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Vinyl Chloride in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

Vinyl Chloride in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document published in the second edition of the Guidelines. The update was prepared by Dr J. Kielhorn, Fraunhofer Institute of Toxicology and Experimental Medicine, Germany, to whom special thanks are due.

The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

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The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
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Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAA	chloroacetaldehyde
CAS	Chemical Abstracts Service
CEO	chloroethylene oxide
DNA	deoxyribonucleic acid
GC	gas chromatography
IUPAC	International Union of Pure and Applied Chemistry
LC_{50}	median lethal concentration
LED_{10}	effective dose corresponding to the lower 95% limit on a dose associated with 10% response
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBPK	physiologically based pharmacokinetic
PVC	polyvinyl chloride
uPVC	unplasticized polyvinyl chloride
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	75-01-4
Molecular formula:	C_2H_3Cl

The IUPAC name for vinyl chloride is chloroethene; it is also known as monochloroethylene.

1.2 Physicochemical properties[1] *(IPCS, 1999)*

Property	*Value*
Physical state	Colourless gas
Boiling point	-13.4 °C
Vapour density	2.2 relative to air at 20 °C
Water solubility	Slightly soluble (1.1 g/litre) at 25 °C
Log octanol–water partition coefficient	1.5
Henry's law constant	2.0–2.8 kPa·m^3/mol at 25 °C; 18.8 kPa·m^3/mol at 20 °C

Under ambient conditions, vinyl chloride is a colourless, flammable gas with a slightly sweet odour. It has a high vapour pressure, a high Henry's law constant and a relatively low water solubility. There are discrepancies in the literature with regard to its Henry's law constant (air–water partition coefficient and log octanol–water partition coefficient), probably due to uncertainties in the absolute aqueous solubility in older studies (IPCS, 1999). Vinyl chloride is soluble in almost all organic solvents. It is heavier than air and can spread over the ground, creating an exposure long distances away from the original source. It can also form explosive mixtures (IPCS, 1999).

1.3 Organoleptic properties

Vinyl chloride has a mild, sweetish odour at high concentrations. The odour threshold value in air is very subjective, ranging from 26–52 mg/m^3 in sensitive individuals to 10 000 mg/m^3, and is far above the present accepted occupational safety threshold values (IPCS, 1999). An odour threshold of 3.4 mg/litre in water has been reported (Amoore & Hautala, 1983).

1.4 Major uses

About 95% of the world production of vinyl chloride (27 million tonnes in 1998) is used for the production of polyvinyl chloride (PVC) and as a co-monomer with ethenyl ethanoate (vinyl acetate) or 1,1-dichloroethene (vinylidene chloride). The

[1] Conversion factor in air: 1 ppm = 2.6 mg/m^3.

remainder goes into the production of chlorinated solvents, primarily 1,1,1-trichloroethane (10 000 tonnes per year) (IPCS, 1999).

1.5 Environmental fate

In the atmosphere, vinyl chloride exists almost entirely in the vapour phase and reacts with hydroxyl radicals and ozone, ultimately forming formaldehyde, carbon monoxide, hydrochloric acid and formic acid; its half-life is 1–4 days (ICPS, 1999). It is stable in the absence of sunlight or oxygen but polymerizes when exposed to air, light or heat (Ministerie van Volkshuisvesting, 1984).

Vinyl chloride has a relatively low solubility in water and a low capacity to adsorb to particulate matter and sediment. Volatilization is the most rapid process for removal of vinyl chloride introduced into surface waters. Half-lives reported for volatilization from surface waters range from about 1 to 40 h (IPCS, 1999).

When released to the ground, vinyl chloride is not adsorbed onto soil but migrates readily to groundwater, where it may be degraded to carbon dioxide and chloride ion or remain unchanged for several months or even years. Vinyl chloride has been reported in groundwater as a degradation product of the chlorinated solvents trichloroethene and tetrachloroethene (IPCS, 1999).

2. ANALYTICAL METHODS

Vinyl chloride is first purged from the water and then collected for gas chromatographic (GC) analysis by headspace/purge and trap. Vinyl chloride is highly volatile and has a low specific retention volume on Tenax-GC, the most commonly used trapping medium in purge-and-trap analysis. Another approach is to bypass the trap altogether by purging directly onto a cryocooled capillary column. A more recent adaptation of the headspace method uses solid-phase microextraction (Shirey, 1995). In some methods, vinyl chloride is converted to the 1,2-dibromo derivative (Wittsiepe et al., 1993). Detection is by electron capture or flame ionization, with mass spectrometry for confirmation (IPCS, 1999). Detection limits are 0.01 µg/litre and below (Benfenati et al., 1991; Wittsiepe et al., 1993).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Atmospheric concentrations of vinyl chloride in ambient air are low, usually less than 3 $\mu g/m^3$. Exposure of the general population may be higher in situations where large amounts of vinyl chloride are accidentally released to the environment, such as a spill during transportation. However, such exposure is likely to be transient. Near vinyl chloride/PVC industry and waste disposal sites, much higher concentrations — up to 8000 $\mu g/m^3$ and 100 $\mu g/m^3$, respectively — have been observed in the past (IPCS, 1999). At sites 1 km from vinyl chloride/PVC polymerization plants, mean concentrations of 500 $\mu g/m^3$ were reported for China (Zhao et al., 1994) and 0.1–13

µg/m^3 for a plant in Finland (Kinnunen, 1996, 1997). A concentration of 10 µg/m^3 was reported in an industrial area of Ulsan, Korea, compared with 1.8 µg/m^3 downtown (Na et al., 2001).

3.2 Water

Owing to its high volatility, vinyl chloride has rarely been detected in surface waters, the concentrations measured generally not exceeding 10 µg/litre, with a maximum of 570 µg/litre from contaminated sites (IPCS, 1999). A recent example is the finding of vinyl chloride at concentrations up to 56 µg/litre, together with other volatile organic compounds, in heavily polluted shallow rivers in Osaka, Japan (Yamamoto et al., 2001). Maximum vinyl chloride concentrations from areas contaminated with chlorinated hydrocarbons were 60 000 µg/litre in leachate (Brown & Donnelly, 1988), 56 000 µg/litre in a contaminated sand aquifer (Semprini et al., 1995) and 12 000 µg/litre in groundwater (Dieter & Kerndorff, 1993). A vinyl chloride concentration of 27 000 µg/litre was detected in site groundwater above a drinking-water aquifer (Peterson et al., 2000).

High concentrations, up to 200 000 µg/litre, were detected in well water in the vicinity of a PVC plant in Finland 10 years after leakages (Salkinoja-Salonen et al., 1995). Concentrations up to 72.3 µg/litre (arithmetric mean 3.75 µg/litre) were measured in 44 downstream residential wells near a hazardous waste site in Taiwan (Lee et al., 2002). The authors reported that the residents used this water but boiled it first. Negligible vinyl chloride was found after the water was boiled for 1 min. Residents were exposed by inhalation while showering with this water.

There are few recent studies of vinyl chloride concentrations in drinking-water. From earlier studies, the highest concentration of vinyl chloride detected in drinking-water in the USA was 10 µg/litre (Fishbein, 1979). In a five-city survey in that country, concentrations of vinyl chloride up to 1.4 µg/litre were detected in drinking-water taken from distribution systems in which PVC pipe was used (Dressman & McFarren, 1978). Vinyl chloride has been detected only occasionally in samples of drinking-water from 100 cities in Germany. The highest level, 1.7 µg/litre, was ascribed to dissolution from PVC tubing (Bauer, 1981).

Unplasticized PVC (uPVC) is increasingly being used in some countries for water mains supplies. Migration of vinyl chloride monomer from uPVC is a possible source of vinyl chloride in drinking-water. In one study, vinyl chloride (2.5 µg/litre of drinking-water) was shown to be released from uPVC in sunlight at 45 °C, but not at 35 °C and below (Al-Malack et al., 2000). Therefore, in countries with hot climates, uPVC pipes may need to be insulated from heat and direct sunlight (Al-Malack et al., 2000; Al-Malack & Sheikheldin, 2001). However, these studies employed a residence time of 30 days. Modern methods of manufacture in all parts of the world should result in a much reduced risk of migration of significant levels of vinyl chloride into drinking-water.

Studies into PVC-bottled drinking-water have identified vinyl chloride at levels of 0.06–0.18 µg/litre (Benfenati et al., 1991) and <0.6 µg/litre (Fayad et al., 1997). The frequency of occurrence of vinyl chloride is expected to be higher in such water than in tap water (IPCS, 1999).

Vinyl chloride is rarely detected in raw water unless from a polluted source, but it may be present in treated water; for example, in a survey in Korea (Chung et al., 1997), vinyl chloride was reported in raw water (<0.013 µg/litre), treated water (maximum 0.48 µg/litre; mean 0.04 µg/litre) and tap water (drinking-water) (maximum 0.25 µg/litre; mean 0.014 µg/litre).

3.3 Food

In the past, packaging with certain PVC materials resulted in vinyl chloride contamination of foodstuffs, pharmaceutical and cosmetic products, vegetable oils, vinegars and mouthwashes. As a result of changes in manufacturing practices and legislative action in many countries, a significant reduction in vinyl chloride levels and in the number of positive samples has been achieved since the early 1970s (IPCS, 1999).

3.4 Estimated total exposure and relative contribution of drinking-water

The relative contribution of drinking-water to vinyl chloride exposure will depend on the extent of any contamination. Pipes manufactured to modern standards should not make a significant contribution to exposure. Boiling reduces the concentration of vinyl chloride in contaminated water. Because vinyl chloride is volatile, exposure by inhalation while showering with contaminated water could be expected.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Vinyl chloride is rapidly and well absorbed after inhalation or oral exposure. In animal and human studies, under steady-state conditions, approximately 40% of inspired vinyl chloride is absorbed after exposure by inhalation, the primary route of exposure to vinyl chloride. Animal studies show absorption of more than 95% after oral exposure. Dermal absorption of vinyl chloride in the gaseous state is not significant (IPCS, 1999).

Data indicate a rapid and widespread distribution of vinyl chloride. Rapid metabolism and excretion limit the accumulation of vinyl chloride in the body. The highest concentrations of metabolites are found in the liver, kidneys and spleen. Placental transfer of vinyl chloride occurs rapidly in rats (IPCS, 1999).

The main route of metabolism of vinyl chloride after inhalation or oral uptake involves oxidation by cytochrome P-450 (CYP2E1) to form chloroethylene oxide (CEO), a highly reactive, short-lived epoxide, which rapidly rearranges to form chloroacetaldehyde (CAA). The primary detoxification pathway for these two reactive

metabolites as well as chloroacetic acid, the dehydrogenation product of CAA, is conjugation with glutathione, catalysed by glutathione *S*-transferase. The conjugation products are further modified to substituted cysteine derivatives (*S*-(2-hydroxyethyl)-cysteine, *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, *S*-carboxymethyl cysteine and thiodiglycolic acid) and are excreted via urine; the metabolite carbon dioxide is exhaled in air (IPCS, 1999).

CYP2E1 and glutathione *S*-transferase isoenzymes are known to have large interspecies and interindividual variation in activity. *In vivo*, CEO is thought to be the most important metabolite with respect to the mutagenic and carcinogenic effects of vinyl chloride. CEO reacts with DNA to produce the major adduct 7-(2'-oxoethyl)guanine and, in lower levels, the exocyclic etheno adducts 1,N^6-ethenoadenine, 3,N^4-ethenocytosine and N^2,3-ethenoguanine. The etheno DNA adducts exhibit promutagenic properties, in contrast to the major adduct 7-(2'-oxoethyl)guanine (Barbin, 1999). A dose–response relationship has been seen for vinyl chloride inhalation exposure and N^2,3-ethenoguanine levels in rat tissues (Swenberg et al., 1999).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

The acute toxicity of vinyl chloride by inhalation is low, 2-h LC_{50}s ranging from 295 g/m^3 for mice to 595 g/m^3 for guinea-pigs and rabbits. Vinyl chloride has a narcotic effect after acute inhalation exposure. In rats, mice and hamsters, death was preceded by increased motor activity, ataxia and convulsions, followed by respiratory failure. No data were available on acute toxicity after oral or dermal application (IPCS, 1999).

5.2 Short-term exposure

Groups of 30 rats given vinyl chloride in soybean oil by gavage at 0, 30, 100 or 300 mg/kg of body weight per day, 6 days per week for 13 weeks, exhibited a dose-related increase in relative liver weight. A dose-related increase in adrenal gland weight (males only) was significant at the highest dose level. Histological changes in the liver and other organs were minimal. Hypertrophy of the endoplasmic reticulum was observed in hepatocytes of animals in the group given 300 mg/kg of body weight per day (Feron et al., 1975; JECFA, 1984). A NOEL of 30 mg/kg of body weight per day was based on the observed increase in liver weight (IPCS, 1999).

5.3 Long-term exposure

Groups of Wistar rats (60–80 per sex per dose) were fed diets containing 1% PVC powder with varying proportions of vinyl chloride monomer, 7 days per week for 135–144 weeks (Feron et al., 1981). Oral exposure to vinyl chloride monomer during the period of feeding was 0, 1.7, 5.0 or 14.1 mg/kg of body weight per day. A variety of neoplastic and non-neoplastic treatment-related liver lesions were found at all treatment levels.

In a further study at lower doses, groups of Wistar rats (100 per sex per dose) were fed diets containing 1% PVC powder with varying proportions of vinyl chloride monomer (0, 0.014, 0.13 or 1.3 mg of vinyl chloride per kg of body weight per day), 4 h per day, 7 days per week, for 149 weeks (Til et al., 1983, 1991). A variety of lesions were observed histologically at the highest dose level of 1.3 mg/kg of body weight per day, including increased incidences of angiosarcomas, neoplastic nodules, hepatocellular carcinoma, cellular foci (clear cell, basophilic and eosinophilic), liver cell polymorphism and cysts. Liver cell polymorphism (variation in size and shape of hepatocytes and their nuclei) has been used for quantifying non-cancer risks from oral exposure to vinyl chloride from this study. The severity and incidence of this liver lesion were statistically significantly increased at a daily dose of 1.3 mg/kg of body weight (LOAEL), but not at 0.13 mg/kg of body weight (NOAEL) (IPCS, 1999; US IRIS, 2000).

A LOAEL of 26 mg of vinyl chloride per m^3 (increased liver weight) was established based on a subchronic (3–12 months) inhalation toxicity study in male rats conducted by Bi et al. (1985). The effect was more pronounced, in a dose-related manner, at the two highest dose levels tested (260 and 7800 mg/m^3). A recent two-generation inhalation reproduction study with vinyl chloride in rats, using exposure concentrations of 26, 260 and 2860 mg/m^3 (Chemical Manufacturers Association, 1998), rendered the same LOAEL (26 mg/m^3) for liver effects. In this study, increased relative liver weights and hypertrophy of centrilobular hepatocytes were found in parental animals at all dose levels and in a dose-dependent manner (IPCS, 1999).

5.4 Reproductive and developmental toxicity

Inhalation studies on rats showed some evidence of reduced fertility and morphological alterations of the testis, with a LOAEL of 26 mg of vinyl chloride per m^3 (Sokal et al., 1980; Bi et al., 1985).

In a two-generation inhalation reproductive study, done in accordance with Good Laboratory Practice, adult CD rats (30 per sex per group) were exposed by whole-body inhalation at 26, 260 or 2860 mg/m^3 for 6 h per day, 5 days per week, for at least 10 weeks prior to mating through day 4 of lactation (94+ days) (Chemical Manufacturers Association, 1998). Alterations in reproductive performance and fertility were not detected at any dose level tested. Centrilobular hypertrophy in the liver and increased relative liver weights, however, were noted at all dose levels tested in a dose-related manner, with increased incidence in P_2 compared with P_1 animals. Whether this increased incidence in P_2 animals was due to *in utero* or juvenile susceptibility or to a longer duration of exposure is not clear (Chemical Manufacturers Association, 1998; IPCS, 1999). The NOEL for reproductive effects was given as >2860 mg/m^3.

Although the available studies on embryotoxicity and teratogenicity did not follow guideline standards, the information leads to the conclusion that there is embryotoxicity or fetal toxicity, including increased numbers of resorptions,

decreased numbers of live fetuses and delayed development, at dose levels producing maternal toxicity. Vinyl chloride treatment did not induce gross malformations. There is evidence for the permeability of the placenta to vinyl chloride (IPCS, 1999).

5.5 Mutagenicity and related end-points

Vinyl chloride induced sister chromatid exchange in human lymphocytes *in vitro*, mutations in Chinese hamster cells, unscheduled DNA synthesis in rat hepatocytes and transformation of BALB/c 3T3 cells. It also caused sex-linked recessive lethal mutations but not aneuploidy, heritable translocations or dominant lethal mutations in *Drosophila*. It was mutagenic to plants, including the yeast *Schizosaccharomyces pombe*, but not to other fungi. It induced gene conversion in yeast, caused DNA damage and mutation in bacteria and, with metabolic activation, bound covalently to isolated DNA (IARC, 1979, 1987; IPCS, 1999).

Vinyl chloride induced chromosomal aberrations, sister chromatid exchange and micronuclei in rodents exposed *in vivo*, but did not induce mutation in the mouse spot test or dominant lethal mutations in rats or mice. It alkylated DNA in several tissues of mice and rats exposed *in vivo* (IARC, 1979, 1987; IPCS, 1999).

Mutations of the *ras* and *p53* genes were analysed in liver tumours induced by vinyl chloride in Sprague-Dawley rats; base pair substitutions were found in the Ha-*ras* gene in hepatocellular carcinoma and in the *p53* gene in angiosarcoma of the liver. These mutations are in agreement with the observed formation and persistence of etheno adducts in liver DNA following exposure of rats to vinyl chloride and with the known promutagenic properties of etheno adducts (Barbin, 1999; IPCS, 1999; Marion & Boivin-Angele, 1999).

5.6 Carcinogenicity

There is sufficient evidence of the carcinogenicity of vinyl chloride to animals. When administered by inhalation, it induced angiosarcomas of the liver in rats, mice and hamsters, Zymbal gland tumours in rats and hamsters, nephroblastomas in rats, pulmonary and mammary gland tumours in mice and forestomach papillomas in hamsters. The minimum concentrations at which compound-related tumours were observed were 26, 130 and 1300 mg/m^3 in rats, mice and hamsters, respectively (Maltoni et al., 1981, 1984; IPCS, 1999).

In an oral life span assay, groups of Wistar rats were fed a diet containing 1% PVC powder with varying proportions of vinyl chloride monomer (0, 1.7, 5.0 or 14.1 mg/kg of body weight per day) for 135 weeks (males) and 144 weeks (females) (Feron et al., 1981). Increased mortality was noted in all treated groups. A mixture of angiosarcomas, hepatocellular carcinomas and neoplastic nodules was observed at the middle and high dietary doses. Only hepatocellular carcinomas and neoplastic nodules were observed at the low dose. Several other rare tumours were identified as possibly being associated with vinyl chloride exposure.

In the extension of the Feron et al. (1981) study in the same laboratory using the same methods but lower doses of vinyl chloride in 1% PVC (Til et al., 1983, 1991), hepatocellular carcinomas and angiosarcomas were found at the highest dose (1.3 mg/kg of body weight per day), although in smaller numbers. A statistically significant increase in the incidence of liver nodules (presumed to be hepatomas) in females and hepatocellular carcinomas in males was observed at 1.3 mg/kg of body weight per day; vinyl chloride at 0.13 mg/kg of body weight per day did not induce tumours.

In two other studies, groups of Sprague-Dawley rats (40 per sex per dose or 75 per sex per dose) were given vinyl chloride monomer in olive oil at dose levels equivalent to 0, 3.3, 16.6 or 50 mg/kg of body weight per day and 0, 0.03, 0.3 or 1 mg/kg of body weight per day, respectively, 5 times a week for 52 or 59 weeks; the studies were terminated at 136 weeks (Maltoni et al., 1981, 1984). In the first study, there was a dose-related increase in angiosarcomas: 18 at 50 mg/kg of body weight per day, 9 at 16.6 mg/kg of body weight per day and 1 at 3.3 mg/kg of body weight per day. In the second study, four angiosarcomas were found at 1 mg/kg of body weight per day, two at 0.3 mg/kg of body weight per day and none at 0.03 mg/kg of body weight per day. Small numbers of other tumours were also found, including nephroblastomas, Zymbal gland carcinomas and hepatomas.

In a study in which Wistar-derived rats (54 per sex per dose) were given vinyl chloride in drinking-water at concentrations of 0, 2.5, 25 or 250 mg/litre (equivalent to 0, 0.12, 1.2 and 12 mg/kg of body weight per day for males and 0, 0.22, 2.2 and 22 mg/kg of body weight per day for females) for 101–152 weeks (unpublished data cited in ECETOC, 1988), malignant tumours occurred with greater frequency in the highest dose group, the increase being more pronounced in females. Liver angiosarcomas occurred only in the highest dose group. In addition, five males in the group given 250 mg/litre developed angiosarcoma in the spleen, and a single subcutaneous angiosarcoma was present in a male in the group given 25 mg/litre.

An increased incidence of mammary gland carcinomas was observed in several experiments in which animals were exposed to vinyl chloride either orally or by inhalation, indicating treatment-related carcinogenic effect, but there was a lack of dose–response (Maltoni et al., 1981, 1984; Drew et al., 1983; IPCS, 1999).

There has been some concern in recent years about early life sensitivity to vinyl chloride (Hiatt et al., 1994; Cogliano et al., 1996). However, there is contradictory evidence (Groth et al.., 1981; Drew et al., 1983) concerning the effects of age on induction of angiosarcoma of the liver in rats. The discrepancy in results with rats is probably due to differences in strain or experimental design. However, evidence from other studies suggests that there is possibly a higher sensitivity to liver tumour induction in different rat strains in the first weeks of life, a life phase much earlier than that studied by Drew et al. (1983). Studies on DNA adduct formation support these results (IPCS, 1999).

6. EFFECTS ON HUMANS

Vinyl chloride is a narcotic agent, and loss of consciousness can occur at 25 g/m^3. Concentrations of vinyl chloride in the region of 2 g/m^3 (which were not unusual prior to 1974) over periods ranging from 1 month to several years have been reported to cause a specific pathological syndrome found in vinyl chloride workers called "vinyl chloride illness," including symptoms of headache, dizziness and unclear vision. Clinical findings include scleroderma of the connective tissue in the fingers, with dermal thickening and subsequent bony changes in the tips of the fingers described as acroosteolysis; peripheral circulatory changes identical with the classical picture of Raynaud disease; enlargement of the liver and spleen, with a specific histological appearance; and respiratory manifestations (IPCS, 1999).

Vinyl chloride is mutagenic and clastogenic in humans. Frequencies of chromosomal aberrations, micronucleus formation and sister chromatid exchanges in the peripheral blood lymphocytes of workers exposed to high levels of vinyl chloride have been shown to be raised compared with controls.

Point mutations were detected in *p53* genes in liver angiosarcomas from highly exposed (before 1974) vinyl chloride autoclave workers (Marion, 1998). Mutations of the *p53* gene were found in 11 of 18 hepatocellular carcinomas from patients with vinyl chloride exposure (Weihrauch et al., 2000). K-*ras*-2 mutations were found in vinyl chloride-associated hepatocellular carcinomas from 6 of 18 patients (Weihrauch et al., 2001); K-*ras*-2 mutations had previously been found in liver angiosarcomas associated with vinyl chloride exposure (DeVivo et al., 1994; Luo et al., 1998).

Although some studies suggest that paternal exposure to vinyl chloride may be associated with adverse reproductive outcomes, the available data cannot be considered conclusive.

A few morbidity studies have reported an elevated incidence of circulatory diseases among vinyl chloride workers. However, large cohort studies have found lower mortality from cardiovascular disease.

There is strong and consistent evidence from epidemiological studies that vinyl chloride exposure causes the rare tumour angiosarcoma of the liver. Brain tumours and hepatocellular carcinoma may also be associated with vinyl chloride. Other cancer sites reported to be in excess, but less consistently, include lung, lymphatic and haematopoietic tissue and skin (IPCS, 1999). In a recent update (Ward et al., 2001) to the mortality and cancer incidence study on workers in the European vinyl chloride industry (Simonato et al., 1991), a strong relationship was observed between cumulative vinyl chloride exposure and occurrence of liver cancer. An even sharper exposure–response relationship was observed for angiosarcoma. A marked exposure–response trend with both duration of employment and cumulative vinyl chloride exposure was present in the 10 known cases of hepatocarcinoma, suggesting that vinyl chloride exposure may be associated with this tumour as well. No strong

relationship was observed between cumulative vinyl chloride exposure and other cancers (Ward et al., 2001).

The update study (Mundt et al., 2000) on a US industry-wide cohort (Wong et al., 1991) observed a strong association between duration of employment in the vinyl chloride industry prior to 1974 and cancers of the liver and biliary tract, mostly resulting from a large excess of deaths due to angiosarcoma of the liver. The brain cancer and emphysema excesses previously reported were not sustained; cancers of connective tissue and soft tissues appeared to be related to employment in the industry.

Children may be at increased risk based on suggested evidence of early life sensitivity in animal studies. However, there is no direct evidence in humans (IPCS, 1999).

7. GUIDELINE VALUE

There is sufficient evidence of the carcinogenicity of vinyl chloride in humans from industrial exposure to high concentrations of vinyl chloride via the inhalation route, and IARC (1979, 1987) has classified vinyl chloride in Group 1. Update studies of the follow-up of mortality and cancer incidence among workers employed in the vinyl chloride industry have shown that there was a marked exposure–response for all liver cancers, angiosarcomas and hepatocellular carcinoma, but no strong relationship was observed between cumulative vinyl chloride exposure and other cancers (Ward et al., 2001).

Animal data show vinyl chloride to be a multisite carcinogen. When administered orally or by inhalation to mice, rats and hamsters, it produced tumours in the mammary gland, lungs, Zymbal gland and skin, as well as angiosarcomas of the liver and other sites.

Evidence indicates that vinyl chloride metabolites are genotoxic, interacting directly with DNA. DNA adducts formed by the reaction of DNA with a vinyl chloride metabolite have also been identified. Occupational exposure has resulted in chromosomal aberrations, micronuclei and sister chromatid exchanges; response levels were correlated with exposure levels.

Long-term feeding studies in rats with vinyl chloride in PVC granules yielded significantly increased incidences of angiosarcoma of the liver at 5.0 mg/kg of body weight per day and of neoplastic liver nodules (females) and hepatocellular carcinoma (males) at 1.3 mg/kg of body weight per day (Feron et al., 1981).

The slope factor (95% upper confidence limit) was taken from the dose–response data for all liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) from the oral diet study with female rats (Feron et al., 1981). Human equivalent doses were calculated using the physiologically based pharmacokinetic (PBPK) model of Clewell et al. (1995a,b, 2001) based on a dose metric of the daily metabolite generated, divided by the volume of the tissue in which the metabolite is produced,

i.e., mg of metabolites per litre of liver (Andersen et al., 1987). The initial vinyl chloride metabolism was hypothesized to occur via two saturable pathways, one representing low-capacity, high-affinity oxidation by CYP2E1, and the other representing higher-capacity, lower-affinity oxidation by other isozymes of cytochrome P-450, both of which were addressed by the PBPK model in calculation of the dose metric (US IRIS, 2000). A linear low-dose extrapolation was conducted drawing a straight line between the LED_{10} and the origin (zero dose). The results were nearly identical to those derived using the linearized multistage model.

There is no evidence that humans are more susceptible to cancer induction than laboratory species, but there is uncertainty regarding differences in sensitivity during early exposure. Therefore, it was assumed that continuous lifetime exposure from birth would double cancer risk, which could be accounted for by a 2-fold uncertainty factor (US IRIS, 2000).

A concentration of vinyl chloride in drinking-water of 0.5 µg/litre was calculated as being associated with an upper-bound excess risk of liver tumours of 10^{-5} for lifetime exposure beginning at adulthood. Exposure from birth would double this risk (US IRIS, 2000). This results in a guideline value of 0.3 µg/litre (rounded figure) for a theoretical risk of 10^{-5}.

As vinyl chloride is a known human carcinogen, exposure to this compound should be avoided as far as practicable, and levels should be kept as low as technically feasible. Vinyl chloride is primarily of concern as a potential contaminant from some grades of PVC pipe and is best controlled by specification of material quality.

8. REFERENCES

Al-Malack MH, Sheikheldin SY (2001) Effect of solar radiation on the migration of vinyl chloride monomer from unplasticized PVC pipes. *Water Research*, 35(14):3283–3290.

Al-Malack MH et al. (2000) Effect of water quality parameters on the migration of vinyl chloride monomer from unplasticized PVC pipes. *Water, Air, and Soil Pollution*, 120:195–208.

Amoore JE, Hautala E (1983) Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *Journal of Applied Toxicology*, 3:272–290.

Andersen M et al. (1987) Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicology and Applied Pharmacology*, 87:185–205.

Barbin A (1999) Role of etheno DNA adducts in carcinogenesis induced by vinyl chloride in rats. *IARC Scientific Publications*, 150:303–313.

Bauer U (1981) [Human exposure to environmental chemicals — investigations on volatile organic halogenated compounds in water, air, food, and human tissues.] *Zentralblatt für Bakteriologie und Hygiene, Abteilung I, Originale B*, 174:1–237 (in German).

Benfenati E et al. (1991) Migration of vinyl chloride into PVC-bottled drinking-water assessed by gas chromatography–mass spectrometry. *Food and Chemical Toxicology*, 29:131–134.

Bi W et al. (1985) Effect of vinyl chloride on testis in rats. *Ecotoxicology and Environmental Safety*, 10:281–289.

Brown KW, Donnelly KC (1988) An estimation of the risk associated with the organic constituents of hazardous and municipal waste landfill leachates. *Hazardous Waste and Hazardous Materials*, 5:1–30.

Chemical Manufacturers Association (1998) *Vinyl chloride combined inhalation two-generation reproduction and developmental toxicity study in CD rats. Final report.* East Millstone, NJ, Huntingdon Life Sciences Inc.

Chung Y et al. (1997) Risk assessment and management of drinking water pollutants in Korea. *Water Science and Technology*, 36(12):309–323.

Clewell HJ et al. (1995a) *The development and validation of a physiologically based pharmacokinetic model for vinyl chloride and its application in a carcinogenic risk assessment for vinyl chloride.* Washington, DC, US Environmental Protection Agency, Office of Health and Environmental Assessment/Occupational Safety and Health Administration, Directorate of Health Standards Programs, 110 pp. (unpublished report prepared by ACF Kayser) [cited in US IRIS, 2000].

Clewell HJ et al. (1995b) Considering pharmacokinetic and mechanistic information in cancer risk assessments for environmental contaminants: Examples with vinyl chloride and trichloroethylene. *Chemosphere*, 31:2561–2578 [cited in US IRIS, 2000].

Clewell HJ et al. (2001) Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model. *The Science of the Total Environment*, 274(1–3):37–66.

Cogliano VJ, Hiatt GFS, Den A (1996) Quantitative cancer assessment for vinyl chloride: Indications of early-life sensitivity. *Toxicology*, 111:21–28.

DeVivo I et al. (1994) Mutant c-Ki-ras p 21 protein in chemical carcinogenesis in humans exposed to vinyl chloride. *Cancer Causes and Control*, 5:273–278.

Dieter HH, Kerndorff H (1993) Presence and importance of organochlorine solvents and other compounds in Germany's groundwater and drinking water. *Annali dell'Istituto Superiore di Sanita*, 29:263–277.

Dressman RC, McFarren EF (1978) Determination of vinyl chloride migration from polyvinyl chloride pipe into water. *Journal of the American Water Works Association*, 70:29–30.

Drew RT et al. (1983) The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice and hamsters. *Toxicology and Applied Pharmacology*, 68:120–130.

ECETOC (1988) *The mutagenicity and carcinogenicity of vinyl chloride: a historical review and assessment.* Brussels, European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC Technical Report No. 31).

Fayad NM et al. (1997) Migration of vinyl chloride monomer (VCM) and additives into PVC bottled drinking water. *Journal of Environmental Science and Health Part A, Environmental Science and Engineering*, 32:1065–1083.

Feron VJ et al. (1975) Observations on the oral administration and toxicity of vinyl chloride in rats. *Food and Cosmetics Toxicology*, 13:633–638.

Feron VJ et al. (1981) Lifespan oral toxicity study of vinyl chloride in rats. *Food and Cosmetics Toxicology*, 19:317–333.

Fishbein L (1979) Potential halogenated industrial carcinogenic and mutagenic chemicals. I. Halogenated unsaturated hydrocarbons. *The Science of the Total Environment*, 11:111–161.

Groth DH et al. (1981) Effects of aging on the induction of angiosarcoma. *Environmental Health Perspectives*, 41:53–57.

Hiatt GS et al. (1994) Vinyl chloride action levels: Indoor air exposures at a Superfund site. In: Andrews J et al., eds. *Hazardous waste and public health: International congress on the health effects of hazardous waste*. Princeton, NJ, Princeton Scientific Publishing, pp. 525–529.

IARC (1979) *Vinyl chloride, polyvinyl chloride and vinyl chloride–vinyl acetate copolymers.* Lyon, International Agency for Research on Cancer, pp. 377–438 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 19).

IARC (1987) *Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1–42.* Lyon, International Agency for Research on Cancer, pp. 373–376 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Suppl. 7).

IPCS (1999) *Vinyl chloride.* Geneva, World Health Organization, International Programme on Chemical Safety, pp. 1–356 (Environmental Health Criteria 215).

JECFA (1984) *Toxicological evaluation of certain food additives and contaminants*. Joint FAO/WHO Expert Committee on Food Additives. Cambridge, Cambridge University Press, pp. 197–215 (WHO Food Additives Series No. 19).

Kinnunen J (1996) [*Ambient air quality in the surroundings of Kilpilahti, 1995 — Part 2: Volatile organic compounds.*] Porvoo, Neste Environmental and Industrial Hygiene Institute, pp. 1–40 (Report No. 960024Y) (in Finnish) [cited in IPCS, 1999].

Kinnunen J (1997) [*Ambient air quality in the surroundings of Kilpilahti, 1996 — Part 2: Volatile organic compounds.*] Porvoo, Neste Environmental and Industrial Hygiene Institute, pp. 1–34 (Report No. 97003Y) (in Finnish) [cited in IPCS, 1999].

Lee LJ-H et al. (2002) Health risk assessment on residents exposed to chlorinated hydrocarbons contaminated in groundwater of a hazardous waste site. *Journal of Toxicology and Environmental Health Part A*, 65(3–4):219–235.

Luo JC et al. (1998) Plasma Asp13-Ki-ras oncoprotein expression in vinyl chloride monomer workers in Taiwan. *Journal of Occupational and Environmental Medicine*, 40:1053–1058.

Maltoni C et al. (1981) Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis. *Environmental Health Perspectives*, 41:3–29.

Maltoni C et al., eds. (1984) *Experimental research on vinyl chloride carcinogenesis.* Princeton, NJ, Princeton Scientific Publishing (Archives of Research on Industrial Carcinogenesis, Vol. II).

Marion MJ (1998) Critical genes as early warning signs: example of vinyl chloride. *Toxicology Letters*, 102–103:603–607.

Marion MJ, Boivin-Angele S (1999) Vinyl chloride-specific mutations in humans and animals. *IARC Scientific Publications*, 150:315–324.

Ministerie van Volkshuisvestine (1984) *Criteria-document over vinylchloride*. [*Vinyl chloride criteria document.*] The Hague, Ministerie van Volkshuisvestine, Ruimtelijke Ordening en Milieubeheer (Publikateiereeks Lucht No. 34).

Mundt KA et al. (2000) Historical cohort study of 10 109 men in the North American vinyl chloride industry, 1942–72: update of cancer mortality to 31 December 1995. *Occupational and Environmental Medicine*, 57(7–12):774–781.

Na K et al. (2001) Concentrations of volatile organic compounds in an industrial area of Korea. *Atmospheric Environment*, 35:2747–2756.

Peterson ML et al. (2000) Characterization of chlorinated hydrocarbons above a drinking water aquifer. In: Wickramanayake GB, ed. *Risk, regulatory, and monitoring considerations*. Columbus, OH, Battelle Press, pp. 79–86.

Salkinoja-Salonen M et al. (1995) Organic halogens in the environment: Studies of environmental biodegradability and human exposure. *Environmental Health Perspectives*, 103:63–69.

Semprini L et al. (1995) Anaerobic transformation of chlorinated aliphatic hydrocarbons in a sand aquifer based on spatial chemical distributions. *Water Resources Research*, 31:1051–1062.

Shirey R (1995) Rapid analysis of environmental samples using solid-phase microextraction (SPME) and narrow bore capillary columns. *Journal of High Resolution Chromatography*, 18:495–499.

Simonato L et al. (1991) A collaborative study of cancer incidence and mortality among vinyl chloride workers. *Scandinavian Journal of Work, Environment and Health*, 17:159–169.

Sokal JA et al. (1980) Experimental studies on the chronic toxic effects of vinyl chloride in rats. *Journal of Hygiene, Epidemiology, Microbiology and Immunology*, 24:285–294.

Swenberg JA et al. (1999) Formation and repair of DNA adducts in vinyl chloride- and vinyl fluoride-induced carcinogenesis. *IARC Scientific Publications*, 150:29–43.

Til HP, Immel HP, Feron FJ (1983) *Lifespan oral carcinogenicity study of vinyl chloride in rats*. Zeist, TNO (Netherlands Organization for Applied Scientific Research), pp. 1–29 (TNO Report V 83.285/291099).

Til HP, Feron VJ, Immel HR (1991) Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Food and Chemical Toxicology*, 29:713–718.

US IRIS (2000) *Integrated Risk Information System*. Bethesda, MD, US National Library of Medicine. Available at http://toxnet.nlm.nih.gov.

Ward E et al. (2001) Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. *Epidemiology*, 12(6):710–718.

Weihrauch M, Lehnert G, Kockerling F (2000) p 53 mutation pattern in hepatocellular carcinoma in workers exposed to vinyl chloride. *Cancer*, 88:1030–1036.

Weihrauch M et al. (2001) High prevalence of K-*ras*-2 mutations in hepatocellular carcinomas in workers exposed to vinyl chloride. *International Archives of Occupational and Environmental Health*, 74(6):405–410.

Wittsiepe J et al. (1993) Gas-chromatographic determination of trace amounts of vinyl chloride and dichloroethenes in water after purge-and-trap preconcentration and conversion into their dibrominated derivatives. *Fresenius' Journal of Analytical Chemistry*, 346:1028–1034.

Wong O et al. (1991) An industry-wide epidemiologic study of vinyl chloride workers, 1942–1982. *American Journal of Industrial Medicine*, 20:317–334.

Yamamoto K et al. (2001) Contamination of vinyl chloride in shallow urban rivers in Osaka, Japan. *Water Research*, 35:561–566.

Zhao M-Y et al. (1994) The study of health effects of vinyl chloride air pollution on population. *Biomedical and Environmental Sciences*, 7:136–143.