

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

**CONTAMINANTS IN SOIL.**

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

**1,2-DICHLOROETHANE**

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## **Statement of Use**

This publication details the derivation of health criteria values for 1,2-dichloroethane. 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, 1,2-dichloroethane.

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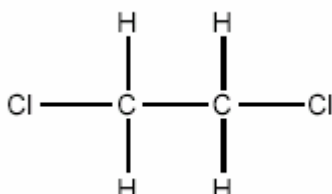
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## 1 Introduction

- 1.1 This report is one of a number on the assessment of risks to human health from contaminants in soil. It presents key data and expert opinion on the toxicology of 1,2-dichloroethane and of its intake from background environmental exposure by the general population. 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 1,2-dichloroethane, which have been established through a review of the scientific literature and a subsequent peer review process. The health criteria values presented will be used to derive Soil Guideline Values (SGVs) for 1,2-dichloroethane.
- 1.3 The overall framework for this review and the associated underlying principles are set out in CLR9 *Contaminants in soil: 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 SGVs is described in CLR10 *The Contaminated Land Exposure Assessment Model (CLEA): Technical Basis and Algorithms* (Defra and Environment Agency, 2002b). SGVs for 1,2-dichloroethane will be published in *SGV 21 Soil Guideline Values for 1,2-Dichloroethane Contamination* (Defra and Environment Agency, in preparation).
- 1.5 This report is principally based on the literature published up to June 1999. It has been updated following a further review of key publications up to May 2003.

## 2 Identity

- 2.1 1,2-Dichloroethane (CAS No 107-06-2), which is also commonly known as ethane dichloride or ethylene dichloride, is a volatile liquid with a vapour pressure of 8.5 kPa at 20°C (IPCS, 1995) and a moderate solubility in water (8.524 g L<sup>-1</sup> at 20°C) (IPCS, 1998).



**Figure 2.1 Structure of 1,2-dichloroethane**

- 2.2 1,2-Dichloroethane is a synthetic chemical with no known natural sources (IPCS, 1995). It was the first chlorinated hydrocarbon to be synthesised (IARC, 1979) and is manufactured by the catalytic vapour-phase or liquid-phase chlorination of ethylene or by oxychlorination of ethylene (Archer, 1979).
- 2.3 The major use (more than 90% of production) is as a chemical intermediate in the synthesis of a number of chlorinated hydrocarbons, in particular vinyl chloride (IARC, 1999; IPCS, 1995). 1,2-Dichloroethane was also added to leaded petrol as a scavenger of lead. In the past it has been used as a grain and soil fumigant, in metal degreasers, varnish removers, soaps and scouring compounds, and as a solvent for cleaning textiles and in organic syntheses (IARC, 1999). The widespread use of 1,2-dichloroethane in a variety of products and manufacturing processes means that it is commonly found on sites contaminated with organic chemicals (Defra and Environment Agency, 2002c).
- 2.4 Atmospheric emissions from industrial processes and petrol usage constitute the largest fraction of all releases of 1,2-dichloroethane to the environment (IARC, 1999). Releases to surface waters or soil are expected to largely volatilise rapidly into the atmosphere, with subsequent photo-oxidation, typically within 4 months (WHO, 1996). The presence of methane can increase the rate of aerobic degradation of 1,2-dichloroethane in waters and soils, although, where volatilisation is restricted, the lifetime in groundwater is expected to be of the order of years (ATSDR, 2001; IPCS, 1998).
- 2.5 To ensure consistency in units throughout this report, where original source data for 1,2-dichloroethane are described in ppm, a conversion factor of 1 ppm = 4.0 mg m<sup>-3</sup> (IPCS, 1995) has been used.

### 3 Toxicity

- 3.1 The toxicity of 1,2-dichloroethane has been reviewed by the German Chemical Society (GDCh-BUA, 1997), the Agency for Toxic Substances and Disease Registry (ATSDR, 2001), the US Environmental Protection Agency (USEPA, 1991), the World Health Organization (WHO, 1987, 1996, 2000a,b, 2003), the International Programme on Chemical Safety (IPCS, 1995, 1998), the Joint FAO/WHO Expert Committee on Food Additives (WHO, 1992), the Health and Safety Executive (HSE) (Gregg *et al*, 1993), and in a Banbury conference (Ames *et al*, 1980). This section and Section 4 are largely based upon these reviews. In general the primary publications have not been consulted, but particular mention is made of those studies which have been used in deriving health criteria values.
- 3.2 **Absorption.** Based on its physical properties and the case reports of deaths arising from oral or inhalation exposures, 1,2-dichloroethane is likely to be absorbed by humans via all routes of exposure (ATSDR, 2001). Studies in rats showed that doses of 25–150 mg kg<sup>-1</sup> bw day<sup>-1</sup> (milligrams per kilogram body weight per day) administered by stomach tube were rapidly and completely absorbed (Reitz *et al*, 1980, 1982; Spreafico *et al*, 1980). Gavaged doses of 100 mg kg<sup>-1</sup> bw day<sup>-1</sup> were more readily absorbed by rats when administered in water rather than in corn oil (Withey *et al*, 1983). In rats, absorption following 6 hour inhalation exposure to 200–1000 mg m<sup>-3</sup> was also rapid (Reitz *et al*, 1980, 1982; Spreafico *et al*, 1980).
- 3.3 A ready absorption of the neat liquid through the skin has been demonstrated in rats (Morgan *et al*, 1991) and guinea pigs (Jakobson *et al*, 1982). In mice the dermal absorption rate arising from a 15 minute skin contact with neat 1,2-dichloroethane was 47 µg min<sup>-1</sup> cm<sup>-2</sup> (Tsurata, 1975).
- 3.4 **Distribution.** The analysis of “several” tissues of oral poisoning victims indicated a wide distribution of 1,2-dichloroethane throughout the body (IARC, 1999). 1,2-Dichloroethane is readily distributed following oral or inhalation exposure in rats (IARC, 1999). After inhalation of radio-labelled compound, the highest levels of radioactivity were found in the adipose tissues although radioactivity was also detected in the liver and kidney, brain and spleen (Spreafico *et al*, 1980). The fact that blood and tissue levels were essentially the same following a single or ten daily oral doses of 50 mg kg<sup>-1</sup> bw in rats indicates that 1,2-dichloroethane is unlikely to bioaccumulate (Spreafico *et al*, 1980).
- 3.5 1,2-Dichloroethane appears in the placenta, and has been detected in human milk following occupational exposure (WHO, 2003). In rats, 1,2-dichloroethane has been detected in fetal tissue following a single 5-hour exposure to 612–8000 mg m<sup>-3</sup> on day 17 of pregnancy (Withey and Karpinski, 1985).
- 3.6 **Metabolism.** Metabolism of 1,2-dichloroethane in rats and mice occurs along two pathways. The initial products from the pathway involving microsomal cytochrome

- P450-mediated oxidation are 2-chloroacetaldehyde, which can be oxidised further to 2-chloroacetic acid and 2-chloroethanol. Both the chlorinated aldehyde and alcohol can also subsequently be conjugated with glutathione (IARC, 1999).
- 3.7 The P450-catalysed/mediated route is thought to become saturated after gavage doses of  $25 \text{ mg kg}^{-1} \text{ bw}$  (D'Souza *et al*, 1988; Reitz *et al*, 1982) or following exposures to atmospheric concentrations in excess of about  $600 \text{ mg m}^{-3}$  (Spreafico *et al*, 1980). The second major pathway, which involves an initial conjugation of 1,2-dichloroethane with glutathione, then becomes more important. The initial conjugate, S-(2-chloroethyl)glutathione, is converted to the reactive glutathione episulphonium ion, which in turn is able to alkylate DNA. Several lines of evidence indicate that the glutathione conjugation pathway is probably of greater significance than the P450 pathway as the major route for DNA damage (and cancer development) (IPCS, 1998).
- 3.8 **Excretion.** In rats, there was a rapid excretion of 1,2-dichloroethane following oral administration or inhalation exposure mainly as soluble metabolites in the urine (ATSDR, 2001). The major urinary metabolites identified in rats after administration by gavage (where they accounted for 60% of a  $150 \text{ mg kg}^{-1} \text{ bw}$  dose) or by inhalation (accounting for 84% of absorbed dose from a  $600 \text{ mg m}^{-3}$  exposure) were thiodiacetic acid (67–70%) and thiodiacetic acid sulphoxide (26–29%) (Reitz *et al*, 1982). Some unchanged 1,2-dichloroethane and carbon dioxide are excreted in the expired air (ATSDR, 2001).
- 3.9 **Acute toxicity.** The lethal oral dose in humans is estimated to be in the range of 20 to 50 mL (about  $300\text{--}750 \text{ mg kg}^{-1} \text{ bw}$ ) (IPCS, 1998). The cause of some of the deaths following ingestion of large single doses was heart arrhythmia (IPCS, 1995). Toxic symptoms include central nervous system (CNS) depression, nausea, vomiting and diarrhoea, and the consequences associated with kidney and liver injury (ATSDR, 2001; IPCS, 1995, 1998, 2000). Single exposure of humans to high (but unspecified) atmospheric concentrations produces anaesthesia and other nervous system effects, nausea and vomiting, liver and kidney toxicity, respiratory distress and lung injury, and heart arrhythmia (ATSDR, 2001; WHO, 2000a,b).
- 3.10 1,2-Dichloroethane demonstrated a moderate acute oral toxicity in rodents and rabbits with  $\text{LD}_{50}$  values in the range of  $413\text{--}860 \text{ mg kg}^{-1} \text{ bw}$  (IPCS, 1995). A similar toxicity was evident in rats exposed by the inhalation route, with  $\text{LC}_{50}$  values for a 6–7.2 hour exposure of  $4000\text{--}6600 \text{ mg m}^{-3}$  (IPCS, 1995). A 6-hour  $\text{LC}_{50}$  of  $1050 \text{ mg m}^{-3}$  has been reported for mice (Gradiski *et al*, 1978).
- 3.11 High single oral doses in laboratory animals produce pathology to the liver, kidney and heart, and blood effects (IPCS, 1995). The non-lethal effects arising from inhalation exposures approaching the  $\text{LC}_{50}$  involve the central nervous system, liver, kidney, lung, heart and adrenals (IPCS, 1995). In female mice there were indications of a depressed immune function as a result of a 3-hour exposure to  $20\text{--}40 \text{ mg m}^{-3}$ . No similar action was present at  $10 \text{ mg m}^{-3}$  (Sherwood *et al*, 1987). Immune function

was not impaired in male rats exposed for 3 hours to 800 mg m<sup>-3</sup> (Sherwood *et al*, 1987).

- 3.12 **Repeated toxicity.** There appear to be no good mechanistic data on the repeated toxicity of 1,2-dichloroethane in humans. Liver changes (an increase in fat content) occurred in rats given 80 mg kg<sup>-1</sup> bw day<sup>-1</sup> in the diet for 5–7 weeks (Alumot *et al*, 1976). No treatment-related effects on growth or liver function were reported in rats exposed for 2 years to dietary concentrations that may have produced doses of around 26–35 mg kg<sup>-1</sup> bw day<sup>-1</sup> (Alumot *et al*, 1976).
- 3.13 The only clear sign of toxicity when 1,2-dichloroethane was administered to rats in their drinking water for 13 weeks involved the kidney. In the highest dose groups (receiving 515–727 mg kg<sup>-1</sup> bw day<sup>-1</sup>) there was mild kidney pathology in the females of one (Fischer 344) of the three tested strains (Osborne-Mendel and Sprague-Dawley were unaffected). Kidney weights were increased in all dosed females, including the lowest dose of 58 mg kg<sup>-1</sup> bw day<sup>-1</sup>, and in the males of all three strains receiving higher doses. In all strains, liver weights were increased, and in males of one of the strains (Sprague-Dawley) this also included the lowest tested dose. Microscopic examination of the liver tissues revealed no abnormalities (Morgan *et al*, 1990; NTP, 1991).
- 3.14 The susceptible (Fischer 344) rat strain was also tested in a 13-week study in which 1,2-dichloroethane was administered by stomach tube. Doses of 240–480 mg kg<sup>-1</sup> bw produced deaths and pathology of the forestomach and thymus (and possibly the brain), but not of the liver or kidney. There were no signs of pathological changes in any organ at 120–150 mg kg<sup>-1</sup> bw day<sup>-1</sup>. Liver and kidney weights were increased throughout the tested dose range, including the lowest tested doses of 18–30 mg kg<sup>-1</sup> bw day<sup>-1</sup> (for an increased kidney weight in the males and an increase in liver weights in the females) (NTP, 1991). Early mortality (unrelated to cancer) was a feature of the 78-week study in which rats were treated by stomach tube with 97 mg kg<sup>-1</sup> bw day<sup>-1</sup>. Even so, a microscopic examination of tissues from the liver or kidney revealed no injury. Mortality was unaffected at 47 mg kg<sup>-1</sup> bw day<sup>-1</sup> (NCI, 1978).
- 3.15 The kidney injury reported in male mice given 1,2-dichloroethane in the drinking water for 13 weeks at doses of about 2500 mg kg<sup>-1</sup> bw day<sup>-1</sup> was not present at 780 mg kg<sup>-1</sup> bw day<sup>-1</sup>. Throughout the tested dose range of around 250–5000 mg kg<sup>-1</sup> bw day<sup>-1</sup>, kidney weights were increased in the females (and at the higher doses there were treatment-related deaths), but this was not associated with any kidney pathology. Although liver weight increases were seen in both sexes, including the males given the lowest tested dose of around 250 mg kg<sup>-1</sup> bw day<sup>-1</sup>, there were no associated pathological abnormalities (NTP, 1991).
- 3.16 In a 14-day study in male mice, the administration of 4.9 or 49 mg kg<sup>-1</sup> bw day<sup>-1</sup> by stomach tube reduced the efficiency of the immune system (a decreased antibody and cell-mediated response) (Munson *et al*, 1982). No convincing signs of immunotoxicity occurred in male mice exposed to 189 mg kg<sup>-1</sup> bw day<sup>-1</sup> administered

in drinking water for 90 days (Munson *et al*, 1982). There were dose-related increases in mortality when female mice received 149 and 299 mg kg<sup>-1</sup> bw day<sup>-1</sup> by stomach tube for 78 weeks (but this may have been tumour-related). Males given 97 and 195 mg kg<sup>-1</sup> bw day<sup>-1</sup> were not affected (NCI, 1978).

- 3.17 A limited early study reported liver, kidney, lung and heart pathology in rats exposed repeatedly for 7 h day<sup>-1</sup> to 800–1600 mg m<sup>-3</sup>, a concentration range that produced an increase in mortality rate. There were no treatment-related deaths following 74 exposures (7 h day<sup>-1</sup>, 5 day week<sup>-1</sup>) to 400 mg m<sup>-3</sup> (Heppel *et al*, 1946). Histological examination revealed no abnormalities in a wide range of organs and tissues, including the liver, kidney, lung and heart, in rats exposed to 200 mg m<sup>-3</sup> for 7 h day<sup>-1</sup>, 5 day week<sup>-1</sup> for 2 years. There was a slightly increased incidence of (unspecified) testes lesions and mild pancreatic pathology which were not thought to be true treatment-related effects (Cheever *et al*, 1990). Changes in blood biochemistry, indicative of a possible effect on liver and kidney function, occurred in older rats exposed to 200 mg m<sup>-3</sup> for 7 h day<sup>-1</sup>, 5 day week<sup>-1</sup> for 12 months. No similar changes occurred at 40 mg m<sup>-3</sup>. Histopathological examinations were not carried out (Spreafico *et al*, 1980).
- 3.18 No liver or kidney pathology was observed in rabbits exposed repeatedly (7 h day<sup>-1</sup>, 5 day week<sup>-1</sup>) to 800, 1600 or 4000 mg m<sup>-3</sup>, even though the higher concentrations resulted in treatment-related deaths (Heppel *et al*, 1946). Similar repeated exposures resulted in injury to the heart of rabbits, the liver of dogs, the heart, liver and lung of cats, the liver and kidney of monkeys, and the lung, liver, kidney and heart of guinea pigs (Heppel *et al*, 1946; Hofmann *et al*, 1971; Spencer *et al*, 1951). There were no signs of toxicity when guinea pigs, rabbits, cats and monkeys were exposed 6–7 h day<sup>-1</sup>, 5 day week<sup>-1</sup> for 3–9 months to 400 mg m<sup>-3</sup>. The extent of the pathological examination of these animals would have been limited (Hofmann *et al*, 1971; Spencer *et al*, 1951). Mice exposed 7 h day<sup>-1</sup> on 17 occasions to 400 mg m<sup>-3</sup> were similarly unaffected (Heppel *et al*, 1946).
- 3.19 An altered immune response was reported when rabbits were exposed 3 h day<sup>-1</sup>, 6 day week<sup>-1</sup> for 7.5–8 months to 10 mg m<sup>-3</sup>. No effects occurred at 2 mg m<sup>-3</sup> (Shmuter, 1977). Immune system impairment was not seen in male rats exposed 5 h day<sup>-1</sup> for 12 days to 400 mg m<sup>-3</sup> (Sherwood *et al*, 1987).
- 3.20 **Reproductive and developmental toxicity.** An increase in spontaneous abortions, premature births and pre-eclamptic toxemia was reported in female workers in a rubber processing plant (GDCh-BUA, 1997), and an increased rate of premature births was seen in female workers and in the wives of male workers in a synthetic fibre factory (Zhao *et al*, 1989). As well as their exposure to 1,2-dichloroethane, the workers were exposed to other chemicals and therefore confident conclusions on cause are not warranted. The problem of mixed exposures is also a feature of the studies that report an association between an increase in adverse birth outcomes (heart defects) and 1,2-dichloroethane levels in the water supply (Bove, 1996; Bove

- et al*, 1995), and a link between an increased incidence of neural tube defects and residence near waste sites contaminated with 1,2-dichloroethane (Croen *et al*, 1997).
- 3.21 Reproduction and development were normal in a two-generation study in which mice were given 1,2-dichloroethane in their drinking water at doses of up to 50 mg kg<sup>-1</sup> bw day<sup>-1</sup> (Lane *et al*, 1982). Development was unaffected when mice were given 510 mg kg<sup>-1</sup> bw day<sup>-1</sup> in their drinking water from days 7 to 14 of pregnancy (Kavlock *et al*, 1979).
- 3.22 No reproductive toxicity was apparent in a generation of rats allowed to reproduce during a 2-year period when their diets provided nominally around 26–35 mg kg<sup>-1</sup> bw day<sup>-1</sup> (Alumot *et al*, 1976). There were no signs of developmental toxicity when rats were given either 1,2-dichloroethane by stomach tube at up to 240 mg kg<sup>-1</sup> bw day<sup>-1</sup> or exposed 6 hours daily to atmospheres containing 1200 mg m<sup>-3</sup> on days 6 to 20 of pregnancy. The exposures were high enough to induce maternal toxicity (Payan *et al*, 1995).
- 3.23 There were no adverse effects on fertility, gestation and survival of the offspring of rats exposed 6 h day<sup>-1</sup>, 5 day week<sup>-1</sup> to 600 mg m<sup>-3</sup> for 60 days prior to mating and throughout gestation and most of lactation (Rao *et al*, 1980). Fetal development was unaffected in rats exposed 7 h day<sup>-1</sup> to 400 mg m<sup>-3</sup> on days 6 to 15 of pregnancy. Fetal deaths did occur at the maternally toxic concentration of 1200 mg m<sup>-3</sup> (Rao *et al*, 1980; Schlacter *et al*, 1979). Embryo and fetal development was normal when rabbits were exposed 7 h day<sup>-1</sup> on days 6 to 18 of pregnancy to 400 or 1200 mg m<sup>-3</sup>, concentrations high enough to produce maternal deaths (Rao *et al*, 1980).
- 3.24 Embryo deaths occurred in rats exposed throughout pregnancy to 200 mg m<sup>-3</sup> (Zhao *et al*, 1989, 1997), and there were reduced fertility, stillbirths and perinatal mortality in rats exposed 4 h day<sup>-1</sup> for 4–6 months to 15–60 mg m<sup>-3</sup> (Vozovaya, 1974, 1977). The quality of the study reports was poor, and the limited information they provide allows no explanation of the discrepancy between these results and those described in paragraphs 3.21 to 3.23.

## 4 Carcinogenicity and genotoxicity

- 4.1 An IARC Working Group in 1999 assigned 1,2-dichloroethane a Group 2B cancer classification (“possibly carcinogenic to humans”) (IARC, 1999). USEPA assessors in 1991 had ranked it as a B2 carcinogen (“probable human carcinogen”) (USEPA, 1991). At the time of the later IARC evaluation, the evidence of carcinogenicity from direct observation in humans was still described as “inadequate”. Occupational studies in the USA and Sweden had indicated an association between 1,2-dichloroethane exposure and an increased risk of dying from cancers of the blood and lymphatic system, or (with less consistent evidence) stomach or pancreas. The usefulness of these studies, however, was limited by poor exposure data and concurrent exposure to other chemicals (IARC, 1999).
- 4.2 The main support for the suspicion that 1,2-dichloroethane would pose a cancer threat to humans was its clear (“sufficient”) evidence of carcinogenicity when given to experimental animals (IARC, 1999). Administration by stomach tube to groups of 50 male and 50 female rats and mice, 5 day week<sup>-1</sup> for 78 weeks, produced multiple tumour types in both species. The rats received time-weighted average doses of 47 or 95 mg kg<sup>-1</sup> bw day<sup>-1</sup> and were kept after 1,2-dichloroethane treatment for a maximum period of 32 weeks; none of the high-dose rats survived to the end of the experiment. The male mice received 97 or 195 mg kg<sup>-1</sup> bw day<sup>-1</sup>, and the females 149 or 299 mg kg<sup>-1</sup> bw day<sup>-1</sup>, and both sexes were killed 13 weeks after the end of treatment. In rats, there was a treatment-induced increase in forestomach cancers, haemangiosarcomas at several sites, and (in males only) subcutaneous fibromas. There was also a low incidence of kidney tumours. Dose-dependent adenocarcinomas of the mammary glands were observed in female rats and mice. Lung tumours (alveolar/bronchiolar adenomas) developed in mice of both sexes. Liver cancers (hepatocellular carcinomas) were seen in the male mice, whereas in the females there were sarcomas and polyps of the endometrium, and possibly tumours of the forestomach (NCI, 1978; Ward, 1980).
- 4.3 Liver haemangiosarcomas were seen in groups of 50 male mice exposed 6 h day<sup>-1</sup>, 5 day week<sup>-1</sup> for 104 weeks to atmospheres containing 40, 120 or 360 mg m<sup>-3</sup>. This tumour type, which is very rarely seen in untreated mice and was not present in any of the 50 unexposed male controls, was found in about 10% of each of the treated groups. There was also an increased incidence of tumours of the liver (hepatocellular adenoma), lung (alveolar/bronchiolar adenoma and carcinoma), mammary gland (adenocarcinoma) and endometrium (endometrial stromal polyps) in the 50 female mice exposed to 360 mg m<sup>-3</sup> (Nagano *et al*, 1998). In the corresponding rat study, groups of 50 males and 50 females were exposed to 40, 160 or 640 mg m<sup>-3</sup> (6 h day<sup>-1</sup>, 5 day week<sup>-1</sup>) for 104 weeks. 1,2-Dichloroethane induced mammary tumours (adenoma, fibroadenoma and adenocarcinoma) and subcutaneous fibroma in both sexes. Peritoneal mesotheliomas also developed in the treated males. Generally the increased tumour incidence was limited to the maximum tested concentration of 640 mg m<sup>-3</sup> (Nagano *et al*, 1998).

- 4.4 Two earlier inhalation studies had not generated any convincing evidence of carcinogenic potential. In the larger of these, groups of 90 male and 90 female rats or mice were exposed to atmospheres containing 20, 40, 200 or 1000 mg m<sup>-3</sup> of 1,2-dichloroethane, 7 h day<sup>-1</sup>, 5 day week<sup>-1</sup> for 78 weeks. The highest test concentration was reduced to 600 mg m<sup>-3</sup> after several days because of early mortality. The corresponding control groups were of 90–134 animals. Surviving rats were killed at week 148 and the surviving mice at week 119. The only possible effect was an increased incidence of fibromas and fibroadenomas in the mammary gland of the treated female rats, compared with the chamber controls, but no increase was seen relative to a non-chamber control group in the same study (Maltoni *et al*, 1980). The other experiment involved the exposure of a single group of 50 male and 50 female rats to 200 mg m<sup>-3</sup> for 7 h day<sup>-1</sup>, 5 day week<sup>-1</sup> for 2 years. A small increase in mammary gland adenomas and fibroadenomas was again identified, but the magnitude of the increase did not achieve statistical significance, and at the time was therefore assumed to be unrelated to treatment (Cheever *et al*, 1990).
- 4.5 There is evidence that 1,2-dichloroethane is carcinogenic by dermal exposure. The incidence of benign lung papillomas was significantly increased in mice that were treated three times weekly for 440–594 days with doses of 126 mg in an acetone vehicle (Van Duuren *et al*, 1979).
- 4.6 1,2-Dichloroethane has been extensively tested for its genotoxic potential *in vitro*. Mutagenic potential has consistently been demonstrated in *Salmonella typhimurium* (in Ames tests) and mutations were induced in *Drosophila melanogaster* (IPCS, 1998). Positive results have also been obtained in mammalian cells in culture involving the detection of gene mutations, unscheduled DNA synthesis and DNA adduct formation (IPCS, 1998). Although a chromosomal action has generally not been detected *in vivo*, either in the bone marrow and peripheral lymphocytes (micronucleus test) (Armstrong and Galloway, 1993; Jensen and Ramel, 1980; King *et al*, 1979) or in germ cells (dominant lethal assay) (Lane *et al*, 1982), 1,2-dichloroethane has consistently given positive results in rodent studies that have investigated DNA adduct formation or DNA damage in a range of tissues (liver, kidney, lung and stomach) (ATSDR, 2001).
- 4.7 DNA damage has been induced by the P450 pathway *in vitro*. Nevertheless, several lines of evidence indicate that the pathway involving the formation of S-(2-hydroxyethyl)glutathione is probably of greater importance as regards genotoxic potential (IARC, 1999). Following an intraperitoneal dose of 0.86 mg kg<sup>-1</sup> bw, a greater level of DNA binding (approximately 2-fold) was seen in mice than in rats (Arfellini *et al*, 1984).

## 5 Derivation of Index Doses

### The recommendations of JECFA

- 5.1 JECFA has recommended that 1,2-dichloroethane should not be used in food, because of its *in vivo* and *in vitro* genotoxicity and carcinogenicity. No acceptable daily intake was allocated (WHO, 1992).

### The IPCS Environmental Health Criteria Document

- 5.2 The IPCS (1995) could not estimate a human exposure “by any route of exposure” that “would not cause adverse effects” and concluded that 1,2-dichloroethane was a probable human carcinogen. It was recommended that all appropriate measures should be taken to eliminate or minimize exposure.

### The IPCS Concise International Chemical Assessment Document (CICAD)

- 5.3 Using the information contained in the 1995 Environmental Health Criteria Document, the IPCS CICAD (IPCS, 1998) outlined criteria for setting guidance values for 1,2-dichloroethane. These were provided as “a possible basis for derivation of limits of exposure and judgement of the quality of environmental media by relevant authorities”. The available data were “considered inadequate to serve as a basis for development of tolerable intakes for non-neoplastic effects” The key issue was the “potential carcinogenicity of 1,2-dichloroethane in humans” (IPCS, 1998).
- 5.4 Although the IPCS CICAD recognised the desirability of reducing exposure “to the extent possible” they considered that the cancer potency demonstrated in the gavage studies in rats and mice conducted by the NCI (paragraph 4.2) would allow an estimate of the cancer risks likely to be posed by low human exposures. Multi-stage modelling of the observed tumour dose–responses, and transformation of the data to a standard 104-week duration and continuous exposure (to equate to lifetime continuous exposure of the human population) resulted in a range of TD<sub>5</sub> values<sup>1</sup> from 6.2 to 34 mg kg<sup>-1</sup> bw day<sup>-1</sup>.
- 5.5 It was suggested that a reduction of these TD<sub>5</sub> doses by a factor of 5000 or 50,000 “might be considered appropriate as a guidance value” as this margin “affords protection similar to that associated with the range for low-dose risk estimates generally considered by various agencies to be ‘essentially negligible’ (i.e. 10<sup>-5</sup> to 10<sup>-6</sup>)”. The guidance values generated (using the 50,000 figure appropriate to the 1:1000,000 lifetime cancer risk) were 0.12–0.68 µg kg<sup>-1</sup> bw day<sup>-1</sup> for ingestion, and 0.36–2.0 µg m<sup>-3</sup> for inhalation. The latter was based on two assumptions: of 100% pulmonary absorption; and that the cancer potency of a systemic dose arising from repeated bolus doses given orally would match that from an inhalation exposure. As a result, the inhalation value was described by the IPCS CICAD as “most likely over estimated ... because of inter-route variations in toxicokinetics”.

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<sup>1</sup> TD<sub>5</sub> is the dose associated with a 5% increase in tumour incidence.

### The WHO drinking water guidelines

- 5.6 In the guidelines on drinking water quality (WHO, 1993, 1996), it was considered that none of the long-term studies on non-carcinogenic effects were suitable for the derivation of a tolerable daily intake (TDI). A cancer risk assessment was undertaken based on the application of a linearised multi-stage model to the dose–response of the haemangiosarcomas seen in male rats in the 78-week gavage study (as described in paragraph 4.2). A concentration of 1,2-dichloroethane in drinking water of  $3 \mu\text{g L}^{-1}$  was estimated to correspond to an excess lifetime cancer risk of 1:1000,000.
- 5.7 The carcinogenic and genotoxic potential of 1,2-dichloroethane was the dominant influence in a revised draft WHO guideline for drinking water (WHO, 2003). An alternative approach was brought to bear on the data from the NCI studies, and this was essentially that proposed in the IPCS CICAD. A margin of safety of 50,000 was applied to the range of  $\text{TD}_{50}$  values ( $6.2$  to  $34 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ) to produce a dose range of  $0.12$  to  $0.68 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . The lower of these figures was chosen as the basis of a drinking-water guideline value of  $4 \mu\text{g L}^{-1}$  (after rounding), based on an adult drinking 2 litres of water per day, and corresponds to an excess lifetime cancer risk of between 1:100,000 and 1:1000,000.

### The WHO air quality guidelines

- 5.8 The *Air Quality Guidelines for Europe* (WHO, 2000a), initially based on a large multi-compound risk assessment programme finishing in 1996, recommended a guideline value for continuous exposure to 1,2-dichloroethane of  $0.7 \text{ mg m}^{-3}$ . The evaluation was undertaken prior to the publication of the Nagano *et al* (1998) study, and concluded that “animal inhalation data do not at present provide positive evidence” of carcinogenicity by this route. The WHO did not wish to use the assessment undertaken by the USEPA of the inhalation cancer risk as it was based on the results of cancer studies involving the oral route of administration. In the view of the WHO there were “deficiencies in extrapolation from oral data to inhalation”.
- 5.9 A guideline value was therefore based upon non-cancer end-points from a number of animal studies (paragraphs 3.18 and 3.19) that “imply a NOAEL [‘no observed adverse effect’ level] of about  $400 \text{ mg m}^{-3}$  and suggest a LOAEL [‘lowest observed adverse effect’ level] of about  $700 \text{ mg m}^{-3}$ ”. A protection (uncertainty) factor of 1000 was considered appropriate in extrapolating from animal data to the general population. This “large protection factor” was said to be warranted to take account of the limitations of the database and the difficulties of establishing a no-effect level in humans.
- 5.10 A web-based source (WHO, 2000b) of the WHO international air quality guidelines summarises the conclusions of a WHO Expert Task Force that met in December 1997. Based on the IPCS CICAD (IPCS, 1998), the unit cancer risk associated with exposure to 1,2-dichloroethane was estimated to be  $(0.5\text{--}2.8) \times 10^{-6}$  per  $\mu\text{g m}^{-3}$ . An

excess lifetime cancer risk of 1 in 1000,000 would therefore equate to an atmospheric concentration range of 0.4–2  $\mu\text{g m}^{-3}$  (WHO, 2000b).

### The recommendations of the USEPA

- 5.11 The USEPA (1991) has not recommended an oral reference dose (RfD)<sup>2</sup> or an inhalation reference concentration (RfC)<sup>3</sup>.
- 5.12 In 1991 a quantitative estimate was published of the cancer risk likely to be posed by oral exposure to 1,2-dichloroethane. A linearised multi-stage procedure was applied to the dose–response of the haemangiosarcomas induced in male rats given 1,2-dichloroethane by stomach tube (paragraph 4.2). The 95% upper bound of risk was calculated based on the cancer incidence seen at week 90 in the rats to approximate lifetime risk. Prior to the extrapolation, the doses administered to the rats were converted to the equivalent human doses, by assuming <50% metabolism in the rats and applying a scaling factor for body surface area. From this, 47  $\text{mg kg}^{-1} \text{bw}$  in the rat was considered equivalent to a human dose of 4.46  $\text{mg kg}^{-1} \text{bw day}^{-1}$ . A “time to event” analysis ensured that account was taken of the early deaths of the high-dose rats. The estimated upper bound slope factor (the lifetime cancer risk per unit dose) was  $9.1 \times 10^{-2}$  per  $\text{mg kg}^{-1} \text{bw day}^{-1}$ . A human exposure for a 70 kg adult of 0.8  $\mu\text{g day}^{-1}$  for life therefore equated to a maximum cancer risk of 1 in 1000,000. (On this basis, the USEPA estimated that drinking water containing 0.4  $\mu\text{g L}^{-1}$  was associated with a cancer risk of 1 in 1000,000.) An analogous exercise with the dose–response of the liver tumours seen in the male mice in the same gavage study generated a slope factor of  $6.2 \times 10^{-2}$  per  $\text{mg kg}^{-1} \text{bw day}^{-1}$ , which was “supportive of the risk estimate” based on the rat data (USEPA, 1991).
- 5.13 A quantitative estimate of the carcinogenic risk from inhalation exposure also used the oral data from the rat study. The assumption of a 100% absorption and metabolism at the low study dose generated an inhalation unit risk of  $2.6 \times 10^{-5}$  per  $\mu\text{g m}^{-3}$ . This would indicate that the upper bound lifetime cancer risk of 1 in 1000,000 is associated with an atmospheric concentration of 0.04  $\mu\text{g m}^{-3}$  (USEPA, 1991). A 95% upper bound estimate of inhalation cancer risk based on the absence of carcinogenic activity reported by Maltoni *et al* (1980) (paragraph 4.4) was  $1 \times 10^{-6}$  per  $\mu\text{g m}^{-3}$ , which is 26 times smaller than the unit risk indicated by the cross route extrapolation of the NTP gavage data.

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<sup>2</sup> The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of non-cancer deleterious effects during a lifetime.

<sup>3</sup> The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure concentration to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of non-cancer deleterious effects during a lifetime.

## The recommendations of the ATSDR

- 5.14 The ATSDR recommended that the “minimal risk level” (MRL)<sup>4</sup> for oral exposure to 1,2-dichloroethane of up to a year (an intermediate MRL) was 0.2 mg kg<sup>-1</sup> bw day<sup>-1</sup>. This was based upon the 13-week drinking water study in rats (paragraph 3.13). Uncertainty factors of 10 each were applied for inter- and intra-species variability, and a factor of 3 was also applied for use of a “minimal LOAEL” of 58 mg kg<sup>-1</sup> bw day<sup>-1</sup> for changes in kidney weights (ATSDR, 2001). Data were considered insufficient to derive an MRL for chronic (lifetime) oral exposure.
- 5.15 For the inhalation route, a chronic MRL of 0.6 ppm (applicable for exposures of a year or more) was recommended, based upon the absence of liver toxicity in a 2-year inhalation study (paragraph 3.18). Although the rats were exposed 7 h day<sup>-1</sup>, 5 day week<sup>-1</sup>, no attempt was made in the derivation of the MRL to convert the only tested concentration of 50 ppm to the equivalent continuous exposure. An uncertainty factor of 3 was applied to accommodate possible inter-species differences. This departure from the usual default of 10 was considered appropriate since a dosimetric adjustment (of 1), which made allowance for the relative blood/gas partition coefficients for rat and humans, had been applied to the rat exposures to convert them to the human equivalent. The default uncertainty factor of 10 to take account of possible inter-individual variations in sensitivity was maintained. The resulting combined uncertainty factor of 30 and a “modifying factor”<sup>5</sup> of 3, to account for deficiencies in the database, was applied to the study NOAEL, which, after rounding, produced the MRL of 0.6 ppm (2.4 mg m<sup>-3</sup>) (ATSDR, 2001).

## Conclusions

- 5.16 The toxic potential of repeated exposure to 1,2-dichloroethane has been examined in a wide range of species. The early studies indicate that the liver and kidney are the most commonly identified target organs, and support the view that rats and mice may be the most sensitive laboratory animal species. In the more detailed studies of dose–response, essentially evaluated only in the rat and mouse, non-tumour pathology is confined, if it is seen at all, to daily oral exposures in excess of 100 mg kg<sup>-1</sup> bw, or from repeated exposure to atmospheric concentrations in excess of 400 mg m<sup>-3</sup>. There is no convincing evidence of reproductive and developmental toxicity in laboratory animals at doses below those causing maternal toxicity. Some unresolved doubts remain over the immunotoxicity of 1,2-dichloroethane, in that activity has been seen in mice exposed to low oral and inhalation exposures. The

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<sup>4</sup> An MRL is an estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse non-cancer health effects over a specified route and duration of exposure.

<sup>5</sup> A modifying factor is a value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors.

immune system of rats seems to be far more resistant to 1,2-dichloroethane exposure.

- 5.17 1,2-Dichloroethane has nevertheless demonstrated a multi-site carcinogenicity in rats and mice exposed orally. Until recently there has been no similar convincing experimental support of its carcinogenicity by the inhalation route. With the publication of the study of Nagano *et al* (1998), this is no longer the case. 1,2-Dichloroethane also causes damage to DNA and it would therefore be prudent to assume that it is a genotoxic carcinogen. The carcinogenic threat to humans is therefore the critical issue in the development of health criteria values by both the oral and inhalation routes of exposure.
- 5.18 The WHO, in deriving drinking-water standards, and the USEPA have analysed tumour data from the long-term gavage studies in rodents in order to estimate the possible lifetime cancer risk to man. The 1993/1996 WHO drinking-water guideline applied a linearised multi-stage mathematical model to the dose–response of the haemangiosarcomas seen in male rats. This generated an estimate of 6 µg as the daily oral dose that would pose a 1:1000,000 excess lifetime cancer risk to humans. Using essentially the same mathematical model applied to the same data point, the USEPA estimated that a dose of 0.8 µg day<sup>-1</sup> would present an excess lifetime cancer risk of 1:1000,000. The difference between these two numbers mainly resides in the use by the USEPA of a dose transformation step converting the rat doses to a human equivalent.
- 5.19 A revised 2003 WHO drinking-water guideline (presently available in draft) adopts the approach to cancer risk estimation documented by the IPCS 1998 CICAD. The long-term gavage study remains the source of key data but information on all tumour types in both species is considered. Application of a factor of 50,000 to the study TD<sub>5</sub> values produced an approximate estimate of a 1:1000,000 excess lifetime cancer risk.
- 5.20 All three Expert Groups (IPCS CICAD, USEPA,WHO) have therefore based their oral risk assessments on the same study, and have applied linear extrapolations of the study findings down to the much lower exposures likely to be experienced by humans. A linearized multi-stage model was favoured in the USEPA and the 1993/1996 WHO evaluation. The 2003 WHO assessment embraced the approach proposed in the 1998 CICAD document and extrapolated from a central estimate of the TD<sub>5</sub> value, rather than the more conservative 95% upper bound of the risk used by the USEPA. The USEPA and the WHO also differ on the need to adjust rodent dose to a human equivalent dose. The IPCS CICAD argued that, as the carcinogenicity of 1,2-dichloroethane is probably due to a metabolite rather than to the parent compound, the incorporation of a scaling factor for the differences in body surface area between rodents and humans was not appropriate. The IPCS CICAD approach is favoured here as the basis of an oral Index Dose. In the CICAD, it was estimated that oral doses of 0.12–0.68 µg kg<sup>-1</sup> bw day<sup>-1</sup> may pose a lifetime cancer risk of 1:1000,000. The low end of this dose range (0.12 µg kg<sup>-1</sup> bw day<sup>-1</sup>) is

recommended as the oral Index Dose. This is consistent with the limit of  $3 \mu\text{g L}^{-1}$  set in EC Council Directive 98/83/EC (EC, 1998), and in the Water Supply (Water Quality) Regulations 2000 (WQ Regs, 2000). There would be an expectation that exposures are in any case kept as low as reasonably practicable.

- 5.21 Both the USEPA (1991) and the IPCS CICAD (IPCS, 1998) had been willing to use the oral cancer data to provide a preliminary estimate of the corresponding inhalation cancer risk. When deriving air quality guidelines, the WHO (1996) was unconvinced that 1,2-dichloroethane was likely to be carcinogenic by the inhalation route. The WHO was content at that time to assume a threshold for inhalation toxicity. Based on a programme of limited studies involving repeated inhalation exposure (and a conservative safety factor to take account of the poor quality of these old experiments), a guideline value of  $0.7 \text{ mg m}^{-3}$  was proposed. The subsequent demonstration by Nagano *et al* (1998) of 1,2-dichloroethane's multi-site carcinogenic action in both rats and mice exposed by inhalation suggests that a health criteria value based on carcinogenic potency is to be preferred. Adopting the IPCS CICAD assumption of equal potency by both routes, the inhalation Index Dose is set equal to the oral Index Dose at  $0.12 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . Again there would be an assumption that exposures should be kept as low as reasonably practicable.

## 6 Intake of 1,2-dichloroethane from food, water and air

- 6.1 The volatility of 1,2-dichloroethane means that the primary background exposure would be expected to be via inhalation of ambient air. No “Total Diet Study” (TDS) of 1,2-dichloroethane concentrations in food has been conducted by the Ministry of Agriculture, Fisheries and Food (MAFF) or the Food Standards Agency (FSA). The IPCS (1995) noted that 1,2-dichloroethane had rarely been detected in foodstuffs in recent surveys, due to the cessation of its use as an fumigant in Canada, the USA and the UK, and its low potential to bioaccumulate in food. The IPCS concluded that intake from food was probably negligible. The FSA is in agreement with this view, and therefore intake from food sources is not included in the calculation of the oral mean daily intake (MDI).
- 6.2 There is no regular reporting of 1,2-dichloroethane in drinking water in the UK. Measurements of 1,2-dichloroethane for four UK water companies were made available to the Environment Agency for 2000–2002. The majority of these were for treated water, sampled at the treatment works, rather than from boreholes. The maximum detected concentration was  $0.31 \mu\text{g L}^{-1}$ , with mean value for individual sampling points varying between 0 and  $0.3 \mu\text{g L}^{-1}$ . Taking  $0.3 \mu\text{g L}^{-1}$  as a representative concentration for UK drinking water, an adult consuming 2 L per day will have a daily intake from drinking water of  $0.6 \mu\text{g}$ . In the absence of any intake from food, this is considered as the adult oral MDI.
- 6.3 The most recent UK study of air concentrations of 1,2-dichloroethane appears to be that of Clark *et al* (1984a,b, cited in IPCS, 1995), which gives average rural concentrations of  $0.08 \mu\text{g m}^{-3}$  and average urban air concentrations of  $1.2 \mu\text{g m}^{-3}$ . WHO (2000a) reports that the average levels in cities varied from  $0.4$  to  $1 \mu\text{g m}^{-3}$ , and that values of  $6 \mu\text{g m}^{-3}$  have been reported near petrol stations and parking garages. These are the same concentrations reported in WHO (1987). ATSDR (2001) cites an EPA database of median concentrations collected at urban sites between 1970 and 1987 of  $0.049 \mu\text{g m}^{-3}$  and  $1.0 \mu\text{g m}^{-3}$  for source-dominated sites. There has been a significant decrease in the use of leaded petrol since these measurements were taken; a significant source of 1,2-dichloroethane in the atmosphere was the anti-knocking agent. Thus ambient air concentrations would now be expected to be lower. A later US study by Kelly *et al* (1994), also cited in ATSDR (2001), gave a median concentration for 83 urban locations of  $0.04 \mu\text{g m}^{-3}$ . In the absence of more recent European measurements, a conservative estimate of ambient outdoor air concentration is therefore  $1 \mu\text{g m}^{-3}$ . If the mean concentration to which the general population is exposed is taken to be  $1 \mu\text{g m}^{-3}$ , then the average daily intake of 1,2-dichloroethane from air for the adult breathing  $20 \text{ m}^3 \text{ day}^{-1}$  is  $20 \mu\text{g day}^{-1}$ .
- 6.4 WHO (2000a) stated that “the few indoor air concentrations available indicate that indoor levels are not higher than outdoor levels”, and therefore an inhalation MDI based on  $1 \mu\text{g m}^{-3}$  is considered to take account of indoor exposures.

## 7 Other sources

- 7.1 Higher exposure would be expected near to landfill and waste sites and from occupational exposure (IPCS, 1995; ATSDR, 2001).
- 7.2 ATSDR (2001) considers that low levels of dermal exposure may occur from old products made with 1,2-dichloroethane, such as cleaning agents, pesticides and adhesives used to glue wallpaper and carpets. IPCS (1995) cites an old German study (Bauer, 1981) in which high levels were found in shampoo ( $7.6 \mu\text{g L}^{-1}$ ), shaving cream ( $122 \mu\text{g L}^{-1}$ ) and cough syrup ( $12.9 \mu\text{g kg}^{-1}$ ). More recent analytical results for cosmetics and pharmaceutical products are not available.
- 7.3 ATSDR (2001) states that 1,2-dichloroethane has been detected in breast milk but current data are not available.

## 8 Conclusions

- 8.1 The Index Doses for oral and inhalation exposures (that is,  $ID_{oral}$  and  $ID_{inh}$ ) of 1,2-dichloroethane for a 70 kg adult are summarised in Table 8.1.

**Table 8.1 Index Doses derived from oral and inhalation studies**

$ID_{oral}$ ( $\mu\text{g kg}^{-1} \text{bw day}^{-1}$ )	$ID_{inh}$ ( $\mu\text{g kg}^{-1} \text{bw day}^{-1}$ )
0.12	0.12

- 8.2 The Index Doses represent doses that pose a minimal risk level from possible exposure from a particular source, with the additional requirement that exposure needs to be reduced to as low a level as reasonably practicable (Defra and Environment Agency, 2002a). Therefore, background exposure to 1,2-dichloroethane is not considered, and the Index Dose itself is the toxicological assessment parameter used for deriving Soil Guideline Values (for details see SGV 21, Defra and Environment Agency, in preparation).
- 8.3 No authoritative assessments of the health risks posed by dermal exposure have been identified. 1,2-Dichloroethane has demonstrated a carcinogenic action in mice treated dermally.

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