van beroepshuidaandoeningen Tweede druk 1983	f 10,-
P 88-2	Gevaarlijke stoffen in de haven; Veilig stuwen in containers; Veilig stuwen van containers Eerste druk 1984	f 13,-
P 89	Blauwzuur; Veilige behandeling in de haven Derde druk 1983	f 10,-
P 90	Zwavelwaterstof; Veilige behandeling in de haven Tweede druk 1982	f 10,-
P 91	Zwavelkoolstof; Veilige behandeling in de haven Tweede druk 1982	f 10,-
P 92	Chloor; Veilige behandeling in de haven Derde druk 1982	f 10,-
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P 94	Fosgeen; Veilige behandeling in de haven Derde druk 1984	f 11,-
P 95	Allylalcohol; Veilige behandeling in de haven Derde druk 1984	f 11,-
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P 98	Acetoncyaanhydrine; Veilige behandeling in de haven Tweede druk 1984	f 11,-
P 99	Chloorpicrine; Veilige behandeling in de haven Tweede druk 1984	f 11,-
P 100	Acrylnitril; Veilige behandeling in de haven Tweede druk 1981	f 10,-
P 101	Zwaveldioxide; Veilige behandeling in de haven Tweede druk 1982	f 10,-
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P 108	Methylbromide; Veilige behandeling in de haven Derde druk 1984	f 11,-

Chemie (gevaarlijke stoffen)

CODE		PRIJS
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P 110	Loodakylverbindingen; Veilige behandeling in de haven Tweede druk 1984	f 11,-
P 111	Paration; Veilige behandeling in de haven Tweede druk 1984	f 11,-
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P 112-2	Ademhalingsbeschermingsmiddelen; Overzicht en beschrijving Eerste druk 1985	f 20,-
P 112-3	Keuzetabel Ademhalingsbeschermingsmiddelen Tweede druk 1983	f 15,-
P 130	Laboratoria; Veiligheid bij gebruik van gevaarlijke stoffen Eerste druk 1982	f 26,-
P 130-1	Laboratoria; Veiligheid en hygiëne Algemeen Tweede druk 1982	f 16,-
P 134-1	Zweminrichtingen; Wettelijke bepalingen Derde druk 1982	f 11,-
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P 134-5	Zweminrichtingen; De opslag en het gebruik van kooldioxide Eerste druk 1980	f 12,-
P 139	Verfverwerking Tweede druk 1986	f 13,-
P 145	Nationale MAC-lijst 1992 Achtste druk 1992	f 16,-
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P 172-2E	Occupational Safety Report; Guideline for compilation Eerste druk 1990	f 15,-
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S 30-1	Algemeen April 1987	f 19,-
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S 30-6	Tetrachlooretheen April 1987	f 9,-

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Commissie preventie van rampen door gevaarlijke stoffen

CODE		PRIJS
CPR 2	Model voor risico-evaluatie van opslag van gevaarlijke stoffen, vloeistoffen en gassen Eerste druk 1982	f 19,-
CPR 3	Organische peroxiden; Opslag Eerste druk 1982	f 29,-
CPR 3-E	Storage of organic peroxides Eerste druk 1982	f 30,-
CPR 4	Experimenten met chloor (rapporten) Eerste druk 1979	f 46,-
CPR 5	Vloeibare zuurstof; Opslag van 0,45 -100 m3 Eerste druk 1983	f 21,-
CPR 6	Vloeibare zwaveldioxide Eerste druk 1983	f 32,50
CPR 7	De bewaring van springstoffen en ontstekingsmiddelen Eerste druk 1983	f 14,-
CPR 8-1	Supplement Autogas (LPG) Supplement 1988	f 22,50
CPR 8-2	LPG-Tankwagens Eerste druk 1985	f 27,50
CPR 8-3	Distributiedepots voor LPG (Butaan, Propaan en hun mengsels) Eerste druk 1991 ISBN 9053071652	f 42,50
CPR 9-1	Vloeibare aardolieprodukten; Ondergrondse opslag in stalen tanks en afleverinstallaties voor motor-brandstof Vijfde druk 1993	f 43,-
CPR 9-2	Vloeibare aardolieprodukten; Bovengrondse opslag kleine installaties Eerste druk 1985	f 29,-
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CPR 11-1	Propaan; Het gebruik van propaan op bouwterreinen Eerste druk 1984	f 35,-
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CPR 11-5	Propaan vulstations van butaan- en propaanflessen Concept eerste druk 1991	f 41,-
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CPR 12-E	Methods for determining and processing probabilities Eerste druk 1988	f127,50
CPR 13	Ammoniak; Vervoer, opslag en toepassingen Tweede druk 1988	f 46,-
CPR 14	Methoden voor het berekenen van fysische effecten Eerste druk 1988	f159,-
CPR 14-E	Methods for the calculation of physical effects Tweede druk 1991	f156,-

CODE		PRIJS
CPR 15	Supplement Handboek brandbestrijdingssystemen (te hanteren naast de Richtlijnen CPR 15-1, 2 en 3 voor de opslag van verpakte gevaarlijke stoffen) Eerste druk 1993 ISBN 9039905614	*f* 40,-
CPR 15-1	Opslag gevaarlijke stoffen in emballage; Opslag van vloeistoffen en vaste stoffen (0 tot 10 ton) Tweede druk 1990 ISBN 9053070338	*f* 20,-
CPR15-1E	Storage of Packaged Hazardous Materials; Storage of liquids and solids (0-10 tons) Eerste druk 1992	*f* 19,-
CPR 15-2	Opslag gevaarlijke stoffen, chemische afvalstoffen en bestrijdingsmiddelen in emballage; opslag van grote hoeveelheden Eerste druk 1991 ISBN 9053072128	*f* 22,50
CPR 15-3	Opslag van bestrijdingsmiddelen in emballage; Opslag van bestrijdingsmiddelen in distributiebedrijven en aanverwante bedrijven (vanaf 400 kg) Eerste druk 1990 ISBN 9053071024	*f* 21,-
CPR15-3E	Storage of Packaged pesticides Storage of pesticides in distribution and related enterprises (in excess of 400 kg) Eerste druk 1992	*f* 21,-
CPR 16	Methoden voor het bepalen van mogelijke schade aan mensen en goederen door het vrijkomen van gevaarlijke stoffen Eerste druk 1990	*f*159,-
CPR 16E	Methods for the determination of possible damage to people and objects resulting from releases of hazardous materials Eerste druk 1992	*f*159,-

R-bladen

CODE		PRIJS
R 1	Voorlopige richtlijnen voor de beveiliging van stookinstallaties met een maximum belasting groter dan 600 kW in de procesindustrie en die gestookt worden met gasvormige of vloeibare brandstoffen Eerste druk 1978	*f* 29,-
R 1-E	Provisional guidelines for the safeguarding of fuel-burning installations with a maximum try and fired gaseous or liguid fuels Eerste druk 1979	*f* 36,-
R 2-E	Guide for the classification of hazardous areas in zones in relation to gasexplosion hazards and to the installation and selection of electrical apparatus Eerste druk 1980	*f* 31,-
R 3-E	Hazard and operability study; Why? When? How? Eerste druk 1979 (Nederlandse uitgave zie V2)	*f* 24,-

Overige publikaties

CODE		PRIJS
OP 1	Experimenten met acrylnitril Eerste druk 1971	*f* 19,-
OP 1-E	Experiments with Acrylonitrile Eerste druk 1972	*f* 19,-
OP 2	Experimenten met acrylnitril; Blusproeven (Nederlands en Engels) Eerste druk 1972	*f* 20,-
OP 3	Experimenten met chloor Eerste druk 1975	*f* 16,-
OP 3-E	Experiments with chlorine Eerste druk 1975	*f* 16,-
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