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 toxic substances in the workplace air. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). It constitutes the first step in a three-step procedure which leads to legally binding occupational exposure limits.

The present report on tetrachloroethane was prepared in cooperation with the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG), an advisory body of the Nordic countries. The joint report on the consequences of occupational exposure to tetrachloroethane, published in Sweden in 1996 (Arbete och Hälsa 1996:28), is included in Part II of this document. Part I consists of a summary of the data presented in Part II, presentation of data becoming available since 1996, and a discussion of the consequences of occupational exposure to the tetrachloroethane isomers. The conclusions in Part I are based on scientific publications which appeared before January 2006, and are entirely DECOS' view.

Occurrence, physical and chemical properties

Tetrachloroethane is a chemical compound occurring in two isomers: 1,1,1,2-tetrachloroethane (CAS number 630-20-6) and 1,1,2,2-tetrachloroethane (CAS number 79-34-5). At room temperature, both isomers are colourless, non-flammable, heavy liquids with a low to moderate volatility. Neither of the isomers is known to occur naturally.

1,1,1,2-Tetrachloroethane is not produced on an industrial scale. It is, however, a common by-product of many industrial chlorination reactions of C_2 hydrocarbons, among which the production of 1,1,2,2-tetrachloroethane.

1,1,2,2-Tetrachloroethane is used as an intermediate in the manufacture of other chlorinated hydrocarbons. In the past, 1,1,2,2-tetrachloroethane was rather extensively used, amongst others having many uses as a solvent. Due to its toxicity, the present production of 1,1,2,2-tetrachloroethylene may be very limited.

Monitoring

Several organisations, including the Nederlands Normalisatie-instituut, the National Institute of Occupational Safety and Health and the Environmental Protection Agency in the United States, and the Health and Safety Executive in the United Kingdom, have described methods, which can be used for analysing 1,1,2,2-tetrachlorethane in workplace air. These methods use subsequently active sampling on sorbent tubes, thermal or liquid desorption, and gas chromatographic analysis. The suitability of the method depends on the origin of the material in the sorbent tube. Further, there are other methods using passive samplers and portable chromatographs.

Current limit values and classification

For 1,1,1,2-tetrachloroethane, no limit values have been established nationally and internationally. For 1,1,2,2-tetrachloroethane, the occupational exposure limit is 7 mg/m^3 (1 ppm) in most countries. A skin notation is added. This indicates that the compound may relatively easily enter the body through the skin which may contribute significantly to the body burden.

Germany and NIOSH have classified it as a suspected and potential carcinogen, respectively; ACGIH as an A3 carcinogen (i.e., a confirmed animal carcinogen with unknown relevance to humans).

Kinetics

1,1,1,2-tetrachloroethane

No data are available on the kinetics (absorption, metabolism, distribution, and excretion) of 1,1,1,2-tetrachloroethane following the main occupational exposure routes, viz., via inhalation and skin contact.

However, there are data on absorption following oral administration. Studies in rats and mice indicate an almost complete absorption. When absorbed, rats appear to exhale unchanced 1,1,2,2-tetrachloroethane six times as much as mice. The metabolism of 1,1,1,2-tetrachloroethane proceeds through both oxidative and reductive pathways resulting in CO_2 – in exhaled air – and trichloroethanol and trichloroacetic acid – in urine – as main metabolites. The data also show that in rats, there is a difference in metabolism of 1,1,1,2- and 1,1,2,2-tetrachloroethane. The amount of trichloro compounds in the urine of rats exposed to 1,1,1,2-tetrachloroethane by inhalation or an intraperitoneal injection was 20 times as high as the amount of trichloro compounds in the urine of rats similarly exposed to the 1,1,2,2 isomer.

1,1,2,2-tetrachloroethane

Experimental animals data show that 1,1,2,2-tetrachloroethane is well absorbed following inhalation and oral administration. No experimental data were available following skin contact. However, for human skin, a steady state flux of 27 µg/cm^2/h has been calculated based on molecular weight, octanol-water partition coefficient, and contact with a saturated aqueous solution (3 mg/mL).

Following absorption, biotransformation of 1,1,2,2-tetrachloroethane may involve a number of oxidative dechlorination pathways, and there is some evidence for a reductive pathway (leading to a carbon-centred radical and subsequent lipid peroxidation in the liver) as well. Following inhalation and oral administration, rats and mice metabolised 1,1,2,2-tetrachloroethane extensively. Generally, CO_2 was the main metabolite. In urine, dichloroacetic acid was found to be the major urinary metabolite. Compared to mice, rats exhaled 4 and 14 times more unmetabolised 1,1,2,2-tetrachloroethane following inhalation and oral administration, respectively, which might render rats more sensitive to CNS effects.

Effects in humans

1,1,1,2-tetrachloroethane

No data are available on the potential irritating or sensitising properties or on the system toxic effects of 1,1,1,2-tetrachloroethane in humans.

1,1,2,2-tetrachloroethane

There are human data available on the effects following exposure to 1,1,2,2-tetrachloroethane.

In 2 male volunteers, dizziness and mucosal irritation were observed within 10 to 12 minutes when exposed to 1000 or 1800 mg/m^3 (144, 262 ppm) 1,1,2,2-tetrachloroethane, but no such effects were seen at exposure up to 90 mg/m^3 (13 ppm) for 10 minutes.

In studies on workers occupationally exposed to 1,1,2,2-tetrachloroethane – published before 1965 –, the liver, the gastrointestinal tract, and the nervous system were the target organs. In one survey, in which especially fine finger tremor was reported, there was not only inhalation exposure but also skin contact, as well as exposure ot acetone.

No statistically significant increases in mortality, overall cancer mortality, and cancer incidences were found in a retrospective study on a cohort consisting of 1099 white men with exposure to 1,1,2,2-tetrachloroethane while using impregnating clothing machinery and some additional exposure to dry-cleaning solvents.

Effects in experimental animals

1,1,1,2-tetrachloroethane

Inhalation of 1,1,1,2-tetrachloroethane or contact with the liquid may cause irritation of the skin and mucous membranes or sensitisation. However, no such experimental animal data were available.

Taking mortality as an end point, 1,1,1,2-tetrachloroethane is not very toxic following single exposure. Four-hour LC_{50} values of 14,600 mg/m^3 (2100 ppm) were found for rats and of 19,500 mg/m^3 (2800 ppm) for rabbits; a dermal LD_{50} of 20,000 mg/kg bw was reported for rabbits.

No data were available from repeated inhalation studies. In repeated-dose gavage studies, besides the CNS, the target organs seem to be the kidney in (male) rats and the liver in mice. When male rats were given daily doses of 104 and 208 mg/kg bw, only findings indicative of hyaline droplet-induced nephropathy were observed. This type of kidney damage is generally not considered to be relevant to humans.

Another effect might be the induction of tumours. In a carcinogenicity study, daily administration of doses of 0, 125, and 250 mg/kg bw/day to Fischer rats, did not induce statistically significant increases in tumour incidences in any of the treated groups. In the females of the low-dose group, however, there was a statistically significant increase in the incidence of fibroadenomas. In $B6C3F_1$ mice, doses of 0, 250, or 500 mg/kg bw caused statistically significant increases in the incidence of hepatocellular adenomas in males and females and of hepatocellular carcinomas in females.

1,1,1,2-Tetrachlorethane was negative in a tumour-initiation/promotion assay in male Osborne-Mendel rats.

In *in vitro* mutation tests, mostly negative results were obtained in bacteria and mammalian cells; tests in yeast and fruit fly were negative as well. In a chromosome aberration assay in Chinese hamster ovary cells, 1,1,1,2-tetrachloroethane produced negative results. In Chinese hamster lung fibroblasts, the compound induced increases in the frequency of numerical chromosomal aberrations (i.c., polyploidy), but not of structural chromosomal aberrations. Other tests, indicative of genetic or primary DNA damage in yeast, fungi, fruit fly, or mammalian cells, produced both positive and negative results. *In vivo*, an increase in hepatic DNA synthesis was found in orally treated rats and mice. Following intraperitoneal injections, 1,1,1,2-tetrachloroethane was bound covalently to DNA in rat and mouse organs. A cell transformation assay in BALB/c-3T3 cells was negative.

Finally, no data were available from reproduction toxicity studies.

1,1,2,2-tetrachloroethane

Experimental animal data indicate that liquid 1,1,2,2-tetrachloroethane is strongly irritating to the skin and mucous membranes. No data were available from experimental animal sensitisation studies. Following single inhalation exposure, effects were reported only at thousands of mg/m^3. In rats, the 4-hour LC_{50} values were 7000 and 8400 mg/m^3 (1000 and 1200 ppm).

Contrary to 1,1,1,2-tetrachloroethane, there were experimental animal data on 1,1,2,2-tetrachloroethane following repeated inhalation exposure. The studies available suggest that the CNS and the liver are the target organs. However, they suffer from several flaws such as insufficient number of animals, inappropriate exposure regimens, very high exposure concentrations, limited number of end points examined, and/or insufficient reporting.

Besides inhalation studies, studies in which 1,1,2,2-tetrachloroethane was repeatedly orally administered were available. The liver was the most sensitive organ. In gavage studies, repeated doses of 200-300 mg/kg bw induced such severe toxicity in rats that experiments were broken off within a few days. In male rats, doses of 1,1,2,2-tetrachloroethane of 104 mg/kg bw affected the liver (increased weights accompanied by mild to moderate cytoplasmic vacuolisation). Contrary to 1,1,1,2-tetrachloroethane, no effects on the kidney or urinalysis parameters were seen.

In 14-week diet studies in rats and mice, DECOS could not establish NOAELs. In male rats, administration of 20 mg/kg bw, the lowest dose tested, induced minimal to mild vacuolisation of hepatocytes. In female mice, 80 mg/kg bw, also the lowest dose, caused minimal to mild hepatocytic hypertrophy in 2/10 females.

What is known about the potential carcinogenic effects of 1,1,2,2-tetrachloroethane? In carcinogenicity studies male and female Osborne-Mendel rats were given time-weighted average doses of 62 and 108 and 43 and 76 mg/kg bw/day, respectively, for 78 weeks followed by a 32-week treatment-free period. Treatment did not cause statistically significant increases in the incidence of any tumour type in any of the groups. $B6C3F_1$ mice were given time-weighted average doses of 142 and 284 mg/kg bw/day for 78 weeks followed by an exposure-free period of 12 weeks. In the high-dose group, mortality was increased. Treatment caused statistically significant increases in the incidences of hepatocellular carcinomas in males and females.

1,1,2,2-Tetrachloroethane had a weakly tumour-initiating and a more strongly tumour-promoting activity in Osborne-Mendel rats in an initiation/promotion assay.

In *in vitro* mutation tests, 1,1,2,2-tetrachloroethane was negative in the majority of tests using *S. typhimurium* strains, in yeast strains, mouse lymphoma cells, and fruit flies. A test for chromosome aberrations in CHO cells was negative as well. Other tests, indicative of genetic or primary DNA damage in yeast, fungi, fruit fly, or mammalian cells, produced both positive and negative results. *In vivo*, 1,1,2,2-tetrachloroethane caused small increases in the frequency of micronuclei in erythrocytes obtained from orally treated mice which reached statistically significance only in male animals at high toxic doses of 700 and 1360 mg/kg bw/day. No UDS or S-phase synthesis was seen in hepatocytes isolated from mice given single oral doses. Following intraperitoneal injections, 1,1,2,2-tetrachloroethane was bound covalently to DNA in rat and mouse organs. In orally dosed mice, binding of 1,1,2,2-tetrachloroethane-derived radioactivity to hepatic DNA was thought to be due to incorporation of metabolic one-carbon fragments rather than adduct formation. In cell transformation assays in BALB/c-3T3 cells, there was one positive and one negative result when tested in the absence of metabolic activation, and two positive results in the presence of metabolic activation.

Finally, there were data on the potential effects on the reproductive tissues and the offspring. 1,1,2,2-Tetrachloroethane affected the reproductive tissues of male rats at dietary doses of 40 mg/kg bw/day and higher and of female rats at 170 mg/kg bw and higher, indicating that it might compromise fertility. However, there were no data from valid studies addressing the potential effects of 1,1,2,2-tetrachloroethane on fertility or pregnancy outcome.

Evaluation

1,1,1,2-tetrachloroethane

Do the available data justify the derivation of a health-based recommended occupational exposure limit?

From *in vitro* and *in vivo* mutagenicity and genotoxicity studies, DECOS concludes that 1,1,1,2-tetrachloroethane is not a stochastic genotoxic compound. Based on the carcinogenicity and genotoxicity data, the committee concludes that 1,1,1,2-tetrachloroethane has been extensively investigated. Although there is insufficient evidence to warrant a classification as ‘known to be carcinogenic to humans’ or as ‘should be regarded as carcinogenic to humans’, they indicate that there is a cause for concern. Therefore, 1,1,1,2-tetrachloroethane is classified as a suspect (non-genotoxic) carcinogen (comparable to EU category 3(A)).

According to DECOS, the qualification of 1,1,1,2-tetrachloroethane as a suspect, non-genotoxic carcinogen, basically warrants the derivation of a health-based limit value.

Are there sufficient data available to allow recommendation of a limit value?

According to DECOS, this is not the case. The committee did not find human or experimental animal inhalation data that could be used as a starting point for deriving a health-based occupational exposure limit. DECOS also considers the oral experimental animals studies as inappropriate. Further, DECOS is of the opinion that the data on 1,1,2,2-tetrachloroethane cannot be used either. Experimental animal data suggest that there are differences between 1,1,1,2- and 1,1,2,2-tetrachloroethane with respect to metabolism and target organs.

DECOS considers the toxicological database for 1,1,1,2-tetrachloroethane too poor to recommend a health-based occupational exposure limit.

1,1,2,2-tetrachloroethane

Do the available investigations justify the derivation of a health-based recommended occupational exposure limit for the other isomer evaluated: 1,1,2,2-tetrachloroethane?

From the mutagenicity and genotoxicity data, DECOS concludes that 1,1,2,2-tetrachloroethane is not a stochastic genotoxic compound. Based on the data on carcinogenicity and mutagenicity, the committee concludes that 1,1,2,2-tetrachloroethane has been insufficiently investigated. While the available data do not warrant a classification as ‘known to be carcinogenic to humans’ or as ‘should be regarded as carcinogenic to humans’, they indicate that there is cause for concern. Therefore, 1,1,2,2-tetrachloroethane is classified as a suspect (non-genotoxic) carcinogen (comparable with EU category 3(B)).

According to DECOS, the qualification of 1,1,2,2-tetrachloroethane as a suspect, non-genotoxic carcinogen, basically warrants the derivation of a health-based limit value.

Are there sufficient data available to allow recommendation of a limit value?

DECOS is of the opinion that the available human and animal experimental data on irritation and acute toxicity do not suggest the need for a short-term (15-minute) exposure limit value.

To derive a health-based recommended occupational exposure limit, DECOS is of the opinion that the available human and experimental inhalation data, which showed that the liver, the gastrointestinal tract, and the nervous system were the target organs, are inappropriate as starting points. Therefore, the committee uses oral studies. The committee could not establish NOAELs in studies in which rats and mice received 1,1,2,2-tetrachloroethane in their diets for 14 weeks. Although the hepatocellular vacuolisation observed by itself is not necessarily an adverse effect, the committee is of the opinion that in this case vacuolisation marks the first step leading to more severe effects such as hypertrophy and necrosis. Therefore, the committee takes the LOAEL of 20 mg/kg bw/day found in the rat study as the starting point for deriving a health-based occupational exposure limit (HBROEL).

To arrive at a HBROEL, extrapolation factors are used. In this respect, the committee notes the mildness of the key effect and the gap between the doses inducing the mild (vacuolisation) and more severe (hypertrophy/necrosis) effects. Further, in the experimental animal study, the animals had continuous access to the test compound without any exposure-free period to recover. On the other hand, workers are exposed 8 hours/day, 5 days/week allowing recovery. Therefore, the committee considers a factor of only 2 justified for the absence of a NOAEL and does not apply a factor for difference in ‘exposure duration’. For intraspecies and interspecies variation, the committee takes a total factor of 10.

Taking the LOAEL of 20 mg/kg bw and applying the total extrapolation factor of 20, the committee recommends a health-based occupational exposure limit of 7 mg/m^3 for 1,1,2,2-tetrachloroethane, assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100%.

Since dermal penetration may contribute significantly to the body burden, the committee considers a skin notation warranted.

Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards of the Health Council recommends a health-based occupational exposure limit for 1,1,2,2-tetrachloroethane of 7 mg/m^3 (1 ppm) as an 8-hour time-weighted average concentration. It also recommends a skin notation.

The committee cannot recommend a health-based occupational exposure limit for 1,1,1,2-tetrachloroethane.

This report contains an additional consideration of the committee about the use of the health-based occupational exposure limit of 1,1,2,2-tetrachloroethane for setting an occupational exposure limit for 1,1,1,2-tetrachloroethane.