Tetrachloroethylene (PER) - 2

Health-based recommended occupational exposure limit for short-term exposure

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp	: Aanbieding advies 'Tetrachloroethylene (PER) - 2'
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Mijnheer de staatssecretaris,

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

In dat kader bied ik u hierbij een advies aan over tetrachloorethyleen (PER), kortdurende blootstelling. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Dit advies is een aanvulling op het in januari 2003 gepubliceerde advies over tetrachloorethyleen (2003/01OSH) en gaat uitsluitend over de afleiding van een gezondheidskundige advieswaarde voor kortdurende blootstelling aan PER.

Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport en de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

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Tetrachloroethylene (PER) - 2

Health-based recommended occupational exposure limit for short-term exposure

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

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2004/03OSH, The Hague, September 2, 2004

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

This report is a supplement to the report 2003/01OSH and contains the assessment of the short-term exposure limit only. Both reports can be found on the website of the Health Council of the Netherlands, www.healthcouncil.nl.

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Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in de lucht waaraan mensen beroepsmatig blootgesteld kunnen worden. Deze aanbevelingen vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden, aangeduid als maximaal aanvaardbare concentraties (MAC-waarden).

In dit rapport bespreekt de commissie de gevolgen van kortdurende blootstelling aan tetrachloorethyleen (PER) en presenteert zij een gezondheidskundige advieswaarde voor kortdurende blootstelling aan deze stof. Dit rapport is een aanvulling op rapport 2003/01OSH, waarin een gezondheidskundige advieswaarde voor blootstelling gemiddeld over een achturige werkdag is afgeleid. De conclusies van de commissie over kortdurende blootstelling zijn gebaseerd op gegevens uit dit eerdere rapport.

Toepassing en effecten

PER wordt onder meer gebruikt als oplosmiddel in stomerijen en bij de extractie en ontvetting van metalen.

Acute blootstelling aan PER via de luchtwegen veroorzaakt neurologische effecten in mens en dier. PER veroorzaakt een reversibel effect op het centrale zenuwstelsel (CZS), hetgeen in het verleden heeft geleid tot het gebruik van PER als humaan narcose-

middel. Hoge blootstellingsconcentraties leiden tot coma, gevolgd door ademhalingsstoornissen en de dood.

Uit onderzoek met gezonde vrijwilligers blijkt dat reversibele, geringe CZS-effecten consistent optreden bij blootstellingsconcentraties van circa 1 500 mg/m^3 en hoger. Deze CZS-effecten omvatten duizeligheid, slapeloosheid, 'licht in het hoofd' en coördinatieverlies. Verwaarloosbare, lichte oogirritatie van voorbijgaande aard wordt waargenomen vanaf circa 530 mg/m^3.

Bij proefdieren heeft inhalatie van hoge, vrijwel dodelijke concentraties PER (circa 5 500-14 000 mg/m^3) tevens histologische en biochemische effecten op de lever. Incidenteel wordt tijdelijke leverschade ook gerapporteerd in gevallen van acute vergiftiging van mensen na inhalatie.

Evaluatie en advieswaarde

De CZS-effecten die leiden tot coördinatiestoornissen beschouwt de commissie als het kritisch effect van kortdurende blootstelling aan PER. Om werknemers hiertegen te beschermen is een gezondheidskundige advieswaarde nodig voor kortdurende blootstelling (tgg 15 minuten). Uit onderzoek met vrijwilligers blijkt dat bij circa 750 mg/m^3 geen CZS- effecten optreden. Deze concentratie beschouwt de commissie dan ook als het geen-geobserveerde-nadelig-effect-niveau (NOAEL). Om rekening te houden met individuele verschillen kiest de commissie een factor 3. Toepassing van deze factor resulteert in een door de commissie geadviseerde gezondheidskundige advieswaarde van 250 mg/m^3, gemiddeld over 15 minuten.

Gezondheidskundige advieswaarde

De Commissie WGD van de Gezondheidsraad beveelt een gezondheidskundige advieswaarde voor beroepsmatige blootstelling aan PER aan van 250 mg/m^3 in de lucht, gemiddeld over een 15 minuten durende werkperiode (TGG 15 min).

Executive summary

Scope

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands sets Health-Based Recommended Occupational Exposure Limits (HBR-OEL) for chemical substances in air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure, which leads to legally binding occupational exposure limits.

In this report, the committee discusses the consequences of short-term occupational exposure to tetrachloroethylene (PER) and recommends a health-based occupational exposure limit for short-term exposure. This report is a supplement to the DECOS report 2003/01OSH, in which a health-based recommended occupational exposure limit for 8 hour is set. The committees' conclusions about the short-term exposure are based on data from this previous report.

Uses and Effects

PER is used as a solvent in dry cleaning, extraction and vapour degreasing of metals, as an intermediate in chemical synthesis, as an anthelminthic, as a heat-change fluid, and as a grain-fumigation agent.

Acute toxic respiratory exposure gives rise to a series of clear-cut neurological effects in humans and experimental animals. PER causes a reversible depression of the

central nervous system (CNS). For this reason, in the past, PER was used as a human anaesthetic. High doses resulted in coma, followed by respiratory failure and death.

In human studies, reversible, slight CNS-effects were observed consistently, when volunteers were exposed to approximately 1,500 mg/m^3 and higher. These CNS-effects included dizziness, sleepiness, light-headedness and impaired motor-coordination. Furthermore, negligible, slight transient irritation of the eyes was reported at exposure levels of approximately 530 mg/m^3.

In animal studies, acute inhalatory exposure causes effects in the liver at doses approaching anaesthetic or lethal effects (about 5,500-14,000 mg/m^3). In humans, temporary liver damage has also been reported in one case of acute poisoning (about 2,700 mg/m^3) by inhalation.

Hazard assessment

The committee considers the CNS-effects as the critical effect for short-term exposure to PER. To protect workers against this effect, a health-based recommended occupational exposure limit for short-term exposure (STEL, 15-min TWA) is warranted. Based on two volunteer studies, the committee concludes that 750 mg/m^3 is a no-observed-adverse-effect-level (NOAEL), which is low enough to avoid CNS-effects in workers. To compensate for differences between individuals the committee applies a factor of 3. Taken this factor into account the committee recommends a HBR-OEL of 250 mg/m^3, as a 15-minute time-weighed average concentration.

Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based recommended occupational exposure limit for PER of 250 mg/m^3, as a 15-minute time-weighed average concentration (15 min TWA, STEL).

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, at the request of the Minister of Social Affairs and Employment (annex A). The purpose of the committee's evaluation is to set a health-based recommended exposure limit for the atmospheric concentration of the substance, provided the database allows the derivation of such a value.

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

1.2 Committee and procedure

This report is a supplement to the DECOS report on PER published in January 2003 (2003/01OSH). It includes a scientific evaluation of the data on short-term exposure and a recommendation for a health-based occupational exposure limit as an 15-minute time-weighed average (15-min TWA; STEL). The members of the committee are listed in annex B.

In 2003, the President of the Health Council released a draft of the supplement for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of this supplement.

1.3 Data

The committee has taken the data of acute exposure to PER from the previous report (2003/01OSH) as basis for this supplement. Furthermore, one additional human study is included. The last search was performed in November 2003.

Chapter 2

Effects

The conversion factors at 25°C, 1 atm are: 1 ppm = 6.89 mg/m^3; 1 mg/m^3 = 0.145 ppm.

2.1 Observations in humans

2.1.1 Acute toxicity

More detailed information on the observations in humans after acute inhalation exposure to PER (up to 4 hour) is given in annex D.

Carpenter (Car37) exposed four male volunteers to 3,272 and 6,435 mg/m^3 (475 and 934 ppm) of PER vapour for 130 and 95 minutes respectively. The 3,272/130 combination gave rise to the following effects: eye irritation, secretion of mucous membranes, sensory changes, slight feeling of elation. The neurological effects became more severe at the 6,435/95 combination, when lassitude, mental fogginess and exhilaration were experienced/observed. Increase of the highest concentration to 10355 mg/m^3 (1500 ppm) after 95 minutes lead to inebriation. Increase to 13,780 mg/m^3 (2000 ppm) forced the subjects to leave the exposure room after 7.5 min; they reported 'ringing in the ears' at this concentration.

Rowe *et al*. (Row52) subjected human volunteers to various exposure regimens. Only the effects of exposure to PER vapour were investigated. At 1,488 mg/m^3 (216 ppm) and higher, reversible neurological effects were reported. These included dizziness, sleepi-

ness, light-headedness and impaired motor-coordination. This study confirms the finding of Carpenter (Car37) and suggests a no-observed-adverse-effect-level (NOAEL) of about 730 mg/m^3 (106 ppm) or lower for acute and overt neurological effects. At this exposure level very slight transient eye irritation was observed. The neurobehavioral findings of Rowe *et al*. are based on a limited number of volunteers using rather crude qualitative observational methods (no neuropsychological tests, EEG, etc.).

Stewart *et al*. (Ste61a) subjected groups of 6 male volunteers to different exposure regimens. Three experiments were carried out. Concentrations of PER were measured in blood and expired air. The effects observed/experienced in two of these experiments during rising concentrations and time were reported and listed in annex D. Very slight, transient eye irritation was reported from 534 mg/m^3 (75-80 ppm) and neurological effects as light-headedness and impaired coordination were reported at 1,570 mg/m^3 (210-244 ppm). No effects were found on serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transferase (SGPT) activities, as well as urobilinogen excretion.

Stewart *et al*. (Ste61b) found an impaired liver function arising 9 days after an acute narcotic exposure to PER, which they attributed to the exposure.

Wayne and Orcutt (Way60) measured the degree of eye irritation by simulating the photochemically induced reactions of oxides of nitrogens with hydrocarbons emitted daily into the atmosphere. No eye irritation was found when volunteers were exposed to a mixture of 140 mg/m^3 PER and 1.9 mg/m^3 nitrogen dioxide.

2.2 Animal experiments

2.2.1 Acute toxicity

Effects in animals after acute inhalation exposure to PER (up to 4 hour) are summarised in detail in annex E. The LC_{50} data are not included in the table but discussed hereafter.

The results of acute inhalation studies will be treated separately for each of the effects caused by PER.

Lethality

Animals exposed to high PER concentrations by inhalation died as a consequence of respiratory failure following CNS depression (narcotic or anaesthetic effects). From a

number of studies the LC_{50} of rats varies between 28,250 (6 h) and 34,600 (8 h) mg/m^3 (Bon80, Poz59) and of mice between 20,500 (6 h) and 40,000 (2 h) mg/m^3 (Fri53, Dup79).

In the study of Holmberg *et al*. (Hol74), the LT_{50} (the time required to kill half of the animals exposed to a defined dose) was found to be 12.2 h (95% confidence limits 11.8-12.5 h) at 25,500 mg/m^3 (3700 ppm) for mice.

In NTP86 a highest non-lethal dose of 16,850 mg/m^3 (2445 ppm) and lowest lethal doses of 18,004 mg/m^3 (2613 ppm) and 26,100 mg/m^3 (3786 ppm) are mentioned for mice and rats, respectively, when these animals have been exposed for 4 h.

Rowe *et al*. (Row52) reported non-lethality for 10- or 14-hour exposures of rats to 13,800 mg/m^3 (2000 ppm) and 4-hour exposure of rats to 20,700 mg/m^3 (3000 ppm), while lethality was found when exposure to the latter dose lasted 5 h or longer. A dose of 82,700 mg/m^3 (12,000 ppm) did not give rise to death when exposure lasted 0.2 h; complete survival was also found at 11,020 mg/m^3 (1600 ppm) for 5 h.

Kennedy and Graepel (Ken91) mentioned in their study an ALC (the approximate lethal concentration, which is the concentration at which mortality was first observed) in rats of 41,340 mg/m^3 (6000 ppm) for a 4-hour exposure.

Neurotoxicity

Most notably are the short-term neurotoxic effects of respiratory exposure. PER has been used in the past for human anaesthesia (Foo43), and it is, therefore, not surprising that effects related to this application are abundantly reported in the literature on acute respiratory toxicity. At doses approaching the lethal dose, respiration is affected. Failure of respiration is the direct cause of death. Concise summaries of a number of original publications are presented in annex E (Car37, DeC83, Fri53, Gol64).

Cardiac arrhythmia

Epinephrine-induced cardiac arrhythmias have been observed in rabbits during respiratory exposure for 1 h to 35,800 mg/m^3 (5,200 ppm) PER (Car83). The author of the original publication considered the influence of PER on this endpoint to be weak (compared with trichloroethylene and methylchloroform, which were investigated for this effect by the same author, although the results were published elsewhere). Little more than half of the exposed rabbits showed an increased sensitivity. Furthermore, the arrhythmias did

only occur early in the exposure period, and after 15 to 30 minutes of exposure the rabbits appeared to adapt and no longer responded to the same degree. In contrast to the effects observed with trichloroethylene and methylchloroform, the sensitivity of the animals did not increase after administration of Lilly 18947, an inhibitor of the oxidative metabolism of trichloroethylene to trichloroethanol and trichloraceticacid. This is not surprising, in view of the marginal oxidative metabolism of PER in mammals (see report 2003/01OSH for information on the metabolism of PER).

No epinephrine-induced arrhythmias have been observed in beagle dogs exposed for 10 minutes to 34,500 or 68,900 mg/m^3 (5,000 or 10,000 ppm) (the latter treatment was not well tolerated) (Rei73).

Hepatotoxicity

Several acute respiratory studies have revealed clear-cut hepatotoxicity, expressed in histopathological and biochemical changes at levels of about 5,500 mg/m^3 and higher. A number of studies are summarised in annex E (Dre78, Kyl63, Ike69, Oga68).

Immunotoxicity

Aranyi *et al*. (Ara86) investigated the influence of PER inhalation (3 h, 172 mg/m^3 (25 ppm) and 345 mg/m^3 (50 ppm)) on mice mortality from *Streptococcal pneumonia* and mouse pulmonary bactericidal activity to inhaled *Klebsiella pneumonia*. Both endpoints were significantly affected; mortality increased and the bactericidal effect decreased.

Chapter 3

Hazard assessment

3.1 Assessment of health risk

Various human studies with volunteers showed that acute exposure to PER results in slight, but transient effects on the central nervous system (CNS). These CNS-effects include dizziness, sleepiness, light-headedness and impaired motor-coordination. The CNS-effects were consistently observed at exposure levels of 1,500 mg/m^3 and higher. At exposure levels of 760 mg/m^3 for 4-6 min and 730 mg/m^3 for 1 hour, no CNS-effects were reported. Negligible, slight transient eye irritation was reported at 534 mg/m^3. Animal studies support the findings in humans in that no CNS-effects were found at 689 and 1378 mg/m^3. The committee considers the slight CNS-effects as an important potential hazard for the workers, which should be avoided. Therefore, the committee advises that a health-based recommended occupational exposure limit for short-term exposure (STEL, 15-min TWA) is warranted.

3.2 Recommendation of the health-based occupational exposure limit

For establishing a short-term exposure limit (STEL), the committee considers the studies by Stewart *et al*. (Ste61a) and Rowe *et al*. (Row52) the most relevant. From these studies 1500 mg/m^3 is considered the lowest-observed-adverse-effect-level (LOAEL) and approximately 750 mg/m^3 the no-observed-adverse-effect-level (NOAEL) for CNS-effects. To compensate for the low number of volunteers in the studies and the limited study design, the committee applies a factor of 3 for intra-individual variation. Taken

these considerations into account the committee recommends a STEL of 250 mg/m^3 as a 15-minute time-weighed average concentration (15 min TWA, STEL).

3.3 Groups at extra risk

The available toxicological information on PER does not point to groups of humans which are at extra risk.

3.4 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based recommended occupational exposure limit for PER of 250 mg/m^3, as a 15-minute time-weighed average concentration (15 min TWA, STEL).

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Fri53 Friberg L, Kylin B, Nystrom A. Toxicities of trichloroethylene and tetrachloroethylene and Fujiwara's pyridine - alkali reaction. Acta Pharmacol Toxicol 1953; 9: 303-312.

Foo43 Foot EB, Bishop K, Apgar V. Tetrachloroethylene as an anaesthetic agent. Anaesthesiology 1943; 4: 283-.

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Ike69 Ikeda T, Nagano C, Okada A. Hepatotoxic effects of trichloroethylene and perchloroethylene in the rat and mouse. (EPA translation TR-78-0135) Igaku to Seibutsugako 1969; 79: 123-129.

Ken91 Kennedy GL, Graepel GJ. Acute toxicity in the rat following either oral or inhalation exposure. Toxicol Lett 1991; 56: 317-326.

Kyl63 Kylin B, Reichard H, Sumegi I, *et al.* Hepatotoxicity of inhaled trichloroethylene, tetrachloroethylene and chloroform. Single exposure. Acta Pharmacol Toxicol 1963; 20: 16-26.

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Row52 Rowe VK, McCollister D, Spencer HC, *et al.* Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. AMA Arch Ind Hyg 1952; 5: 566-579.

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Ste61b Stewart RD, Erley MS, Schaffer BS, *et al.*. Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene. Industrial Medicine and Surgery 1961; 30: 327-330.

Way60 Wayne LG and Orcutt JA. The relative potentials of common organic solvents as precursors of eye-irritants in urban atmospheres. J Occup Med 1960: 383-388.

A	Request for advice
B	The Committee
C	Comments on the public review draft
D	Effects in human subjects after acute exposure
E	Effects in animals after acute exposure

Annexes

Annex **A**

Request for advice

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

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

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

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

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

genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

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

Annex **B**

The committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- LJNGM Bloemen
- epidemiologist and biochemist, Dow Chemical, Terneuzen
- PJ Boogaard
  toxicologist; Shell International BV, The Hague
- PJ Borm
  toxicologist; Centre of Expertise in Life Sciences, Hogeschool Zuyd, Heerlen
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  epidemiologist; IRAS, Utrecht University, Utrecht
- AAJP Mulder, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- TM Pal
  occupational physician; Netherlands Center for Occupational Diseases, Amsterdam
- IMCM Rietjens
  professor of toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
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- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- RA Woutersen
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- TMM Coenen, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

Secretarial assistance: F Smith.
Lay-out: J van Kan/M Javanmardi.

Annex C

Comments on the public review draft

A draft of the present report was released in 2003 for public review. The following organisations and persons have commented on the draft document:

- E Bal, Health and Safety Executive, Great Britain
- H Greim, Senatskommission der Deutschen Forschungsgemeinschaft, Germany
- RD Zumwalde, National Institute for Occupational Safety and Health, USA

Annex **D**

Effects in human subjects after acute exposure

Effects observed in human subjects after acute exposure to PER.

Number of volunteers	Exposure regime and duration	Concentration mg/m^3 (ppm)	Observed effects	Ref.
4 males (health status not specified)	6 minutes (exposure chamber)	34450 (5000)	All showed vertigo, nausea, retarded mental activity increased salivation and left room < 6 min	Car37
5 males	7.5 minutes (exposure chamber)	13780 (2000)	All showed faintness, very light narcosis and left room	
4 males	some minutes (exposure chamber)	10335 (1500)	All showed definite hilarious, dizziness and left room	
4 males	95 min (exposure chamber)	6435 (934)	Lassitude, mental fogginess and exhilaration. Increase in concentration leads to inebriation.	
4 males	130 min (exposure chamber)	3272 (475)	All showed slight eye irritation, increased salivation, increased mucous secretion from nasal passages, tightness in frontal sinuses, sweetish metallic taste, and increased perspiration of hands. One subject experienced a slight feeling of elation.	
3 males	some minutes (pretest)	344 (50)	All detected odour	
4 (sex not specified)	1-2 min (exposure chamber)	7303 (1060)	Marked irritation of eyes and upper respiratory tract tolerated for 1 min (three subjects). One subject that tolerated exposure for 2 min reported considerable dizziness. Rapid and complete recovery. No statistics reported.	Row52
2 males	10 min (exposure chamber)	4134 (600)	Irritation of eyes and nose, dizziness, tightness and numbness about the mouth, some loss of inhibitions. Good motor coordination requires mental effort. Complete recovery within one hour. No statistics reported.	

4 males	2 h (exposure chamber)	1929 (280)	All reported light-headedness, burning sensation in eyes, congestion of frontal sinuses, thickness of the tongue, tightness about the mouth, irresponsibility, and impaired motor coordination, mental effort required for motor co-ordination. One subject reported transient nausea after 30 min exposure. Recovery within 1 hour, except one subject who felt unwell for several hours. No statistics reported.	
4 (sex not specified)	45-120 min (exposure chamber)	1488 (216)	All reported eye irritation (slight stinging sensation) within 20-30 minutes and congestion of frontal sinuses with discharge. Slight dizziness reported by 2 and sleepiness by 3 subjects. Recovery within 1 hour. No statistics.	
6 (sex not specified)	1 h (exposure chamber)	730 (106)	Very slight transient eye irritation when peak concentrations occurred during dosage of liquid PER (necessary to maintain vapour concentration) in exposure room. No statistics reported.	
21 yr old healthy male worker, cleaning stairs	3.5 h (closed room: 3h limited ventilation; 30 min no ventilation)	2707 (393) (3h 375 ppm followed by 30 min 1100 ppm) (mix of 393 ppm PER and 230 ppm of another dry-cleaning solvent (Stoddard solvent)	Unconscious subject removed from room, showing semi comatose with a strong odour of chlorinated hydrocarbons. After 15 min oxygen administration, he was completely conscious and rational without neurological abnormalities. Two-three weeks later, in the absence of any clinical symptoms, liver functions became abnormal (mainly urinary urobilinogen, alkaline phosphatase, serum bilirubin and SGPT).	Ste61b
12 healthy males, 30-59 yr[a]	> 30 min (exposure chamber)	1570 (210-244)	Slight light-headedness; increase effort necessary to maintain a normal test of balancing ability (Romberg test)	Ste61a
	6-30 min (exposure chamber)	1378 (200)	Romberg's sign and heel-to-toe tests normal.	
	4-6 min (exposure chamber)	758(10-120)	Slight soft palate irritation and dryness noticeable (subjective response)	
	1-4 min (exposure chamber)	534 (75-80)	Very slight eye irritation (a mild burning sensation) Subjects became unaware of irritation after a few minutes of exposure. No statistics reported.	
8-11 males Subjects served as own control exposed to heat only or sunlight	90 sec (eye exposure mask)	140 (incl 1.9 mg/m^3 NO_2) in warm irradiated air to simulate urban air pollution. Controls: PER/NO_2/heat PER/NO_2/sun light	No eye irritation observed No control without NO_2	Way60

[a] Subjective effects reported during rising concentrations and time after exposure of two experiments of each 6 volunteers. Each volunteer received a complete pre-employment history and physical examination, chest X-ray, in some cases, lumbar spine X-ray, C.B.C., urinalysis and orthorater eye examination. No effects on serum glutamic oxaloacetic transaminase (SGOT); serum glutamic pyruvate transaminase (SGPT) and urobilinogen excretion were noted during the exposures (Ste61a).

Annex **E**

Effects in animals after acute exposure

Effects observed in animals after acute exposure to PER.

Species	Exposure regime and duration	Concentration mg/m^3 (ppm)	Observed Effects	Ref.
Rats (sex, strain not specified) n=2-4/group no control	8 h (inhalation chambers)	213590 (31000), 130910 (19000), 62010 (9000), 31005 (4500), 18948(2750)	At 213590 mg/m^3 all rats once completely anaesthetized, died within a few minutes. At 130910 mg/m^3 one died after 30 min, whereas the others recovered due to immediate removal. No deaths in lower dose groups. Autopsy of surviving animals showed congestion and granular swelling of liver (130910 and 62010 mg/m^3). Lower concentrations showed less pronounced effects. Dead rats as well as central nervous system of survivors were not studied.	Car37
Mice (sex, strain not specified) n=15/group no control	10 min forced inhalation	84058 (12200), 46852 (6800)	Complete immobility in a rotating cylinder (= measurement of narcosis degree) after 3.5 and 5.5 min forced inhalation. The narcotic effect is significantly (p=0.001) greater compared to a group exposed to trichloroethylene. Mortality data were not reported.	Fri53
Beagle dogs, male; trained to breath through a one-way face mask and accept venipuncture n=5 (34500 mg/m^3) n=12 (68900 mg/m^3) n=13 control	7 min house-air followed by 10 min exposure by one-way face mask	68900 (10000), 34500 (5000)	Animals were dosed 8 µg/kg epinephrine twice: after 2 min house-air (control period) and after 5 min PER exposure. ECG observed no increased sensitivity to epinephrine-induced cardiac arrhythmias during control and exposure period. Highest dose was associated with excitement and struggling.	Rei73
Male, new Zealand rabbits; n = 9-17 Rabbits served as own control	1 h (inhalation chamber)	35800 (5200)	Animals were challenged up to 3 µg/kg IV epinephrine during (7.5, 15, 30, 45 and 60 min) and 15 and 30 min post-exposure. Some rabbits died (numbers not reported). Their death was related to a CNS depressant effect and not to cardio toxicity. Fifty percent showed increased sensitivity to epinephrine-induced cardiac arrhythmias observed by ECG. After 15-30 min adaptation occurred.	Car83

Female rats, (strain not specified); trained for reaction within 2 min to avoid or escape response; n=8-10 Rats served as own control	4 h (inhalation chambers)	15847 (2300)	Eighty percent lost both escape and avoidance responses due to overt ataxia, which disappeared after further exposures. No statistics or other clinical effects reported.	Gol64
Adult male CD1 rats n=15/group Rats served as own control	1 h (inhalation chamber)	13780 (2000), 6890 (1000), 3445 (500)	Effects on rat serum enzymes indicating hepatotoxicity, SGOT, SGPT, SG-6-P and SOCT were measured 24 h prior, 1, 24 and 48 h after exposure. The highest concentration lead to market increases (p<0.01) of the activities of all four enzymes after 24 and 48 h. Less but substantial increases (p<0.01) were found after exposure to 6890 mg/m^3. Marginal increases were found when enzyme activity was measured within 1 h after exposure, or when the animals were exposed to 3445 mg/m^3. Clinical effects were not studied.	Dre78
Female mice, strain not specified n=20/group n=20 control (n=10 for each parameter in time)	4 h (inhalation chamber)	11024 (1600), 5512 (800), 2756 (400), 1378 (200)	A dose dependent fatty infiltration (but no necrosis) in the liver at all doses, as well as a significantly dose-dependent increase of extractable fat was observed at 2756 mg/m^3 and higher, when measured 24 and 72 h after exposure. No effects on SOCT. Clinical effects were not studied.	Kyl63
Mice and rats	4 h	7400 (1074)	Centrilobulair fatty degeneration and increases of lipids and triglycerides in livers of mice. No such changes occurred in rats. Clinical effects were not studied.	Ike69
Male, Swiss OF1 mice n=10/group n=10 control	4h (inhalation chamber), followed by 'behaviour' swimming test during 3 min	5650 (820), 4713 (684), 4472 (649), 4106 (596)	Significant dose-related decrease of immobility in behavioural despair swimming test at 5650, 4713 and 4472 mg/m^3 (p< 0.05). ID50 (50% decrease in immobility) was 4900 mg/m^3 (95% confidence interval 4600-5500 mg/m^3).	Dec83
Female Cb mice (n not specified)	3 h (inhalation chamber)	5512 (800)	Livers were isolated 0, 4, 8 and 20 h after exposure. Clear-cut decrease (to 45% of control) of liver-ATP content in mice, which lasted till observation was terminated (to 55% of control after 20 h). Furthermore, marked (up to 160%) and rather persistently increased liver lipid levels and liver triglyceride levels were found. Clinical effects were not studied.	Oga68
Female CD1 mice n=140/group n=140 control	3 hr (inhalation chambers) followed by *streptococcus* infection or ^{35}S *K. pneumoniae* inhalation	345 (50), 172 (25)	The host susceptibility to laboratory-induced respiratory infection was examined by *streptococcus* infection in 140 mice, whereas *in vivo* pulmonary bactericidal activity (clearance) of alveolar macrophages was examined by ^{35}S *Klebsiella pneumonia* inhalation in 18 mice. At 345 mg/m^3, a significant ($p \leq$ 0.01) increased susceptibility (i.e. mortality) to experimentally induced respiratory streptococcus infection over a 14-day observation period and a significant ($p \leq$ 0.05) decreased pulmonary bactericidal activity (to *Klebsiella pneumoniae*) was observed. Clinical effects were not studied.	Ara86

Abbreviations: SGOT serum glutamic oxaloacetic transaminase; SGPT serum glutamic pyruvate transaminase; SG-6-P serum glucose-6-phosphate; SOCT serum omithine carbamyl transferase