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Ministry of Social Affairs and Employment

Health-based recommended occupational exposure limit for n-heptane

Dutch expert committee on occupational standards (met Nederlandstalige samenvatting)

RA 6/93

Labour Inspectorate

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An update of the document published in 1981 (RA 1/81)
Dutch expert committee on occupational standards (met Nederlandstalige samenvatting)

**This is a report of the Dutch Expert Committee on occupational standards (DECOS).
The draft-document has been prepared by J.T.J. Stouten**

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SAMENVATTING

1. INLEIDING

Dit rapport is een evaluatie van literatuur over de toxicokinetiek en de toxische effecten van n-heptaan, die na het verschijnen van het criteriumdocument van de WGD in 1981 is gepubliceerd, en, daarmee samenhangend, een herevaluatie van de huidige grenswaarde.

2. MONITORING

NIOSH heeft een methode gepubliceerd voor het meten van koolwaterstoffen met een kookpunt tussen 36 en 126 °C, waaronder n-heptaan. CONCAWE, een Europese organisatie van olieconcerns op het gebied van bescherming van milieu en gezondheid, heeft een gestandaardiseerde en gevalideerde methode beschreven voor het meten van alle componenten van benzinedamp in de lucht op de werkplek. Deze methode lijkt ook geschikt voor de bepaling van concentraties van n-heptaan. Daarnaast is persoonlijke bemonstering met passieve dosimeters mogelijk.
Er zijn geen uitgewerkte methoden voor biologische monitoring, maar m.b.v. gaschromatografische technieken is bepaling van n-heptaan en zijn metabolieten in bloed of urine mogelijk.

3. GRENSWAARDEN

In Nederland, Groot-Brittannië en de V.S. geldt een grenswaarde van 400 ppm (1600 mg/m^3), 8-uur tgg; in Duitsland van 500 ppm (2000 mg/m^3), terwijl Zweden een norm van 200 ppm (800 mg/m^3), 8-uur tgg, hanteert. Daarnaast zijn er limietwaarden voor korte perioden van 10-30 min., variërend van 300 (1200 mg/m^3) (Zweden) tot 1000 ppm (4000 mg/m^3) (Duitsland).

4. TOXICOKINETIEK

Na inhalatie bedraagt de retentie van n-heptaan bij mens en proefdier (rat) 25-30%. Op basis van de resultaten van in vitro studies met rattehuid is niet te verwachten dat de huid een belangrijke opnameroute is voor vloeibaar n-heptaan.

n-Heptaan wordt geoxideerd tot voornamelijk 2- en 3-heptanol, die vervolgens hoofdzakelijk als sulfaatconjugaten worden uitgescheiden in de urine. Daarnaast is, in theorie, de vorming van een groot aantal andere metabolieten (heptanolen, heptanonen, hydroxyheptanonen, heptadiolen, heptadionen) mogelijk, waarvan een aantal ook zijn aangetoond in de urine van werkers en proefdieren (ratten). Hoewel het neurotoxische 2,5-heptadion is gedetecteerd in de urine van een aantal van de onderzochte werkers, zijn er te weinig kwantitatieve gegevens om te kunnen beoordelen in hoeverre en in welke mate dit γ-diketon wordt gevormd.

5. EFFECTEN

Bij de mens kan huidcontact met vloeibaar n-heptaan leiden tot irritatie, dermatitis en blaarvorming. Blootstelling aan 400 ppm van een mengsel dat n-heptaan bevatte, veroorzaakte enige lichte mate van oogirritatie.
Er zijn geen gegevens betreffende systemische effecten bij de mens, noch gegevens uit dierproeven naar carcinogeniteit en reproductietoxiciteit. n-Heptaan is negatief in vitro mutageniteitstesten in bacteriën, gist en een dierlijk levercelsysteem.
In een chronische inhalatieproef waarin ratten gedurende 26 weken werden blootgesteld aan 400 en 3000 ppm (1668, 12510 mg/m^3) n-heptaan, werden geen neuropathologische afwijkingen, noch effecten op het lichaamsgewicht gevonden. Van het beperkt aantal klinisch-chemische parameters dat werd onderzocht, was alleen de alkalische fosfatase-activiteit in het serum van de vrouwtjesratten enigszins (significant in de 3000 ppm-groep) verhoogd. Deze verhoging wordt echter niet relevant geacht m.b.t. de evaluatie van het gezondheidsrisico van werkers.

6. ADVIESWAARDE

De advieswaarde is gebaseerd op de hierboven beschreven chronische inhalatie-proef met een "no-adverse-effect level" van 3000 ppm (12510 mg/m^3). Rekening houdend met de blootstellingsduur en het beperkte onderzoeksdoel (neurotoxiciteit) wordt een onzekerheidsfactor van 10 voorgesteld, hetgeen resulteert in een advieswaarde van 300 ppm (1250 mg/m^3), 8-u tgg. Ten einde irritatie te voorkomen wordt een limietwaarde voor kortdurende overschrijdingen (15 min.) van 400 ppm (1580 mg/m^3) geadviseerd.

(datum afronding advies: augustus 1993)

1. INTRODUCTION

In 1981, the Dutch Expert Committee on Occupational Standards (DECOS) has published a criteria document on n-heptane, including the recommendation of a health-based occupational exposure limit (Werkgroep van Deskundigen, 1981).
This present supplementary document is an updating of data on toxicology and a reconsideration of the health-based occupational exposure limit of n-heptane. It is prepared at the request of the Directorate-General of Labour of the Ministry of Social Affairs and Employment.
The data are derived mainly from the reviews by the German Society for Petroleum Sciences and Coal Chemistry (DGMK), titled "Wirkung von n-Heptan auf Mensch und Tier" ("Effects of n-heptane on man and animals") (Angerer et al, 1986) and by Low et al (1987). Critical publications were reviewed and evaluated, as will be indicated in the text. In addition, literature was retrieved from the on-line databases Chem Abs and Medline, starting from 1984. The final search has been carried out in September 1991 and included Chem Abs 1991 vol 115/12 and Medline 12-91.

2. OCCUPATIONAL EXPOSURE LIMITS AND PREVIOUS EVALUATION BY (INTER)NATIONAL BODIES

2.1 OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits in The Netherlands and in some other countries are presented in Table 1.

Table 1. Occupational exposure limits in The Netherlands and in some other countries.

Country	Year	Level mg/m^3	Level ppm	Time relation	Notes	Reference
The Netherlands	1989	1600	400	MAC-TWA		Arbeidsinspectie, 1989
FRG	1991	2000 4000	500 1000	MAC-TWA STEL-TWA (30 min; 4 times/ workday)	[1]	DFG, 1991
Sweden	1989	800 1200	200 300	TLV-TWA TLV-STEL	[1]	National Board of Occupational Safety and Health, 1989
United Kingdom	1991	1600 2000	400 500	TLV-TWA STEL-TWA (10 min)		Health and Safety Executive, 1991
USA-ACGIH	1991/92	1640 2050	400 500	TLV-TWA		ACGIH, 1991
USSR	1984	300		MAC-Ceiling	[2]	INRS, 1986

[1] limit for "heptanes"
[2] limit for saturated C1-C10 aliphatic hydrocarbons, measured as C

2.2 PREVIOUS EVALUATION BY (INTER)NATIONAL BODIES

DECOS has published an evaluation of the toxicological data on n-heptane in 1981 (Werkgroep van Deskundigen, 1981). n-Heptane was concluded to be slightly toxic following

acute and dermal exposure. Acute inhalatory exposure to levels up to 8000 ppm (33360 mg/m^3)[1] did not cause effects in experimental animals. From a three-month study (6 h/d, 5 d/w), in which rats and dogs were exposed to "rubber solvent" (41% C_6-alkanes and -cycloalkanes; 53.6% C_7-alkanes and -cycloalkanes), a no-effect level of 930 ppm (3878 mg/m^3) was derived. Furthermore, no neurotoxic effects were found in experimental animals in subchronic studies.

Only one out of seven volunteers complained of slight irritation of mucous membranes following exposure to 430 ppm (1793 mg/m^3) for fifteen minutes.

Based on these data a health-based occupational exposure limit of 400 ppm (1600 mg/m^3) was recommended.

Finally, the lack of mutagenic and carcinogenic data was noted.

The evaluations of ACGIH and NIOSH are considered to be not relevant. The former includes data up to 1976 only (ACGIH, 1986-1989), while the latter has been published in 1977.

DFG has not published a criteria document on n-heptane in "Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten" (Henschler, 1990), nor did the Nordic or Swedish Expert Groups in Arbete och Hälsa.

However, the Swedish National Board of Occupational Safety and Health has evaluated the toxicological data on n-heptane in order to assess the scientific arguments for halving the Swedish occupational exposure limit. The available toxicological data did not provide scientific arguments for lowering the exposure limit (Arbetarskyddsstyrelsen, 1988).

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1 when the exposure levels were presented in ppm or mg/m^3 only, the following conversion factors are used in this document: 1 ppm = 4.17 mg/m^3; 1 mg/m^3 = 0.24 ppm.

3. ANALYTICAL METHODS

3.1 ENVIRONMENTAL MONITORING

NIOSH method S 89 has been replaced by another method based on the same principles. This method is intended for determining hydrocarbons within the boiling point range 36-126 °C, including n-heptane (Eller, 1984).
CONCAWE, the Oil Companies' European Organization for Environmental and Health Protection, has published a standardized validated method for monitoring personal exposure to gasoline vapour in air which allows sampling and recovery of all components, including n-heptane (Coker et al, 1989).
Finally, breathing zone air levels can be measured using commercially available passive diffusion badges (Seifert and Abraham, 1983; Seifert et al, 1987).
According to Low et al (1987), vapour concentrations of n-heptane can be monitored continuously using an infrared spectrophotometer. However, this method can only be used in the absence of other aliphatic hydrocarbons, since they all absorb at the same wavelenght.

3.2 BIOLOGICAL MONITORING

Gas chromatographic methods (headspace, solvent extraction, flame ionisation detection) for the determination of n-heptane in rat blood (Kimura et al, 1988, Perbellini et al, 1986) and tissues (Perbellini et al, 1986; Savolainen and Pfäffli, 1980) have been published.
Headspace gas chromatography has been used for the measurement of n-heptane concentrations in human blood and tissues in determining partition coefficients (Perbellini et al, 1985).

The metabolites of n-heptane in human and rat urine were identified using solvent extraction or purge and trap methods followed by analysis by gas chromatography and mass spectrometry and quantified by gas chromatography using a flame ionisation detector. It has to be taken into account that these methods cause formation of some artifactual cyclic compounds (Bahima et al, 1984; Perbellini et al, 1986).

4. TOXICOKINETICS

4.1 ABSORPTION

4.1.1 Pulmonary

In the DGMK report a study is cited in which volunteers exposed to 1 and 3 mg/m^3 (0.24, 0.72 ppm) for 10 minutes retained approximately 25% (Täuber, 1986).
Dahl et al (1988) exposed rats to 417 mg/m^3 (100 ppm) for 80 minutes and determined an uptake rate of 45 μg/kg/min. From this, a retention (i.e (1-$C_{alveolar}/C_{inhaled}$) x 100%) of 29% can be calculated.

4.1.2 Percutaneous

There are no human data on the percutaneous absorption of n-heptane.
Tsuruta (1982) determined the penetration rate in a diffusion cell (the receptor site filled with a 0.9% NaCl solution) using abdominal rat skin: 0.15 μg/cm^2/h.

4.2 DISTRIBUTION

Blood/air and tissue/air partition coefficients are presented in Table 2.

Table 2. Blood/air and tissue/air partition coefficients of n-heptane.

	blood	fat	brain	muscle	liver	kidney	heart	lung	reference
human	1.9 2.85	385	12.4	12.5	10.8	8.9	6.1	2.5	Perbellini et al, 1986 Gargas et al, 1989
rat	4.75 5.4	379		4.2	15.0				Gargas et al, 1989 Imbriani et al, 1985

At the end of a six-hour exposure to 1860 ppm (7680 mg/m^3) the mean n-heptane concentration in the blood of rats was 5.7 mg/l; the concentrations in liver, muscle, kidney, and nervous tissue homogenates were 25.6, 22.9, 10.1, and 18.4 mg/l, respectively. Twenty-four hours postexposure no quantifiable amounts could be detected in blood or tissue homogenates (Perbellini et al, 1986).

A dose-dependent increase was found in the concentrations of n-heptane in the brain and perirenal fat of rats exposed to 100, 500, and 1500 ppm ((420, 2100, 6200 mg/m^3), 6 h/d, 5 d/w, for one or two weeks (see Table 3). Accumulation occurred. After a recovery period of two weeks following the two-week exposure period, no n-heptane could be detected in the blood or these tissues (Savolainen and Pfäffli, 1980).

Table 3. Concentrations of n-heptane (in μg/g) in rat brain and perirenal fat following exposure to 100, 500, and 1500 ppm (420, 2100, 6200 mg/m^3) (from Savolainen and Pfäffli, 1980).

exposure time	brain			perirenal fat		
	100 ppm	500 ppm	1500 ppm	100 ppm	500 ppm	1500 ppm
1 w, 5 d/w, 6 h/d	1.1	1.8	3.5	2.2	34.1	125.7
2 w, 5 d/w, 6 h/d	1.4	4.4	13.5	3.4	47.4	181.4

Pellizzari et al (1982) identified C_7H_{16} in the milk of non-occupationally exposed nursing mothers in four US urban sites.

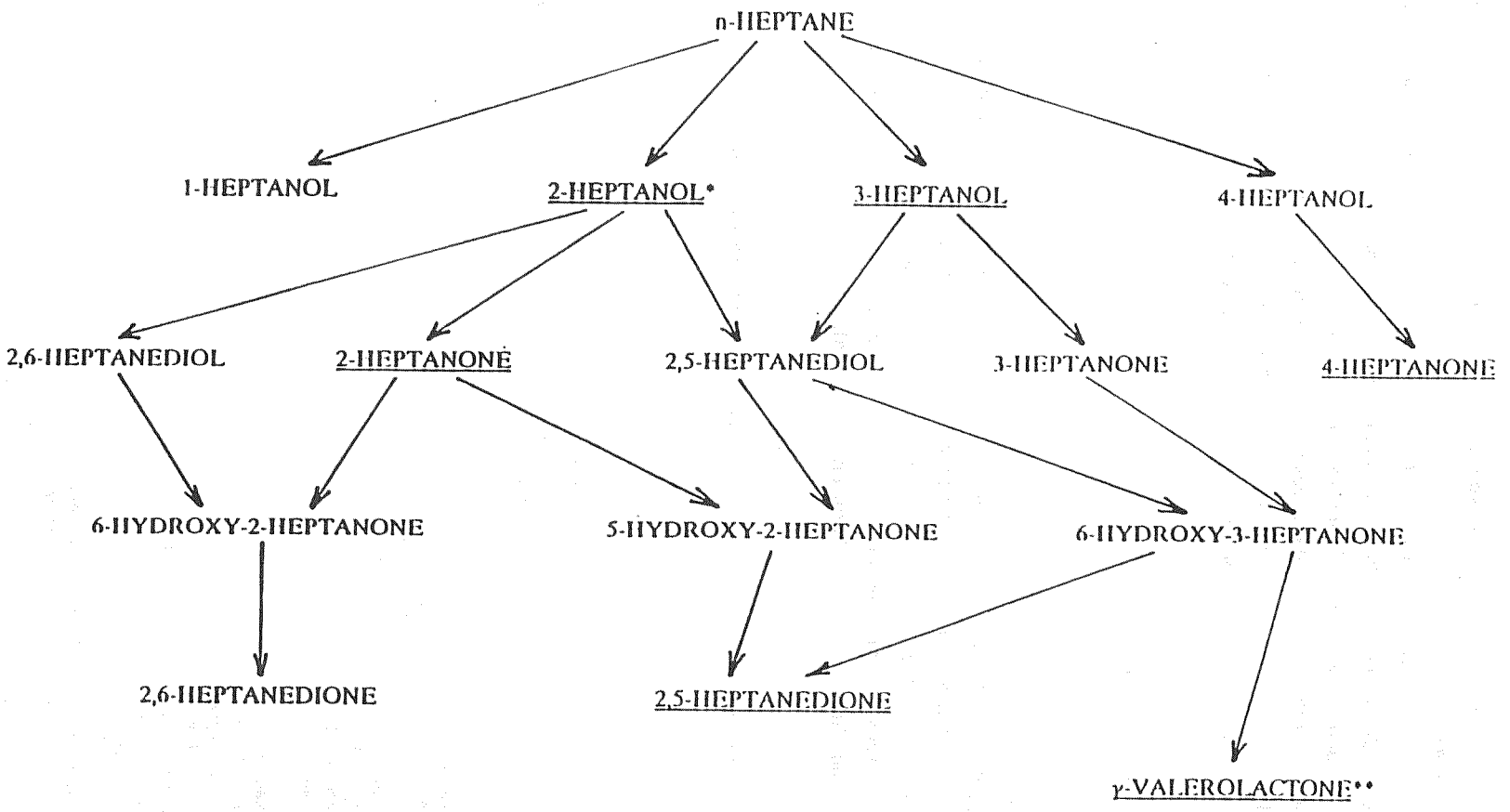
4.3 BIOTRANSFORMATION

In the seventies, in vitro experiments with rat liver microsomes have shown that at least three cytochrome P-450 isozymes are involved in the metabolism of n-heptane. The main metabolite was 2-heptanol (74%), resulting from ω-1 hydroxylation. Other metabolites formed were: 3-heptanol (11%), 1-heptanol (9.5%), and 4-heptanol (6%) (Täuber, 1986; Low et al, 1987).

From these in vitro data and the urinary excretion data (see section 4.4) a metabolism scheme can be presented (see Figure 1, page 8). The biotransformation processes include a number of oxidative steps which are considered typical of n-alkane metabolism. These oxidations include hydroxylations and dehydrogenations leading to monohydroxy, dihydroxy, hydroxyketo, and diketo derivatives (Bahima et al, 1984; Low et al, 1987; Perbellini et al, 1986). The hydroxyketo metabolites are converted to cyclic products (pyran and furan derivatives) during analytical processing (Bahima et al, 1984; DiVicenzo et al, 1977; Fedtke and Bolt, 1987; Perbellini et al, 1982, 1986; Täuber, 1986). γ-Valerolactone may be formed by subsequent reactions of oxidation, deacetylation, and lactonization; this might be an analytical artifact as well (Perbellini et al, 1982, 1986).

Of interest is the formation of 2,5-heptanedione, since this compound caused neurotoxicity in rats (Couri and Milks, 1985). The formation of 2-heptanol and 6-hydroxy-2-heptanone is believed to be more favoured than that of 2,5-heptanedione, since aliphatic hydroxylation occurs more readily at the ω-1 than at the ω-2 position (Low et al, 1987). Indeed, only very

Figure 1. Metabolic pathways of n-heptane (from: Bahima et al, 1984; Perbellini et al, 1986)



* underlined are those metabolites detected in urine of workers exposed to C_6-C_8 satured hydrocarbons including n-heptane

** might be an artefact due to analytical proceedings

small amounts of 2,5-heptanedione were found in the urine of rats exposed to n-heptane (see Table 4).

In the urine of workers (n=8) exposed to a mixture of heptanes and hexanes γ-valerolactone and 2-heptanol were the main metabolites, while 2,5-heptanedione was excreted in smaller amounts in a number of samples only (see Table 4).

Comparison of the excretion data suggests that man may form more 2,5-heptanedione than rats. However, the human data and their reporting are too limited to evaluate the extent of 2,5-heptanedione-formation and the possible neurotoxic effects resulting.

4.4 EXCRETION

Bahima et al (1984) identified 14 metabolites in the urine of female rats exposed to 2000 ppm (8340 mg/m^3), 6 h/d, 5 d/w, for twelve weeks (see Table 4). The data from the urine of male rats, exposed to 1860 ppm (7680 mg/m^3) for six hours, were similar (see Table 4) (Perbellini et al, 1986). In the urines of five shoe factory and three rubber factory workers, exposed to mixtures of C_6-C_8 saturated hydrocarbons, some of these metabolites were found also (see Table 4) (Perbellini et al, 1986).

Table 4. Urinary excretion data in rats exposed to n-heptane and workers exposed to mixtures of C_6-C_8 saturated hydrocarbons.

	rat		man[a]
	♀ Wistar[b]	♂ Sprague Dawley[c]	
exposure	2000 ppm (8340 mg/m^3), 6 h/d, 5 d/w, 12 w	1860 ppm (7680 mg/m^3), 6 h	1-47 ppm (5-196 mg/m^3)
metabolite			
1-heptanol	29 (1.5%)	nr[d]	nr
2-heptanol	561 (29.9%)	264 (46.3%)	650
3-heptanol	382 (20.3%)	201 (35.2%)	390[e]
4-heptanol	17 (0.9%)	nr	nr
2,5-heptanediol	14 (0.8%)	nr	nr
2,6-heptanediol	142 (7.6%)	nr	nr
2-heptanone	11 (0.6%)	20 (3.5%)	170[e]
3-heptanone	nq[d]	8 (1.5%)	nr
4-heptanone	nr	7 (1.2%)	280[e]
6-hydroxy-2-heptanone	434 (23.0%)	nq	nr
5-hydroxy-2-heptanone	74 (4.0%)	nq	ni[d]
6-hydroxy-3-heptanone	14 (0.7%)	nr	nr
2,6-heptanedione	7 (0.4%)	ni	ni
2,5-heptanedione	2 (0.1%)	4 (0.8%)	250[e]
γ-valerolactone	191 (10.2%)	65 (11.5%)	3490

[a] mean values in μg/l (n=8) (from Perbellini et al, 1986)
[b] mean values in μg/18 h (n=6) (from Bahima et al, 1984)
[c] mean values in μg/24 h (n=5) (from Perbellini et al, 1986)
[d] nr = not reported, nq = not quantified, ni = not identifiable
[e] not always detectable

The heptanols are eliminated in the urine not in the free form, but mainly as sulphate and to a lesser extent as glucuronide derivates (Low et al, 1987, Täuber, 1986).
As has already been mentioned in section 4.3 (page 7), some cyclic excretion compounds have been detected (Bahima et al, 1984; Perbellini et al, 1986), but these are or might be artefacts formed during analytical processing (Bahima et al, 1984; DiVicenzo et al, 1977; Fedtke and Bolt, 1987; Perbellini et al, 1982, 1986; Täuber, 1986).

4.5 BIOLOGICAL MONITORING

Lüdersdorf et al (1985) found a significant correlation between the concentrations of n-heptane in blood of parquet floorers and environmental levels of heptane isomers. Depending on the activities exposure ranged from 14 to 60 ppm (59-249 mg/m^3) (median: 22 ppm or 90 mg/m^3), for 10-30 minutes, and from 9 to 81 ppm (36-336 mg/m^3) (median: 38 ppm or 157 mg/m^3) and from less than 0.2 to 27 ppm (<1-111 mg/m^3) (median: 0.5 ppm or 2 mg/m^3), for 10-60 minutes. No details were presented.
From the rat and human urinary excretion data (see Table 4, page 9), it may be concluded that measurement of 2-heptanol, 3-heptanol, or γ-valerolactone might offer possibilities for biological monitoring. However, these compounds are not specific metabolites, since they are respectively formed by 2-heptanone (methyl n-amyl ketone), 3-heptanone (ethyl n-butyl ketone), and n-hexane as well (Krasavage et al, 1982; Perbellini et al, 1981).

4.6 SUMMARY

There is very little information on the toxicokinetics of n-heptane.
After inhalation approximately 25% will be retained in human volunteers and about 30% in rats. The in vitro penetration rate through rat skin of 0.15 μg/cm^2/h indicates that percutaneous absorption of liquid n-heptane through human skin is not very likely to occur to a great extent.
The solubility of n-heptane in blood, organs, and tissues is of the same order of magnitude, that in fatty tissue being a factor of 30-40 greater.
n-Heptane is oxidized primarily to 2- and 3-heptanol. These are excreted in the urine mainly as their sulphate conjugates and to a lesser extent as glucuronides. The heptanols are converted by additional oxidations to numerous products including diols, hydroxy ketones, and diketones. The formation of the neurotoxic 2,5-heptanedione is not favoured in rats. It was detected in the urine of some workers as well, but the data are too limited to allow an assessment of the extent of its formation and its possible resulting neurotoxicity.
There were no detailed investigations on biological monitoring available.

5. EFFECTS

5.1 ANIMAL EXPERIMENTS

5.1.1 Irritation and sensitization

The sensory irritation of the upper part of the respiratory tract was studied in CF-1 mice by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}). The RD_{50} was extrapolated to be 17400 ppm (72560 mg/m^3). In addition, experiments with cannulated mice showed some pulmonary irritation at equally high levels (Kristiansen and Nielsen, 1988).

***conclusion*. Based on its RD_{50} it is concluded that the sensory irritation potency of n-heptane is very low.**

5.1.2 Toxicity following acute or subacute exposure

Biochemical parameters related to the brain (RNA and glutathione concentrations; acid proteinase, NADPH-diaphorase, and superoxide dismutase activities) were investigated by exposing male rats to 100, 500, and 1500 ppm (417, 2085, 6255 mg/m^3) of n-heptane (purity not indicated), 6 h/d, 5 d/w, for one or two weeks (Savolainen and Pfäffli, 1980). The most important outcome of this study was that no clinical signs of neuropathy (e.g., hindlimbs paralysis) were observed. Whether the reversible changes in some of these parameters are treatment-related, as was claimed by the authors, is questionable, since no dose-effect or dose-effect-time relation could be established. In addition, it is unknown whether (changes in) these parameters are appropriate predictors for (potential) neurotoxicity.

Potential hepatotoxic effects were studied in female rats by daily intraperitoneal injections of 1 ml/kg (0.68 g/kg) of n-heptane (AR Grade), for two or seven days. The following parameters were investigated: hepatic alkaline phosphatase and fructose-1,6-diphosphate aldolase activity; serum alkaline phosphatase, fructose-1,6-diphosphate aldolase, acetyl cholinesterase, and carboxylesterase activity and serum total protein, albumin, and cholesterol levels (Goel et al, 1982). The significant changes in most of these parameters pointed to damage and inflammation of the liver. From the paper it could not be concluded whether pathological examinations have been conducted.

In a follow-up experiment (same dose, same route, same duration) the effects on a number of other hepatic biochemical parameters were studied (Goel et al, 1988). The results, such as increase in lipid peroxidation, loss of total sulfhydryl groups, and depressed biotransforma-

tion activity, again indicated that intraperitoneal administration of n-heptane might have some effects on the liver.

***conclusion*. From a subacute (6 h/d, 5d/w, 2 w) inhalation study it can be concluded that the no-adverse effect level (NAEL) for neurotoxicity will be higher than 1500 ppm (6255 mg/m^3), since exposure to this level did not affect a number of neurobiochemical parameters.**
Intraperitoneal injection of 1 ml/kg (0.68 g/kg) for up to seven days may result in adverse hepatic effects, but because of this way of administration (bolus dose, considerable first-pass metabolism) this study is considered to be less relevant for extrapolation to workers. An overall NAEL for subacute exposures could not be derived from the studies available.

5.1.3 Toxicity following subchronic or chronic exposure

Only toxicity data from subchronic exposure to heptane mixtures were available for the previous DECOS document (Werkgroep van Deskundigen, 1981). One of the studies discussed was that of Carpenter et al (1975) investigating the effects of "rubber solvent", a mixture consisting of 41% C_6-alkanes and -cycloalkanes; 53.6% C_7-alkanes and -cycloalkanes. However, since the percentage of n-heptane is lower than 23.4, the results of this study should be considered not easily interpretable with respect to the health effects of n-heptane.
In a separate study, not referred to in the previous document, Carpenter et al (1976) had studied the effects of "50 thinner", a mixture consisting of 64.8% n-heptane and 33 % toluene. Groups of 25 male rats and four male dogs were exposed to 0, 140, 300, and 600 ppm (540, 1200, 2400 mg/m^3), 6 h/d, 5 d/w, for 67 days (13 w). Body weight was registered five times during the study. Animals were sacrificed after three, eight, and thirteen weeks, and haematological and blood chemistry parameters were investigated. An extensive histological examination was performed as well. No tissue damage was observed. Apart from a significant increase in serum alkaline phosphatase levels in the rat intermediate and high dose group at week 3, no effects were found on the haematological and blood chemistry parameters. The significantly increased body weights of rats exposed to the intermediate and to the high level for 66 days and of dogs exposed to the high level for 36 and 48 days were considered not to be treatment-related, since not any micropathological changes indicative of organ damage were observed.
Recently studies on n-heptane have been performed, but their scope was rather limited.
Bahima et al (1984) exposed female rats to 2000 ppm (8340 mg/m^3) of n-heptane, 6 h/d, 5 d/w, for twelve weeks. Every four weeks, rats were assessed for ataxia, loss of equilibrium, and hind- and forelimb weakness by observing gait and grasp of wire mesh. No evidence of peripheral neuropathy was noted.
Frontali et al (1981) investigated the neurotoxicity of n-heptane (analytical grade; purity 99%) by exposing male rats to 1500 ppm (6255 mg/m^3), 9 h/d, 5 d/w, for up to 30 weeks.

The animals were regularly weighted and subjected to a neuromuscular function test (measurement of hindlimb spread on landing after dropping from 32-cm height). In addition, animals were sacrificed after seven and fourteen weeks for histological examination of nerve tissues as was done after the end of experiment as well. There were no differences as to weight and neuromuscular function when compared to controls. Histologically, no signs of degeneration of the nerve tissues examined were observed.

Bio/dynamics Inc (1980) conducted a chronic, 26-week inhalation study of n-heptane (purity: >98.5%). Rats of both sexes were exposed to 0, 400, and 3000 ppm (1668, 12510 mg/m^3), 6 h/d, 5 d/w. A full physical assessment and individual body weights were recorded weekly. Laboratory studies (haematology, clinical chemistry, urinalysis) were performed at weeks 13 and 26. At weeks 9, 18, and 27 animals were randomly withdrawn from test and submitted to the Institute of Neurotoxicology of the Albert Einstein College of Medicine for examination of central and peripheral nervous tissues. The survivors at the end of test at week 29 were examined at the latter institute also. Two animals died during, but not due to, exposure. Observations revealed some treatment-related effects (moderate rapid or laborated breathing; prostration; insensitiveness to sound stimuli) in the first week. However, these effects were transient and not noted in the second and following weeks. Body weights, body weight gain, and haematological and urinalysis parameters were comparable with controls. As to the clinical chemistry parameters (alkaline phosphatase, serum glutamic pyruvic transaminase, blood urea nitrogen, glucose) only the alkaline phosphatase activity measured in the serum of the female rats after 26 weeks had changed. This increase was dose-dependent and small, and only significant in the high dose group ($p<0.05$; increase approximately 50%). This may point to an effect on the intestines. However, since no (histo)pathological examinations have been performed, the toxicological significance of this finding cannot be assessed, but may be doubtful.

At the Institute of Neurotoxicology of the Albert Einstein College of Medicine, where central and peripheral nervous tissues were examined, no treatment-related neuropathological changes were found (Institute of Neurotoxicology, 1980).

Potential hepatotoxic effects were studied in female rats receiving two-weekly intraperitoneal injections of 1 ml/kg (0.68 g/kg) of n-heptane (AR Grade), for 45 days (Goel et al, 1980, 1988). A number of biochemical parameters in the liver and the blood were investigated (see section 5.1.2). The changes in these parameters indicate adverse effects on the liver. Gross observation revealed no differences between the livers of the exposed and those of the control animals. Histological examination revealed some degenerative changes. The liver capsule was greatly thickened and infiltrated with lymphocytes.

***conclusion*. Based on these data no conclusions can be drawn with respect to the toxic effects of n-heptane following (sub)chronic exposure by inhalation: in the studies using n-heptane the scope was too limited (neurotoxicity), while in the studies using mixtures the concentrations tested were too low or the percentages of n-heptane too small.**

However, n-heptane is not very likely to be neurotoxic. From a chronic study a NAEL of 3000 ppm (12510 mg/m^3) may be derived, since exposure to this level 6 h/d, 5 d/w, for 26 weeks did not result in neuropathological changes.
Intraperitoneal injection of 1 ml/kg (0.68 g/kg), twice a week, for 45 days, resulted in some adverse hepatic effects, but because of this way of administration (bolus dose, considerable first-pass metabolism) this study is considered to be less relevant for extrapolation to workers.

5.1.4 Carcinogenicity

There are no life-time/carcinogenicity studies available.

5.1.5 Mutagenicity

Brooks et al (1988) have tested the genotoxic potential of n-heptane (purity not specified). n-Heptane was not mutagenic when tested at concentrations up to 250 μg/ml in - for volatile solvents modified - bacterial assays using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 and *E. coli* strains WP_2 and WP_2 *uvr A*, with and without induced rat liver S9 mix. In a similar modified assay using the yeast *S. cerevisiae* JD1 concentrations up to 5 mg/ml did not induce mitotic gene conversions.
The rat liver (RL_4) chromosome assay for volatile compounds was negative as well (maximum concentration tested: 10 μg/ml).
Because of cytotoxicity no higher doses could be tested in the bacterial and rat liver assays.

***conclusion*. Data from in vitro tests do not indicate a genotoxic potential for n-heptane.**

5.1.6 Reproduction toxicology

No data available.

5.1.7 Other studies

In vitro experiments in which benzo[a]pyrene hydroxylase and 7-ethoxycoumarin deethylase activities were measured in rat liver and lung microsomes showed that n-heptane may interfere with normal detoxication reactions (i.e., the cytochrome P-450-dependent monooxygenase pathway) (Rabovsky et al, 1986).

5.2 OBSERVATIONS IN MAN

5.2.1 Irritation

Liquid n-heptane is a degreasing agent. Prolonged contact for one hour can cause irritation and dermatitis, for five hours blistering (Herrmann, 1986; Low et al, 1987).
According to Herrmann (1986) the reports on the irritative effects of n-heptane vapour are conflicting. No mucous irritation was noted in volunteers exposed to 1000-5000 ppm (4170-20850 mg/m^3), but in other reports slight irritation was observed (no exposure data indicated).
In the previous document (Werkgroep van Deskundigen, 1981) the conclusion from the study of Carpenter et al (1975) on the sensory responses to inhalation of "rubber solvent" containing 23.4% C_7-alkanes was mentioned. Exposure up to 2000 ppm (8100 mg/m^3) for 15 minutes caused only minimal irritation and 430 ppm (1700 mg/m^3) was judged to be a tolerable occupational exposure level.
When exposed to "50 thinner", a mixture consisting of 64.8% n-heptane and 33 % toluene, one out of five volunteers complained of irritation of the eyes (dryness) at levels of 430 and 500 ppm (1700, 2000 mg/m^3; 15 min). Three and four persons, respectively, complained of "tasting something". When exposed to 530 ppm (2100 mg/m^3) for 30 min, four volunteers reported eye irritation and "tasting something" (Carpenter et al, 1976).

***conclusion*. Liquid n-heptane can cause dermal irritation. The irritation potency of n-heptane vapours to the mucosa is probably not very high: exposure to 1000-5000 ppm (4170-20850 mg/m^3) did not result in irritation, but irritation from unknown concentrations was reported. Exposure for 30 min to approximately 500 ppm (2085 mg/m^3) of a mixture containing about 65% heptane caused irritation of the eyes and complaints of "tasting something".**

5.2.2 Occupational exposure

The only data available are from two Italian studies on mainly female workers.
Crespi et al (1979) examined eighteen workers of a tire factory. They had been exposed for one to nine years to vapours of a solvent containing more than 95% of n-heptane and traces or small percentages of other hydrocarbons such as toluene and benzene. Although the workers complained of numbness and paraesthesia of the limbs, neurological examination did not show any signs of peripheral neuropathy. Twelve of these workers (mainly women; mean age: 35.5 y) underwent a neurophysiological examination. The motor conduction velocity and the distal latency of the peroneal nerve did not differ from those of age-

matched controls. However, the amplitude desynchronisation of the muscle action potential evoked at the extensor digitorum brevis significantly increased.
Since no details were presented with respect to exposure levels and the control group, no conclusions can be drawn from this study.
In the other study the neurophysiological effects of exposure to technical heptane, consisting of 38-40% n-heptane, 27-30% 2-methylhexane, 8-10% 3-methylhexane, and 17-21% methylcyclohexane (n-hexane less than 0.2%) in 47 female and three male rubber shoe factory workers (mean age: 37.3 ± 6 y; mean exposure time: 5.8 ± 1.9 y) were investigated. At the time of the investigation environmental levels were determined by personal air sampling: 45 ppm (186 mg/m^3) n-heptane (mean; range: 7-179 ppm or 28-747 mg/m^3), 19 ppm (79 mg/m^3) 3-methylhexane (mean; range: 4-69 ppm or 18-286 mg/m^3), and 61 ppm (254 mg/m^3) of the other heptane isomers (mean; range: 9-227 ppm or 38-946 mg/m^3). No data on previous exposure levels were presented. Subjective complaints related to impairment of touch (dysaesthesia) or weakness (asthenia) were not confirmed by clinical neurological examination. Some subclinical neuropathy was demonstrated by the neurophysiological examination. Of the parameters investigated both the distal sensory conduction velocity and the distal latency of the sensory action potential of the median nerve were significantly affected when compared to the two control groups involved (Soleo et al, 1987).
No conclusions can be drawn from this study with respect to the neurotoxic effects of n-heptane. Firstly, there was considerable exposure to, particularly, heptane isomers. Secondly, these kind of effects are the result of long-term exposure as well and, therefore, previous levels are of great interest in evaluating the health risk following exposure to n-heptane. Thirdly, the adequacy of the control groups may be questioned. The first control group is very similar with respect to sex, but no details are given with respect to age and other matching criteria. In addition, this group may be chemically exposed, although to other compounds. The second group is not occupationally exposed, but consists mainly of men. In addition, no data were presented on age and other matching criteria.

***conclusion*. No new data from valid human studies were available.**

5.3 SUMMARY

5.3.1 Animal data

The sensory irritation potential of n-heptane will be very low as can be seen from its RD_{50} of 17400 ppm (72560 mg/m^3) in mice.
Inhalatory studies on n-heptane are limited to the investigation of its neurotoxic effects. At the highest concentration tested, i.e. 3000 ppm (12510 mg/m^3), 6 h/d, 6 d/w, for 26 weeks,

no neuropathological effects were noted in rats of both sexes. At this level a small increase in the alkaline phosphatase activity was observed in the serum of the female rats, but its toxicological significance could not be assessed.
Intraperitoneal administration of 1 ml/kg (0.68 g/kg) of n-heptane to female rats for seven subsequent days may result in adverse effects on the liver; administration (same dose, same route) twice a week, for 45 days, caused some degenerative changes.
There were no lifetime/carcinogenicity studies available. n-Heptane was negative in four in vitro genotoxicity tests.
There were no data on reproduction toxicology available.

5.3.2 Human data

Liquid n-heptane causes irritation, dermatitis, and blistering of the skin, depending on the duration of contact. Exposure up to 5000 ppm (20850 mg/m^3) did not result in mucous membrane irritation. Subjective complaints were reported by volunteers exposed to approximately 500 ppm (2000 mg/m^3) of mixtures for 15 to 30 minutes.
In two Italian studies neurophysiological effects were reported in mainly female workers occupationally exposed to mixtures of hydrocarbons including n-heptane. However, due to a number of flaws no conclusions can be drawn from these data.

6. EVALUATION OF HUMAN HEALTH RISKS

6.1 GROUPS AT EXTRA RISK

There are no data to designate groups at extra risk.

6.2 ASSESSMENT OF HEALTH RISKS

There are no new valid human data available to be used for deriving a health-based occupational exposure limit.

In addition, there were no data available from lifetime/carcinogenicity studies, nor from reproduction toxicology studies. In vitro mutagenicity testing did not indicate a genotoxic potential. Since, in addition, structural analysis of n-heptane and its metabolites (see page 8) does not point to the presence of potentially eletrophilic DNA-reactive groups, it is not very likely that n-heptane will act like a genotoxic carcinogen.

The toxicological database is limited. In the previous criteria document a no-adverse effect level of 930 ppm (3700 mg/m^3) was derived from a thirteen-week inhalation study using male rats (n=25) and dogs (n=4). In the next higher dose group (2000 ppm or 7900 mg/m^3) initial lacrimation in one dog and some initial loss of coordination in two dogs were observed, while in rats an increase in serum alkaline phosphatase activity, but no histopathological organ changes were found. However, since the animals were exposed to "rubber solvent" containing at most 23,4% n-heptane, this study is of limited significance only. The same holds for the study using "50 thinner" consisting of 64.8% n-heptane and a substantial amount of toluene (32%).

Studies using n-heptane are limited to the investigation of its possible neurotoxic effects. In a chronic, 26-week inhalation study no neuropathological effects were seen in rats of both sexes exposed to 3000 ppm (12510 mg/m^3), 6 h/d, 5 d/w. No effects were noted with respect to body weight, body weight gain, and haematological and urinalysis parameters. Of the limited number of clinical chemistry parameters, only a small, but significant increase in serum alkaline phosphatase activity in the serum of female rats was found at the end of the exposure period. Although this may point to some adverse effects on the intestines, no organ pathological examinations were performed, hampering the assessment of the toxicological significance of this finding. Since the increase in alkaline phospatase activity in the serum of female rats was small and the only parameter affected, it is tentatively considered not to be adverse, and 3000 ppm (12510 mg/m^3), the highest dose tested, is considered to be a no-adverse effect level.

Taking into account the limited scope and exposure time of the study a safety factor of 10 is proposed leading to a health-based occupational exposure limit of 300 ppm (1250 mg/m^3).
n-Heptane vapours are not likely to be very irritative to the mucosa, since exposure to up to 5000 ppm (20850 mg/m^3) did not cause such effects. However, exposure to 1000 ppm (4170 mg/m^3), for six minutes, and to 2000 ppm (8340 mg/m^3), for four minutes, resulted in slight vertigo (see previous document, Werkgroep van Deskundigen, 1981). It is noted that these data are from a study performed in 1929. According to NIOSH (NIOSH, 1977) vapours were generated by dripping liquid from a buret on a cotton gauze in front of a fan and concentrations were computed from the quantity of material introduced. Although periodical checks were performed by sampling and analysis, the method used for determining the chamber vapour concentration was not described.
More recent data concern mixtures. Exposure to approximately 400 ppm (1580 mg/m^3) of n-heptane containing mixtures resulted in some extent of irritation (Carpenter et al, 1975, 1976).
Based on these data, 400 ppm (1580 mg/m^3) is proposed as a short-term exposure limit (15 min).
Finally, it should be noted that the neurotoxic metabolite 2,5-heptanedione has been detected in the urine of some of eight workers exposed to mixtures of C_6-C_8 satured hydrocarbons, but that the data and their reporting is too limited to allow an assessment of the risk for neurotoxicity resulting from it.

skin notation. Assuming a skin notation has to be added when exposure to the skin (i.e., hands and forearms) to liquid n-heptane during one hour leads to an additional uptake of 10% of the maximum allowed uptake by inhalation according to the MAC, the following calculation can be made.
Using the rat skin permeation rate of 0.15 μg/cm^2/h, estimated in vitro by Tsuruta (1982), dermal uptake will be 0.3 mg and far less than 10% of the amount taken up by inhalation. Therefore, no skin notation has to be added.

6.3 RECOMMENDED OCCUPATIONAL EXPOSURE LIMIT

The Dutch Expert Committee for occupational standards recommends a health-based occupational exposure limit for n-heptane of 300 ppm (1250 mg/m^3) as an eight-hour TWA concentration.
For short-term exposure a fifteen-minute limit of 400 ppm (1580 mg/m^3) is recommended.
(Note: the Dutch Expert Committee is aware of the fact that the limits proposed being very close may imply that control of occupational air levels will be determined by the short-term exposure limit.)

7. RECOMMENDATIONS FOR RESEARCH

In order to get an insight in the toxic effects of n-heptane the following studies are recommended:

* a 90-day full toxicity inhalation study according to the OECD/EEC guidelines

* standard testing for clastogenicity (in, e.g., CHO cells)

* reproduction toxicity inhalation (screen) study

* study of the metabolism in man, especially the formation of 2,5-heptanedione

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RAPPORTEN VAN DE WERKGROEP VAN DESKUNDIGEN
(op alfabetische volgorde)

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Acrylaten	13/87
Aflatoxine B1, B2, G1 en G2	6/87
Allylglycidylether	1/92
Amyl acetate	4/90
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Carbon disulphide	9/92
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Chloor	6/80
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Chroom en chroomverbindingen	6/85
Cyclohexane	15/90
Cyclohexanol	3/90
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

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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	
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

Publikatiebladen

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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,-
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P 93	Chloorwaterstof; Veilige behandeling in de haven Tweede druk 1982	*f* 10,-
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P 102	Epichloorhydrine; Veilige behandeling in de haven Tweede druk 1984	*f* 11,-
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P 105	Broomwaterstof; Veilige behandeling in de haven Tweede druk 1984	*f* 10,-
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P 108	Methylbromide; Veilige behandeling in de haven Derde druk 1984	*f* 11,-

Chemie (gevaarlijke stoffen)

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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,-
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P 134-4	Zweminrichtingen; De opslag en het gebruik van zwavelzuur Vierde druk 1988	*f* 11,-
P 134-5	Zweminrichtingen; De opslag en het gebruik van kooldioxide Eerste druk 1980	*f* 12,-
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Voorlichtingsbladen

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Commissie preventie van rampen door gevaarlijke stoffen

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R-bladen

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Overige publikaties

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OP 12	De opslag en het vervoer van acrylnitril Eerste druk 1970	f 22,50
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