

**Department for Environment, Food and Rural Affairs  
and the Environment Agency**

**CONTAMINANTS IN SOIL:**

**COLLATION OF TOXICOLOGICAL DATA  
AND INTAKE VALUES FOR HUMANS.**

**VINYL CHLORIDE**



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Environment Agency, Rio House, Waterside Drive, Aztec West, Almondsbury, BRISTOL, BS32 4UD.

Tel: 01454 624400 Fax: 01454 624409

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## **Statement of Use**

This publication details the derivation of health criteria values for vinyl chloride. The report has been written for technical professionals who are familiar with the risks posed by land contamination to human health but who are not necessarily experts in risk assessment. It is expected to be of use to all parties involved with or interested in contamination, but in particular to those concerned with the assessment of land contamination.

## **Keywords**

Index Dose, land contamination, risk assessment, human health, vinyl chloride.

## **Environment Agency Contact**

Albania Grosso, Human Health Principal Scientist, Ecosystems & Human Health Science Group, Environment Agency, Isis House, Howberry Park, Walingford, Oxon OX10 8BD

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# Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
<b>2</b>	<b>Identity</b>	<b>2</b>
<b>3</b>	<b>Toxicity</b>	<b>3</b>
<b>4</b>	<b>Carcinogenicity and genotoxicity</b>	<b>6</b>
<b>5</b>	<b>Derivation of Index Doses</b>	<b>8</b>
	The recommendations of JECFA	8
	The WHO guidelines for drinking-water quality	8
	The WHO air quality guidelines for Europe	8
	The recommendations of the EC Drinking Water Directive	9
	The recommendations of the RIVM	9
	The recommendations of the USEPA	9
	The recommendations of the ATSDR	11
	Conclusions	11
<b>6</b>	<b>Intake of vinyl chloride from food, water and air</b>	<b>13</b>
<b>7</b>	<b>Other sources</b>	<b>14</b>
<b>8</b>	<b>Conclusions</b>	<b>15</b>
	<b>References</b>	<b>16</b>

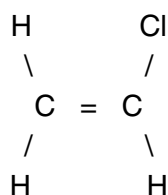


## 1 Introduction

- 1.1 This report is one of a number of reports on the assessment of risks to human health from contaminants in soil. Key data and expert opinion are presented on the toxicology of vinyl chloride and its intake, by the general population, from background environmental exposure. It may be necessary to update this report in the future to incorporate new toxicological data as scientific knowledge advances.
- 1.2 The aim of this report is to set out authoritative health criteria values for vinyl chloride, which have been established through a review of the scientific literature and a subsequent peer-review process. The health criteria values presented herein will be used to derive Soil Guideline Values (SGVs) for vinyl chloride.
- 1.3 The overall framework for this review and the associated underlying principles are set out in CLR9 *Contaminants in Soils: Collation of Toxicological Data and Intake Values for Humans* (Department for Environment, Food and Rural Affairs (Defra) and Environment Agency, 2002a). Reference to CLR9 is necessary to understand the concepts, terms and approach used in this report.
- 1.4 The computer model used for deriving the SGVs is described in CLR10 *The Contaminated Land Exposure Assessment Model (CLEA): Technical Basis and Algorithms* (Defra and Environment Agency, 2002b). SGVs for vinyl chloride will be published in SGV 17 *Guideline Values for Vinyl Chloride Contamination* (Defra and Environment Agency, in preparation).
- 1.5 This report is principally based on the literature published up to June 2000. The report has been updated following a further review of key publications up to October 2002.

## 2 Identity

- 2.1 Vinyl chloride (CAS No 75-01-4) has the chemical formula  $C_2H_3Cl$ , and is formed by the chlorination of ethylene. Synonyms include chloroethene (IUPAC recommended name), chloroethylene, 1-chloroethylene, ethylene monochloride, monochloroethene, monochloroethylene, and vinyl chloride monomer or VCM. The structure of vinyl chloride is shown in Figure 2.1.



**Figure 2.1 Structure of Vinyl chloride**

- 2.2 Vinyl chloride is a colourless gas (boiling point,  $-13.4^{\circ}\text{C}$ ) at room temperature and pressure, but is easily liquefied under pressure and is usually stored and transported as a liquid (IPCS, 1999). Its solubility in water is between 1.1 and  $2.8 \text{ g L}^{-1}$  (ATSDR, 1997). Many salts have the ability to form complexes with vinyl chloride and can increase its solubility in water (ATSDR, 1997).
- 2.3 Vinyl chloride is used almost exclusively by the plastics industry for the production of PVC (polyvinyl chloride) and several copolymers. There do not appear to be any natural sources of vinyl chloride, but anaerobic, reductive dehalogenation of 1,1,2-trichloroethene, tetrachloroethene and 1,1,1-trichloroethane to vinyl chloride at hazardous waste and landfill sites has been reported (Smith and Dragun, 1984; Eduljee, 1998). Vinyl chloride has also been reported to be a degradation product of trichloroethene and tetrachloroethene in groundwater (WHO, 1996).
- 2.4 Vinyl chloride released to surface water will migrate to the atmosphere in a few hours or days. When released to the terrestrial environment, however, it will readily migrate to groundwater, where it may remain unchanged for several months or years (WHO, 1996). Because of its very high vapour pressure (333 kPa at  $20^{\circ}\text{C}$ ; IPCS, 1999), all vinyl chloride in the atmosphere is expected to exist in the vapour phase (ATSDR, 1997). In the atmosphere, vinyl chloride reacts with hydroxyl radicals, having a half-life of a few hours to several days (ATSDR, 1997; IPCS, 1999).
- 2.5 Where studies have reported vinyl chloride levels in ppm, a conversion factor of  $1 \text{ ppm} = 2.6 \text{ mg m}^{-3}$  (IARC, 1987; IPCS, 1999) has been used to ensure consistency in units throughout this report.

### 3 Toxicity

- 3.1 Reviews of the literature on the toxicity of vinyl chloride have been published by the International Agency for Research on Cancer (IARC, 1987), the International Programme on Chemical Safety (IPCS, 1999), the World Health Organization (WHO, 1984, 1993, 1996, 2000), the Agency for Toxic Substances and Disease Registry (ATSDR, 1997) and the United States Environmental Protection Agency (USEPA, 1984, 1985a,b, 2000). This section is based largely on these reviews, except where otherwise cited.
- 3.2 **Absorption.** No data on the absorption of vinyl chloride in humans after oral exposure have been found. Several studies in rats indicate rapid and almost complete absorption from the gastrointestinal tract (ATSDR, 1997). Different forms of vinyl chloride have been used in different studies: aqueous solution, a solution in corn oil, and powdered PVC containing a high proportion of the monomer. The lowest absorption reported (about 85%) was with the monomer in powdered PVC, although it was suggested that vinyl chloride was encapsulated by PVC (ATSDR, 1997).
- 3.3 Inhalation absorption of vinyl chloride in humans and rats is rapid and substantial. In a study of five young adult men exposed to concentrations of 7.5–60 mg m<sup>-3</sup> of the vapour by gas mask, retention (the difference between inhaled and exhaled concentrations) reached a maximum within 15 minutes, declined rapidly after 30 minutes of exposure, and then increased to a relatively constant value. An average retention of 42% (range 30–70%) was estimated (Krajewski *et al*, 1980).
- 3.4 No studies of absorption of vinyl chloride in humans after dermal exposure have been identified. In a study in which rhesus monkeys were exposed in chambers to high concentrations of the vapour (2080–18,200 mg m<sup>-3</sup>), dermal absorption was far less significant (only 0.023–0.031%) than inhalation absorption (Hefner *et al*, 1975).
- 3.5 **Distribution.** Data from rat studies suggest that distribution of vinyl chloride is rapid and widespread. Rapid metabolism and excretion limit accumulation of vinyl chloride in the body. The highest concentrations are found in the liver, kidneys and spleen. Placental transfer of vinyl chloride occurs rapidly in rats (IPCS, 1999).
- 3.6 **Metabolism and excretion.** The major metabolic pathway for vinyl chloride is oxidation by cytochrome P450 isoenzymes (probably CYP2E1 and CYP2B1) to form a highly reactive, short-lived, epoxide intermediate, 2-chloroethylene oxide, which rapidly rearranges to 2-chloroacetaldehyde. Both these intermediates are detoxified mainly by conjugation with glutathione (ATSDR, 1997; USEPA, 2000).
- 3.7 Metabolism and elimination pathways of vinyl chloride are dose-dependent and saturable. At low concentrations, vinyl chloride metabolites are excreted primarily in the urine, while at higher concentrations vinyl chloride is eliminated unchanged in

exhaled air. Neither vinyl chloride nor its metabolites accumulate in the body (ATSDR, 1997; USEPA, 2000).

- 3.8 **Acute toxicity.** At high concentrations, the acute effects of human inhalation of vinyl chloride are arterial hypertension (Kotseva, 1996), central nervous system effects (headaches, drowsiness, dizziness, ataxia, loss of consciousness) and possible peripheral nervous system effects. Exposure information is not available, but central nervous system effects (nausea and dizziness) have been reported in volunteers exposed to 31,200 mg m<sup>-3</sup> for 5 minutes (IPCS, 1999). No studies of the effects of ingested vinyl chloride in humans have been found.
- 3.9 **Repeated toxicity.** The systemic toxicity of vinyl chloride has been established by observations on exposed workers and by numerous animal studies. Vinyl chloride produces toxic effects in several organ systems. In humans, the principal non-cancer effects following chronic inhalation exposure occur in the liver (fibrosis, necrosis, hypertrophy, hyperplasia). The liver is also the most sensitive organ in experimental animals.
- 3.10 Numerous sub-chronic and chronic inhalation studies have been conducted, but the lifetime feeding study in rats by Til *et al* (1983, 1991) has been most widely used as a basis of chronic toxicological assessments, particularly for non-cancer effects. The “no observed adverse effect” level (NOAEL) and “lowest observed adverse effect” level (LOAEL) values reported by the authors include correction for volatilisation from the diet and less than complete absorption from the 1% PVC powder added to the diet. Non-neoplastic effects in the liver (cysts and areas of hepatocellular alteration) were observed at 1.3 mg kg<sup>-1</sup> bw day<sup>-1</sup> (milligrams per kilogram body weight per day) with a NOAEL of 0.13 mg kg<sup>-1</sup> bw day<sup>-1</sup>.
- 3.11 Foci of altered liver cells (basophilic foci) were seen even at 0.014 mg kg<sup>-1</sup> bw day<sup>-1</sup>, the lowest dose tested. This is considered to be a pre-neoplastic effect (indicative of an early stage in the development of cancer). In an earlier oral toxicity study from the same laboratory (Feron *et al*, 1981), areas of cellular alteration in the livers of rats were found at the lowest dose level tested (1.7 mg kg<sup>-1</sup> bw day<sup>-1</sup>).
- 3.12 Several sub-chronic inhalation studies in rats have shown increased liver weight and adverse histopathological changes in the liver. The six-month inhalation study by Bi *et al* (1985) showed increased liver weight at slightly lower doses than in other reported studies. No NOAEL was determined and the LOAEL was 26 mg m<sup>-3</sup> (or 5.2 mg m<sup>-3</sup> when corrected for the exposure regime).
- 3.13 **Reproductive and developmental toxicity.** Epidemiological studies on the potential developmental toxicity of vinyl chloride in the wives of production workers and in communities living around PVC production plants have been inconclusive. Case reports of effects on libido and potency in male vinyl chloride production workers have similarly not provided conclusive results (Barlow and Sullivan, 1982; ATSDR, 1997; McLaughlin and Lipworth, 1999).

- 3.14 Developmental toxicity in animals has been observed only at doses above those causing maternal toxicity (USEPA, 2000). In inhalation studies, maternal and fetal toxicity was observed at 1300 mg m<sup>-3</sup> in mice and 3900 mg m<sup>-3</sup> in rats, with no evidence of teratogenicity in either species (USEPA, 2000).
- 3.15 In a two-generation study designed to assess potential maternal and/or embryo–fetal developmental and reproductive toxicity, rats were exposed by inhalation to 0, 26, 260 or 2860 mg m<sup>-3</sup> (Thornton *et al*, 2002). In the embryo–fetal developmental study, female rats were exposed to vinyl chloride from gestation days 6 to 19. In the reproductive study, F<sub>0</sub> male and female rats were exposed for a 10-week pre-mating and 3-week mating period. Pups were then selected post-weaning to undergo a second exposure mating period. The results indicated that exposure up to 2680 mg m<sup>-3</sup> did not adversely affect embryo–fetal development or reproductive capability over two generations. The liver was affected, as evidenced by an increase in liver weight and centrilobular hypertrophy, in both generations of female parents at all three dose levels, although these effects were considered to be non-adaptive responses to vinyl chloride exposure (USEPA, 2000). The NOAELs based on this study were 2860 mg m<sup>-3</sup> for both embryo–fetal development and reproduction (Thornton *et al*, 2002).
- 3.16 Using physiologically based pharmacokinetic (PBPK) modelling, the USEPA (2000) estimated that the tissue concentrations (average daily concentration for vinyl chloride metabolites in the liver of 30 mg L<sup>-1</sup>) for hepatic effects seen in the lifetime oral toxicity study by Til *et al* (1983, 1991) were lower than those producing no testicular effects in adult males but producing hepatic effects in offspring in the two-generation study outlined above (paragraph 3.15; average daily concentration for vinyl chloride metabolites in the liver of 298 mg L<sup>-1</sup>). This demonstrates that adverse liver effects may occur at tissue concentrations considerably lower than in the reproductive study (USEPA, 2000).
- 3.17 In a 12-month rat inhalation study at dose levels of 0, 26, 260 and 7800 mg m<sup>-3</sup>, testicular toxicity (damage to seminiferous tubules) was observed at doses of 260 mg m<sup>-3</sup> and above, with 26 mg m<sup>-3</sup> being a NOAEL (USEPA, 2000).

## 4 Carcinogenicity and genotoxicity

- 4.1 Many studies of workers exposed via inhalation to vinyl chloride have revealed a greater than expected incidence of angiosarcoma of the liver (ASL). However, this is a rare tumour and the total number of reported cases world-wide remains small: 197 cases associated with vinyl chloride exposure up to 1998 (Kielhorn *et al*, 2000). Other types of cancer, including hepatocellular carcinoma (HCC) and cancers of the brain, lung and respiratory tract and the lymphatic/haematopoietic system (IARC, 1987), have shown an excess, sometimes statistically significant, among vinyl chloride workers, in at least some studies. However, a number of reviewers have concluded that there is no persuasive evidence for an association between vinyl chloride and any cancer other than angiosarcoma (Doll, 1988; Blair and Kazerouni, 1997; McLaughlin and Lipworth, 1999). No non-occupational cases of ASL linked to vinyl chloride exposure have ever been reported (Elliott and Kleinschmidt, 1997). No studies examining the risk of cancer in humans as a consequence of exposure to vinyl chloride by the oral route have been located.
- 4.2 The Equitable Environmental Health Study of 1978 (cited by WHO, 2000) investigated cancer rates in 10,173 workers employed for one or more years in 37 vinyl chloride and polyvinyl chloride production plants. The average duration of employment before 1973 was 8.7 years. A weighted exposure of  $1665 \text{ mg m}^{-3}$  was estimated and, considering the total population at risk to be 12,000, a unit exposure lifetime cancer risk from an average exposure of 9 years was calculated as  $0.75 \times 10^{-5}$  per  $1 \text{ mg m}^{-3}$ . This value was used by WHO (2000) to derive a risk factor by conversion to a lifetime risk of haemangiosarcomas of  $4.7 \times 10^{-4}$  per  $1 \text{ mg m}^{-3}$  ( $0.75 \times 10^{-5} \times 2.8 \times 22.4$ ), where 2.8 is the correction for air volume inhaled in a full week from that in a working week, and 22.4 is an average conversion from a 10-year exposure to a lifetime, taking into account the time course of haemangiosarcomas. A  $10^{-6}$  risk occurs at a concentration of  $2.1 \text{ } \mu\text{g m}^{-3}$ . The WHO uses the term "haemangiosarcoma" rather than specifically ASL, although it appears that in their health risk evaluation (WHO, 2000) the term is used to indicate angiosarcomas found in the liver.
- 4.3 In the studies of Feron *et al* (1981) and Til *et al* (1983, 1991), described in paragraphs 3.10 and 3.11, rats fed vinyl chloride showed an increased incidence of hepatic angiosarcoma and hepatocellular carcinoma at doses of  $1.3 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  and above with pre-neoplastic lesions noted at the lowest dose tested ( $0.014 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ). Increased incidences of angiosarcoma of the liver have also been found after inhalation of vinyl chloride vapour in mice, rats and hamsters (lowest dose,  $130 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ; Maltoni *et al*, 1981, 1984, described by USEPA, 2000). For the lower exposures used (up to about  $1000 \text{ mg m}^{-3}$ ), the data suggest a linear dose-response relationship. Maltoni's studies were very extensive, involving nearly 7000 animals over a 10-year period. Statistically significant excesses of various other cancers were also found. These included nephroblastomas (lowest dose,  $260 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ), neuroblastomas ( $26,000 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ), mammary gland

adenocarcinomas ( $13 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ), Zymbal gland carcinomas ( $26,000 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ) and forestomach papillomas ( $78,000 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ). Some species differences were observed in the target organs.

- 4.4 USEPA (1985a, 2000) considers vinyl chloride to be a human carcinogen (Group A) by the oral and inhalation route, and highly likely to be carcinogenic by the dermal exposure route. IARC (1987) also concluded that there is sufficient evidence in humans and animals for vinyl chloride to be considered carcinogenic to humans (Group 1).
- 4.5 There is clear evidence that vinyl chloride is genotoxic in both humans and animals. Genotoxicity studies have been reviewed by Giri (1995), ATSDR (1997) and USEPA (2000). Lymphocytes from workers occupationally exposed to vinyl chloride show increases in chromosome aberrations, micronuclei and sister chromatid exchange. An increased frequency of chromosome aberrations in peripheral lymphocytes has also been found in people exposed to vinyl chloride monomer following accidental environmental release (Hüttner and Nikolova, 1998). *In vivo* vinyl chloride causes chromosome aberrations in rats and micronuclei in mice. Vinyl chloride is positive in tests for gene mutations in bacteria (*Salmonella typhimurium*) and yeast (*Schizosaccharomyces pombe*) and positive in tests for chromosome aberrations in mammalian cells in culture.
- 4.6 *In vitro* and *in vivo* studies have indicated that both the short-lived epoxide metabolite, 2-chloroethylene oxide, and the chloroacetaldehyde metabolite interact directly with DNA and RNA to form etheno adducts (Kielhorn *et al*, 2000). The epoxide is the reactive intermediate that is considered to be mainly responsible for the genotoxic/carcinogenic properties of vinyl chloride, while the acetaldehyde may account for the non-neoplastic toxicity (Chiang *et al*, 1997; USEPA, 2000). Studies have demonstrated that the mutation spectrum in liver tumours (both ASL and HCC) of humans and animals exposed to vinyl chloride is consistent with etheno adduct-induced mutations and is distinctly different from the spectrum observed in spontaneous tumours (Kielhorn *et al*, 2000).
- 4.7 It is clear that vinyl chloride is a genotoxic carcinogen and, therefore, Index Doses, rather than tolerable daily intakes, are derived here. Reference should be made to the discussion of non-threshold substances in CLR9 (Defra and Environment Agency, 2002a).

## 5 Derivation of Index Doses

### The recommendations of JECFA

- 5.1 The Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA), in considering vinyl chloride as a food contaminant (WHO, 1984), did not give a numerical value for a tolerable intake, but instead recommended that exposure via food should “be reduced to the lowest levels technologically attainable”.

### The WHO guidelines for drinking-water quality

- 5.2 The WHO (1996) guideline value for vinyl chloride in drinking water is based on considerations of cancer risk. Using the results of the feeding study on rats, which provide the most protective value (Til *et al*, 1983, 1991, discussed in paragraphs 3.10 and 4.3), and application of the linearised multi-stage model (LMS) to calculate excess cancer risk, the WHO calculated the human lifetime exposure for a  $10^{-5}$  risk of ASL to be 20  $\mu\text{g}$  per person per day. It was assumed for humans that the number of cancers at other sites may equal that of ASL; WHO therefore applied an additional correction factor of 2 for cancers other than angiosarcoma. Thus, WHO estimated that an exposure of 10  $\mu\text{g}$  per day equated to an overall excess lifetime cancer risk of  $10^{-5}$ . Assuming a daily water intake of 2 L, WHO proposed a drinking-water guideline of 5  $\mu\text{g L}^{-1}$  (concentrations of 50 and 0.5  $\mu\text{g L}^{-1}$  were calculated as being associated with excess risks of  $10^{-4}$  and  $10^{-6}$ , respectively). A daily intake of 10  $\mu\text{g}$  equates to 0.14  $\mu\text{g kg}^{-1}$  bw for a 70 kg adult. The WHO guidelines for drinking water are under revision, and draft proposals include a lower guideline value for vinyl chloride associated with a revised estimate of overall excess lifetime cancer risk ( $10^{-5}$  at 0.3  $\mu\text{g L}^{-1}$ ).<sup>1</sup>

### The WHO air quality guidelines for Europe

- 5.3 WHO (2000) has estimated cancer risk on the basis of epidemiological studies and primarily the occupational study performed by Equitable Environmental Health (1978) (described in paragraph 4.2). This study indicates a  $10^{-6}$  risk of angiosarcoma at an exposure of 2.1  $\mu\text{g m}^{-3}$ . As in the derivation of the drinking-water quality guideline outlined above, the WHO assumes that the number of cancers in other sites may equal that of angiosarcomas; therefore the best estimate for excess cancer risk is that a  $10^{-6}$  risk occurs as a result of continuous lifetime exposure to 1.0  $\mu\text{g m}^{-3}$ . Exposure to 1  $\mu\text{g m}^{-3}$  vinyl chloride is equivalent to a daily intake of 0.3  $\mu\text{g kg}^{-1}$  bw for a 70 kg adult breathing 20  $\text{m}^3$  of air daily.

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<sup>1</sup> WHO (2003) *Guidelines for Drinking Water Quality*, 3rd Edn., Draft Documents on Chemicals. Accessed [August 2003] on-line at: [http://www.who.int/docstore/water\\_sanitation\\_health/GDWQ/draftchemicals/list.htm](http://www.who.int/docstore/water_sanitation_health/GDWQ/draftchemicals/list.htm)

### The recommendations of the EC Drinking Water Directive

- 5.4 The EC Drinking Water Directive (98/83/EC; EC, 1998), which is enacted in UK law,<sup>2</sup> specifies a regulatory limit for vinyl chloride of  $0.5 \mu\text{g L}^{-1}$ . This value corresponds to the value estimated by the WHO in 1996 to equate to an overall excess lifetime cancer risk of  $10^{-6}$  (detailed in paragraph 5.2). Assuming a daily water intake of 2 L, this is equivalent to an intake of  $1 \mu\text{g day}^{-1}$  or  $0.014 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  for a 70 kg adult.

### The recommendations of the RIVM

- 5.5 The MPR (maximum permissible risk) value for human oral exposure to vinyl chloride recommended by the Dutch National Institute for Public Health and the Environment (RIVM), in the context of soil clean-up, is  $0.6 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  (Baars *et al*, 2001). This is based on the studies of Feron *et al* (1981) and Til *et al* (1983, 1991), detailed in paragraphs 3.10 and 3.11, and the estimation of an oral intake resulting in a lifetime excess cancer risk of  $10^{-4}$ .
- 5.6 An MPR value of  $3.6 \mu\text{g m}^{-3}$  is recommended by RIVM for inhalation exposure to vinyl chloride (Baars *et al*, 2001). The MPR value of  $3.6 \mu\text{g m}^{-3}$  vinyl chloride is calculated to result in a  $10^{-4}$  lifetime excess cancer risk based on the rat and mice studies of Maltoni *et al* (1981, 1984, described by USEPA, 2000), which are considered by RIVM to be “elaborate and well-conducted”. Epidemiological studies were not used to derive an inhalation MPR because of shortcomings such as a lack of exact exposure levels and information on the duration of exposure. Exposure to  $3.6 \mu\text{g m}^{-3}$  vinyl chloride is equivalent to a daily intake of  $1 \mu\text{g kg}^{-1} \text{ bw}$  for a 70 kg adult breathing  $20 \text{ m}^3$  of air daily.

### The recommendations of the USEPA

- 5.7 The USEPA (2000) has derived oral and inhalation reference doses and concentrations (RfD and RfC, respectively), an oral cancer slope factor, and inhalation unit risk using a physiologically based pharmacokinetic (PBPK) model to extrapolate animal exposure data to humans. For the oral RfD, the principal study referenced was that of Til *et al* (1983, 1991) and the critical effects were the non-neoplastic (non-cancerous) end-points, liver cell cysts and polymorphisms, with an observed NOAEL of  $0.13 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ . The corresponding human NOAEL derived from PBPK modelling was  $0.09 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ . An uncertainty factor of 30 was applied, comprising a factor of 3 for inter-species differences, to take account of toxicodynamic differences (the PBPK model already takes account of toxicokinetic differences), and a factor of 10 for human variability. An oral RfD of  $3 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$

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<sup>2</sup> The Water Supply (Water Quality) Regulations 2000 for England and Wales, Statutory Instruments, 2000, No 3184.

Viewed [May 2003] on-line at: <http://www.dwi.gov.uk/regs/si3184/3184.htm>

The Water Supply (Water Quality) (Scotland) Regulations 2001, SSI No 207.

Viewed [June 2003] on-line at: <http://www.hms.o.gov.uk/legislation/scotland/ssi2001/20010207.htm>

was thus derived. It should be noted that RfDs are only established by the USEPA for non-carcinogenic end-points for which a threshold can be assumed to exist. To protect against carcinogenic risks, the USEPA uses unit risk factors, which are described below.

- 5.8 Cancer slope factors of  $7.2 \times 10^{-1}$  and  $7.5 \times 10^{-1}$  per  $\text{mg kg}^{-1} \text{bw day}^{-1}$  for the oral route were derived by the linearised multi-stage (LMS) model and the  $\text{LED}_{10}$ /linear method respectively, applying the results of the lifetime dietary study of Feron *et al* (1981). The latter method calculates a linear extrapolation from the  $\text{LED}_{10}$  (the lower 95% limit on a dose that is estimated to cause a 10% tumour response) to zero dose. The LMS and  $\text{LED}_{10}$  estimates correspond to lifetime excess risks of cancer of  $1.03 \times 10^{-5}$  and  $1.07 \times 10^{-5}$ , respectively, for the ingestion of  $1 \mu\text{g day}^{-1}$  by an adult weighing 70 kg.
- 5.9 The study of Til *et al* (1983, 1991) was also used to derive the inhalation RfC, since the NOAEL from that study was calculated by the PBPK model to be 10-fold lower than the dose at which a transient increase in liver weight was seen in the inhalation study of Bi *et al* (1985), which the USEPA suggested was incompletely reported. The USEPA also considers there to be ample toxicological and kinetic data on which to perform route-to-route extrapolation and apply PBPK modelling. Based on the NOAEL from the Til *et al* study, a human inhalation NOAEL of  $2.5 \text{ mg m}^{-3}$  was calculated by PBPK modelling. Applying an uncertainty factor of 30, as for the oral RfD, an inhalation RfC of  $0.1 \text{ mg m}^{-3}$  was derived. This equates to an inhaled intake of  $2 \text{ mg day}^{-1}$  for an adult breathing  $20 \text{ m}^3$  per day and  $30 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for a 70 kg adult. As for the RfD, the RfC does not consider carcinogenic risk.
- 5.10 Inhalation unit risk estimates ranging from 0.9 to  $4.4 \times 10^{-6}$  per  $\mu\text{g m}^{-3}$  were obtained from results of the rat and mouse inhalation studies of Maltoni *et al* (1981) using the LMS and  $\text{LED}_{10}$ /linear approaches. The USEPA recommends the more conservative estimate of  $4.4 \times 10^{-6}$  per  $\mu\text{g m}^{-3}$ . Although exposure characterisation in the human studies was not considered adequate for recommended excess risk estimates, the estimates obtained by using these studies, which ranged from  $2.8 \times 10^{-7}$  to  $2.8 \times 10^{-6}$  per  $\mu\text{g m}^{-3}$ , were nevertheless regarded by the USEPA as providing support for the recommended values based on the animal studies.
- 5.11 The above risk estimates are based on the assumption of continuous lifetime exposure beginning in adulthood. Because of evidence from animal studies of increased sensitivity in early life, the USEPA recommends the application of an extra 2-fold uncertainty factor if exposure begins in early life.
- 5.12 The USEPA (1996) has also set a maximum contaminant level (MCL) of  $0.002 \text{ mg L}^{-1}$  for drinking water based on a 1987 estimate of a  $10^{-4}$  excess cancer risk. This implies an intake of  $4 \mu\text{g day}^{-1}$  for an adult consuming 2 L of water per day, which equates to  $0.06 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for a 70 kg adult.

### The recommendations of the ATSDR

- 5.13 The ATSDR (1997) also used the rat study by Til *et al* (1983, 1991) to derive a “minimal risk level” (MRL) for chronic oral exposure to vinyl chloride. Its value of  $0.02 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  was derived from the uncorrected LOAEL for increases in pre-neoplastic hepatocellular basophilic foci of  $0.018 \text{mg kg}^{-1} \text{bw day}^{-1}$  (this is derived from the same study as quoted in paragraphs 3.10 and 3.11 and is given as  $0.014 \text{mg kg}^{-1} \text{bw day}^{-1}$  in the original paper by Til *et al* (1991)) and an uncertainty factor of 1000 (100 for intra- and inter-species variations, and 10 for use of a LOAEL). The USEPA (2000) commented that the ATSDR did not address the appropriateness of using a pre-neoplastic end-point for the derivation of a chronic oral MRL which is intended to be protective only against non-cancer risk.
- 5.14 The ATSDR has not derived a chronic duration inhalation MRL for vinyl chloride because of the lack of a suitable NOAEL or LOAEL. The ATSDR has used the sub-chronic inhalation study on rats (Bi *et al*, 1985, described in paragraph 3.12) to derive an intermediate-duration MRL. It used the LOAEL of 10 ppm ( $26 \text{mg m}^{-3}$ ) for increased liver weight (uncorrected for exposure regime) from this study and applied an uncertainty factor of 300 (100 for inter- and intra-species variations and 3 for the use of a minimal LOAEL), to give an intermediate-duration MRL of 0.03 ppm ( $0.078 \text{mg m}^{-3}$ ). For a 70 kg adult (breathing  $20 \text{m}^3$  of air per day), this is equivalent to an intake of  $22 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ .

### Conclusions

- 5.15 The USEPA RfD and RfC values are based on non-carcinogenic end-points and are therefore not appropriate for the derivation of an Index Dose for a genotoxic carcinogen such as vinyl chloride. The ATSDR’s MRL is similarly inappropriate as it is defined as an exposure that is likely to be without appreciable risk of non-carcinogenic adverse effects.
- 5.16 The starting point for the  $\text{ID}_{\text{oral}}$  is the EC/UK drinking-water guideline of  $0.5 \mu\text{g L}^{-1}$ . For a 70 kg adult drinking 2 L of water per day, this concentration corresponds to an intake of  $0.014 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ . This is adopted here as the  $\text{ID}_{\text{oral}}$ .
- 5.17 The estimates of excess lifetime cancer risk resulting from this oral intake range from 1 to  $21 \times 10^{-6}$ , based on estimates published by the WHO (1996), RIVM (Baars *et al*, 2001) and USEPA (2000). However, these estimates of excess cancer risk result from extrapolation from animal data, and the various models used for these calculations are subject to a number of limitations. The results from the various models available for estimating cancer risk may vary widely, and may give an impression of precision that cannot be justified in the light of the approximations and assumptions upon which they are based. For this reason, the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) does not support the routine use of such models to estimate cancer risk in

humans from low exposures to non-threshold carcinogens, on the basis of animal data.

- 5.18 The WHO has not proposed a guideline value for air quality but has estimated from epidemiological studies that an ambient air concentration of  $1 \mu\text{g m}^{-3}$  would give rise to an excess lifetime cancer risk of  $10^{-6}$ . This estimate is within the range of excess risk ( $0.56$  to  $5.6 \times 10^{-6}$ ) published by the USEPA (2000) on the basis of epidemiological evidence. At this concentration, a 70 kg adult inhaling  $20 \text{ m}^3$  of air per day would be exposed to  $0.3 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ , which is recommended here as the  $\text{ID}_{\text{inh}}$ . Higher estimates of excess lifetime cancer risks for exposure at the  $\text{ID}_{\text{inh}}$  ( $2$  to  $28 \times 10^{-6}$ ) result from the risk estimates published by USEPA (2000) and RIVM (Baars *et al*, 2001). However, these estimates are all based on animal data, and are subject to the limitations noted above.
- 5.19 The oral and inhalation Index Doses recommended above are lower than the RfDs, RfCs and MRLs recommended by the USEPA and ATSDR and are therefore also protective against non-carcinogenic effects.

## 6 Intake of vinyl chloride from food, water and air

- 6.1 In the past, vinyl chloride was detected in various foodstuffs as a result of migration from PVC food wrappings and containers. In the UK it was estimated that in 1974 the maximum likely intake per person would be up to  $1.3 \mu\text{g day}^{-1}$ , but that by 1976 this figure had already fallen to  $0.1 \mu\text{g day}^{-1}$  (MAFF, 1978). No recent data on foodstuffs have been located in the EU, but levels in foods are required to be non-detectable (below  $10 \mu\text{g kg}^{-1}$  of food). At the very low concentrations of vinyl chloride monomer now present in PVC packaging, ATSDR (1997) considers that there is essentially no migration of vinyl chloride monomer into food, and that inhalation is the most important route of exposure for the general population.
- 6.2 No reports of UK measurements of vinyl chloride in drinking water or ambient air have been found.
- 6.3 The WHO (1993) stated that concentrations up to a few  $\mu\text{g L}^{-1}$  had been found in drinking water. In the USA, the majority of drinking-water supplies do not contain vinyl chloride above the detection limit of  $1 \mu\text{g L}^{-1}$  and ATSDR estimated that only 0.9% of the population were exposed to levels  $>1 \mu\text{g L}^{-1}$  and 0.3% to levels  $>5 \mu\text{g L}^{-1}$  (ATSDR, 1997). The UK drinking-water standard for vinyl chloride (detailed in paragraph 5.4) is now  $0.5 \mu\text{g L}^{-1}$ . Exposure via this route should therefore be less than  $1 \mu\text{g day}^{-1}$  for an adult consuming 2 L of drinking water daily
- 6.4 Concentrations of vinyl chloride in air are low, usually less than  $3 \mu\text{g m}^{-3}$  (IPCS, 1999). Higher concentrations have been observed near vinyl chloride/PVC production sites and waste disposal sites, where concentrations up to  $100 \mu\text{g m}^{-3}$  and  $8000 \mu\text{g m}^{-3}$ , respectively, have been observed. Indoor air concentrations of up to  $1 \text{mg m}^{-3}$  of vinyl chloride have been measured in houses near landfill sites in the USA. Higher levels within dwellings compared to outdoor air adjacent to landfills is assumed to be accounted for by subsurface migration of vinyl chloride vapour (IPCS, 1999). Some paints can be a source of vinyl chloride; for example, levels of 75 and  $10 \mu\text{g m}^{-3}$  were detected in a room being painted with a red latex paint during and after painting, respectively (IPCS, 1999).

## 7 Other sources

- 7.1 Emissions to air and water from vinyl chloride and PVC manufacturers are responsible for most of the vinyl chloride released to the environment (ATSDR, 1997). Vinyl chloride has been detected in gas and leachate from landfills and in groundwater due to the reductive halogenation of the more highly chlorinated chloroethenes under anaerobic conditions (see paragraph 2.3; WHO, 1996).
- 7.2 The occurrence of small amounts of vinyl chloride has also been reported in mainstream cigarette smoke at levels of 1.3 to 15.8 ng per cigarette by Smith *et al* (1997). A range of 5.6 to 28 ng vinyl chloride per cigarette is reported by ATSDR (1997).

## 8 Conclusions

- 8.1 The Index Doses derived from oral and inhalation exposure (that is,  $ID_{oral}$  and  $ID_{inh}$ ) for vinyl chloride are shown in Table 8.1.

**Table 8.1 Index Doses derived for vinyl chloride**

$ID_{oral}$ ( $\mu\text{g kg}^{-1} \text{bw day}^{-1}$ )	$ID_{inh}$ ( $\mu\text{g kg}^{-1} \text{bw day}^{-1}$ )
0.014	0.3

- 8.2 The Index Dose represents a dose that poses a minimal risk from possible exposure from a particular source, with the additional requirement that exposure should be reduced to as low a level as reasonably practicable (the “ALARP” principle; Defra and Environment Agency, 2002a). Therefore, background exposure to vinyl chloride is not considered, and the Index Dose itself is the toxicological assessment parameter used for deriving Soil Guideline Values for vinyl chloride (for details, see SGV 17, Defra and Environment Agency, in preparation).

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