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1,4-Dioxane 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 on selected chemicals in 1998 and on microbiological aspects in 2002. The third edition of the GDWQ was published in 2004, and the first addendum to the third edition was published in 2005.

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 and 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 of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background 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 documents for the third edition and addenda.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, 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. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert 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

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

Dr J. Cotruvo, J. Cotruvo Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Working Group Meeting for the first addendum to the third edition of the GDWQ, held on 17–21 May 2004. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants in the meeting is gratefully acknowledged.

The WHO coordinator was Dr J. Bartram, Coordinator, Water, Sanitation and Health Programme, WHO Headquarters. Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters. Mr Robert Bos, Water, Sanitation and Health Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. 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

BOD	biochemical oxygen demand
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
DNA	deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
GC	gas chromatography
GDWQ	*Guidelines for Drinking-water Quality*
HEAA	β-hydroxyethoxyacetic acid
IARC	International Agency for Research on Cancer
K_m	Michaelis-Menten constant
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MS	mass spectrometry
n.d.	not detected
NDEA	*N*-nitrosodiethylamine
NOAEL	no-observed-adverse-effect level
PBPK	physiologically based pharmacokinetic
ppm	part per million
TDI	tolerable daily intake
UV	ultraviolet
V_{max}	maximum rate of metabolism
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.: 123-91-1
Molecular formula: $C_4H_8O_2$

1.2 Physicochemical properties[1] *(IARC, 1987)*

Property	*Value*
Physical state	Colourless, inflammable liquid
Melting point	11.8 °C
Boiling point	101 °C
Density	1032.9 g/litre at 20 °C
Water solubility	Miscible with water
Vapour pressure	4.9 kPa at 25 °C
Stability	Stable in light
Reactivity	Reacts with oxygen to form peroxide

1.3 Major uses and sources in drinking-water

1,4-Dioxane is used as a stabilizer in chlorinated solvents. It is also used as a solvent for cellulose acetate, ethyl cellulose, benzyl cellulose, resins, oils, waxes, oil and spirit-soluble dyes (Budavari et al., 1996) as well as for electrical, agricultural and biochemical intermediates and for adhesives, sealants, cosmetics, pharmaceuticals, rubber chemicals and surface coatings (Anon., 1970). In Japan, 1,4-dioxane is used as a solvent and surface-treating agent for artificial leather and was formerly used as a stabilizer for trichloroethylene (IARC, 1987).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Water

The results of nationwide surveys in Japan show that the concentration of 1,4-dioxane in surface water ranged from n.d. to 35 µg/litre in 1990, from n.d. to 8.8 µg/litre in 1991, from n.d. to 19 µg/litre in 1992, from n.d. to 13 µg/litre in 1993, from n.d. to 15 µg/litre in 1994, from n.d. to 7.6 µg/litre in 1995, from n.d. to 9.02 µg/litre in 1996 and from n.d. to 42.8 µg/litre in 1997 (Japan Ministry of the Environment, 1999). It was also reported, as a result of another nationwide survey in Japan in 1995–1996, that the level of 1,4-dioxane ranged from n.d. to 16 µg/litre in 19 surface water samples from 10 sites of 6 rivers, from 0.3 to 0.9 µg/litre for 3 coastal seawater samples from 3 sites and from n.d. to 79 µg/litre for 25 groundwater samples from 25 sites (Abe, 1997). The concentration of 1,4-dioxane in raw water for the water supply ranged from n.d. to 9.1 µg/litre (Magara et al., 1998). There was a high correlation between the concentrations of 1,4-dioxane and 1,1,1-trichloroethane (Abe, 1999).

[1] Conversion factor in air: 1 ppm = 3.6 mg/m^3.

1,4-Dioxane was found at a concentration of 0.2–1.5 µg/litre in tap water samples from six cities in Kanagawa, Japan, in 1995–1996 (Abe, 1997).

2.2 Food

The level of 1,4-dioxane in various cooked food samples, analysed by GC-MS, ranged from n.d. to 11 µg/kg, with a detection limit of 2 µg/kg (S. Iizuka, personal communication).

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

1,4-Dioxane is well absorbed via the oral and inhalation routes. In rats, more than 95% is taken up from the gastrointestinal tract following administration of up to 1000 mg/kg of body weight. Complete absorption was indicated in rats following exposure by inhalation to 180 mg/m^3 for 6 h, compared with a maximum of 80% in humans. Uptake (on a mg/kg of body weight basis) is approximately 5–8 times greater in rats than in humans (Young et al., 1977, 1978).

No data are available on dermal uptake of 1,4-dioxane in humans, although about 3% of applied 1,4-dioxane was absorbed over a 24-h period in non-human primates under non-occluded conditions (Marzulli et al., 1981). *In vitro* human skin studies indicate that 3.2% of an applied dose passes through excised skin with occlusion and 0.3% under non-occluded conditions. The high volatility of 1,4-dioxane in air is likely to account for these differences (ECETOC, 1983).

Animal studies have shown that 1,4-dioxane is distributed to the blood, liver, kidney, spleen, lung, colon and skeletal muscle, with selective uptake in liver and kidney (Mikheev et al., 1990; DeRosa et al., 1996). Covalent binding was found to be significantly higher in the liver, spleen and colon than in other tissues. PBPK modelling by Reitz et al. (1990) predicted that the area under the curve liver values for humans would be lower than those for rats or mice continuously exposed to low concentrations of 1,4-dioxane in air or water. Metabolic rate constants developed for rats in a PBPK model were K_m = 29.4 mg/litre and V_{max} = 13.7 mg/kg of body weight per hour (Reitz et al., 1990). Those for humans were K_m = 3.0 mg/litre and V_{max} = 6.35 mg/kg of body weight per hour.

The main metabolite in animals and humans is HEAA. Other metabolites determined in animal studies include 1,4-dioxan-2-one, β-hydroxyethoxyacetaldehyde, diethylene glycol, oxalic acids and carbon dioxide. Unchanged 1,4-dioxane is excreted in the urine and expired air (DeRosa et al., 1996).

Young et al. (1978) demonstrated the pharmacokinetics of 1,4-dioxane in rats to be dose dependent. Oral doses of 10, 100 and 1000 mg of [^{14}C]1,4-dioxane per kg of body weight administered to rats resulted in about 99%, 85% and 75% of radiolabelled metabolites in urine and approximately 0.5%, 5% and 25% in expired

air as 1,4-dioxane, respectively. Excretion in faeces (1–2%) and expired carbon dioxide (2–3%) was not affected by the dosage. With low oral or intravenous doses of 3 and 10 mg/kg of body weight, elimination of 1,4-dioxane from plasma was linear, with a half-time of 1.1 h; above 30 mg/kg of body weight, plasma clearance was characterized by non-linear kinetics. Because pulmonary and renal clearance rates were not significantly different between low and high doses, saturation is thought to be associated with biotransformation rather than elimination. The authors estimated that metabolism of 1,4-dioxane in rats is saturated at plasma levels above 100 mg/ml.

Inhalation exposure of rats to 1,4-dioxane at 180 mg/m^3 for 6 h resulted in about 99% being excreted as HEAA. At the end of the exposure, the elimination half-time of 1,4-dioxane from plasma was 59 min. The excretion half-time of HEAA was 2.7 h, and its renal clearance was 121 ml/min. Renal clearance of 1,4-dioxane was 0.34 ml/min, compared with a metabolic clearance of 75 ml/min. Steady-state plasma levels following inhalation at 180 mg/m^3 were similar in humans and rats: 10 mg/ml and 7.3 mg/ml, respectively. Simulation of repeated daily exposure to 180 mg/m^3 for 8 h per day indicated that 1,4-dioxane would never accumulate to concentrations above those attained after a single 8-h exposure (Young et al., 1977).

In summary, 1,4-dioxane is rapidly absorbed and metabolized and does not accumulate in the body, but metabolism to HEAA is dose dependent, becoming saturated at high doses.

4. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO *TEST SYSTEMS*

4.1 Acute exposure

Oral LD_{50} values are in the range of 5400–7300 mg/kg of body weight in rats, 5900 mg/kg of body weight in mice, 3300–4000 mg/kg of body weight in guinea-pigs and 2000 mg/kg of body weight in rabbits (DeRosa et al., 1996). LC_{50} values following inhalation for 2 h were found to be 46 g/m^3 in rats and 37 g/m^3 in mice (RTECS, 2000). The dermal LD_{50} in rabbits was 7600 mg/kg of body weight, although there were no equivalent toxicological effects in Wistar rats treated with 8300 mg/kg of body weight (DeRosa et al., 1996). The main acute effects at near-lethal doses in experimental animals (rats, mice, guinea-pigs, rabbits or dogs) are central nervous system depression (e.g., narcosis) and severe gastric, pulmonary, hepatic and renal lesions (DeRosa et al., 1996).

4.2 Short-term exposure

Administration of 50 000 mg of 1,4-dioxane per litre (equivalent to 7230 and 9812 mg/kg of body weight per day in rats and mice, respectively) in drinking-water for 67 days resulted in the death of both rats and mice. Histological examination of surviving animals revealed severe hepatic and renal lesions (cellular degeneration, etc.) (Fairley et al., 1934). Male SD rats administered 0, 10 or 1000 mg of 1,4-dioxane per kg of body weight per day in drinking-water for 11 weeks demonstrated increased relative

liver weight and a minimal degree of liver lesion at 1000 mg/kg of body weight per day, but not at 10 mg/kg of body weight per day (Stott et al., 1981).

4.3 Long-term exposure

Sherman rats of both sexes received 100, 1000 or 10 000 mg of 1,4-dioxane per litre in their drinking-water for 716 days. The 10 000 mg/litre group exhibited decreased body weight gain, survival rate and water consumption. Other histopathological data for animals receiving 1000 or 10 000 mg/litre pointed to renal tubular epithelial and hepatocellular degeneration and necrosis. The NOAEL was 100 mg/litre (male: 9.6 mg/kg of body weight per day; female: 19 mg/kg of body weight per day) (Kociba et al., 1974). In F344/DuCrj rats receiving 200, 1000 or 5000 mg/litre in drinking-water for 104 weeks, a slight increase in liver spongiosis hepatitis was detected at 200 mg/litre (equivalent to 16–21 mg/kg of body weight per day) in males (Yamazaki et al., 1994).

In Wistar rats inhaling 400 mg/m^3 (equivalent to 105 mg/kg of body weight per day) of 1,4-dioxane vapour for 2 years (7 h per day, 5 days per week), no changes related to the chemical exposure were evident on microscopic examination (Torkelson et al., 1974).

4.4 Reproductive and developmental toxicity

SD rats were given 1,4-dioxane at 0.25, 0.5 or 1.0 ml/kg of body weight per day (258, 516 or 1033 mg/kg of body weight per day) by gavage on days 5–14 of pregnancy (sperm = day 0). Maternal toxicity, as evidenced by reduced food consumption during the administration period, was observed at 1.0 ml/kg of body weight per day. No adverse effects on numbers of implantations, live fetuses or post-implantation loss or on the incidence of fetuses with malformations were detected. Decreased weight of fetuses and delayed ossification of the sternebrae occurred at 1.0 ml/kg of body weight per day. These findings indicate that the NOAEL for developmental toxicity is 516 mg/kg of body weight per day, based on the decreases in maternal food consumption and fetal weight and delayed ossification (Giavini et al., 1985).

There appear to be no published studies on reproductive toxicity.

4.5 Genotoxicity and related end-points

1,4-Dioxane, with or without metabolic activation, did not induce differential DNA repair in *Escherichia coli* K-12 uvrB/recA (Hellmér & Bolcsfoldi, 1992) and was not mutagenic in *Salmonella typhimurium* (Khudoley et al., 1978; Stott et al., 1981; Haworth et al., 1983) or in L5178Y mouse lymphoma cells (McGregor et al., 1991). In Chinese hamster ovary (CHO) cells, it did not produce chromosomal aberrations, although it did cause a slight increase in sister chromatid exchange in the absence of metabolic activation (Galloway et al., 1987). It has also been reported to cause morphological transformation of BALB/c 3T3 mouse cells (Sheu et al., 1988).

Oral administration of 1,4-dioxane to rats caused DNA strand breaks in liver cells (Kitchin & Brown, 1990). However, no covalent DNA binding was detected in rat liver (Stott et al., 1981). No induction of unscheduled DNA synthesis was observed in rat hepatocytes after either *in vivo* treatment or *in vitro* cell treatment with 1,4-dioxane, even when the animals had previously been exposed to 1,4-dioxane by inhalation at 36 000 mg/m^3 for 1 week (Goldsworthy et al., 1991). In the same study, no induction of unscheduled DNA synthesis in rat nasal epithelial cells was observed (Goldworthy et al., 1991).

Of three studies on the induction of bone marrow micronuclei, one was negative with male C57BL/6 and CBA mice (Tinwell & Ashby, 1994) and one was inconclusive with male B6C3F1 mice (McFee et al., 1994), whereas the third gave a clear positive result for male and female C57BL/6 mice and a negative result for male BALB/c mice (Mirkova, 1994). Overall, these results suggest possible weak, strain-specific clastogenic activity.

1,4-Dioxane has no structural alerts for mutagenicity. It is negative *in vitro* in the *Salmonella* assay, the mouse lymphoma assay and cytogenetic assays in CHO cells. Conflicting results were obtained in the *in vivo* micronucleus assay, although this is surprising, in view of the uniformly negative nature of other data. The weight of evidence indicates that 1,4-dioxane is probably non-genotoxic.

4.6 Carcinogenicity

In the long-term drinking-water study in rats conducted by Kociba et al. (1974), hepatocellular carcinomas, cholangiomas and nasal squamous cell carcinomas were observed only in the 10 000 mg/litre group. The NOAEL for carcinogenicity in this study was 1000 mg/litre (male: 94 mg/kg of body weight per day; female: 148 mg/kg of body weight per day).

Osborne-Mendel rats and mice were administered 1,4-dioxane in their drinking-water for 110 and 90 weeks, respectively. The doses in the rat study were equivalent to 0, 240 and 530 mg/kg of body weight per day for males and 0, 350 and 640 mg/kg of body weight per day for females. Incidences of nasal cavity squamous cell carcinomas were significantly increased in male rats (0/33, 12/25 and 16/33 in the control, low-dose and high-dose groups) and in female rats (0/34, 10/35 and 8/35 in the control, low-dose and high-dose groups). Treated females also demonstrated a statistically significant dose-dependent elevation of liver adenomas. In the mouse study, the administered doses were equivalent to 0, 720 and 830 mg/kg of body weight per day for males and 0, 380 and 860 mg/kg of body weight per day for females. Combined incidences of liver carcinomas and adenomas increased in a dose-dependent manner in males (2/49, 18/50 and 24/47 in the control, low-dose and high-dose groups) and females (0/50, 12/48 and 29/37 in the control, low-dose and high-dose groups) (NCI, 1978).

Crj:BDF1 mice of both sexes administered 1,4-dioxane at 0, 500, 2000 or 8000 mg/litre in drinking-water for 104 weeks showed increased incidences of combined

hepatocellular adenomas and carcinomas: 22/50, 36/50, 45/50 and 44/50 in the control, low-dose, mid-dose and high-dose groups for males; and 4/50, 36/50, 50/50 and 47/50 in the control, low-dose, mid-dose and high-dose groups for females. Thus, a NOAEL for hepatocellular tumours could not be derived. One nasal cavity tumour occurred in a high-dose female. The LOAEL for all tumours was 500 mg/litre (66–77 mg/kg of body weight per day) (Yamazaki et al., 1994).

F344/DuCrj rats of both sexes administered 1,4-dioxane at 0, 200, 1000 or 5000 mg/litre in drinking-water for 104 weeks showed increased incidences of combined hepatocellular adenomas: 0/50, 2/50, 4/50 and 24/50 in the control, low-dose, mid-dose and high-dose groups for males; and 1/50, 0/50, 5/50 and 38/50 in the control, low-dose, mid-dose and high-dose groups for females. Hepatocellular carcinomas were seen only at the high doses in both sexes (14/50 for males; 10/50 for females). Peritoneal mesotheliomas, subcutaneous fibromas, mammary fibroadenomas, nasal cavity tumours and mammary adenomas were also increased in both sexes in the high-dose group. The NOAEL for hepatocellular tumours was considered to be 200 mg/litre (16–21 mg/kg of body weight per day), and the LOAEL for all tumours was 1000 mg/litre (81–103 mg/kg of body weight per day), because of the nature of the hepatocellular adenomas (usually spontaneous) and the frequency of the incidences (Yamazaki et al., 1994).

In a long-term rat inhalation study, no carcinogenic effects were observed (Torkelson et al., 1974). Male A/J mice administered 1,4-dioxane by intraperitoneal injection 3 times per week for 8 weeks for total doses of 400, 1000 and 2000 mg/kg of body weight exhibited an increase in the multiplicity of lung tumours to 0.97 per mouse at the high dose compared with 0.28 per mouse in controls given vehicle alone (Maronpot et al., 1986). In a mouse lung adenoma assay, 1,4-dioxane produced a significant increase in the incidence of lung tumours in males given an intermediate intraperitoneal dose, whereas no such increase was noted in males given a lower or higher intraperitoneal dose, in females given the three intraperitoneal doses or in either males or females given 1,4-dioxane orally (Stoner et al., 1986).

Male SD rats were administered 1,4-dioxane by gavage once a day, 5 days per week for 7 weeks, at doses of 100 or 1000 mg/kg of body weight beginning 5 days after partial hepatectomy and injection of a single dose of 30 mg of NDEA per kg of body weight to initiate hepatocarcinogenesis. The high dose increased the multiplicity of hepatic foci to 4.7 per cm^2 compared with 1.3 per cm^2 with NDEA initiation alone. Without partial hepatectomy or the NDEA initiation, 100 or 1000 mg of 1,4-dioxane per kg of body weight alone did not induce foci (Lundberg et al., 1987). Application of 0.2 ml to the skin of Swiss-Webster mice 3 times a week after initiation with dimethylbenzanthracene resulted in an increase in the numbers of tumours in skin, lungs and kidneys (King et al., 1973).

5. EFFECTS ON HUMANS

Two cases of lethality due to an occupational exposure to 1,4-dioxane have been described (DeRosa et al., 1996). Haemorrhagic nephritis, centrilobular liver necrosis,

severe epigastric pain, convulsion and coma were found as the major effects. The levels or length of exposure could not be estimated in one case. In the other, the workers were exposed by inhalation to 1,4-dioxane at levels ranging between 750 and 2340 mg/m^3 for 1 week.

In volunteer short-term exposure studies (720 or 1080 mg/m^3 for 15 min; 5760 mg/m^3 for 10 min; 19 800 mg/m^3 for 1 min), mucous irritation in eyes, nose and throat was noted as a clinical sign (DeRosa et al., 1996). After exposure to 1,4-dioxane at 180 mg/m^3 for 6 h, only mild eye irritation was noted, with no other clinical signs, as demonstrated by chest X-ray, electrocardiograms, respiratory function tests, blood determinations and urinalysis (Young et al., 1977).

In a cohort study of 74 workers exposed to an estimated 0.02–48 mg of 1,4-dioxane per m^3 for an average duration of 25 years, no clinical signs or mortality was related to the chemical exposure. No increase of chromosomal aberrations in peripheral lymphocytes of six workers was noted compared with controls. High serum transaminase levels were found in 6 of 24 current workers, but the authors concluded that these changes could have been related to habitual alcohol consumption (Thiess et al., 1976). In another occupational cohort study of 165 workers exposed for at least 1 month over about 20 years to 1,4-dioxane at between 0.36 and 61 mg/m^3, the observed number of cancer deaths was not different from that expected (Buffler et al., 1978).

A comparative mortality study in Denmark was conducted with 19 000 cases in the cancer registry (Hansen, 1993). In male workers at companies dealing with 1,4-dioxane, the standard proportionate incidence ratio for liver cancer was significantly increased (1.64). Although alcohol consumption could not account for this increase, co-exposure to chemicals other than 1,4-dioxane and the exposure period and dose were not controlled for.

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

1,4-Dioxane can be analysed by various techniques with detection limits as low as 0.1 µg/litre.

1,4-Dioxane is extracted by hexane–methylene chloride (80:20, v/v), transferred to a C_{18} solid-phase cartridge and eluted by acetonitrile. This solution is analysed by GC-MS. The detection limit of this method is 50 µg/litre (Song & Zhang, 1997). In another method, 1,4-dioxane is trapped with activated carbon and subsequently measured by GC-MS (Harris et al., 1974). A detection limit of 0.1 µg/litre is obtained when 1,4-dioxane is measured by GC-MS using 1,4-dioxane-d_8 (Abe, 1997). Solvent extraction and GC-MS analysis can give a quantification limit of 3 µg/litre with good specificity. However, this technique requires a large volume of sample, about 1 litre, for analysis.

6.2 Treatment and control methods and technical achievability

It should be technically possible to achieve a concentration of 50 µg/litre using advanced water treatment.

It is difficult to remove 1,4-dioxane from water or to decompose it in water because of its high water solubility and non-volatility from water. 1,4-Dioxane is not removed to any appreciable extent by air stripping, coagulation or oxidation by chlorine or potassium permanganate; granular activated carbon can achieve about 50% removal (Zenker et al., 2003). 1,4-Dioxane was effectively removed by biological activated carbon treatment. The microbial community living in a biological activated carbon filter can remove 1,4-dioxane at 50% or less (Inamori, 1999). It is recognized that although a removal of 1,4-dioxane at 50–60% could be achieved by acclimated activated sludge of a chemical plant, 1,4-dioxane was easily desorbed with water from sludge (Abe, 1999).

1,4-Dioxane in dilute aqueous solution is degraded by using a UV/hydrogen peroxide process in a UV semibatch reactor to aldehydes (formaldehyde, acetaldehyde and glyoxal), organic acids (formic, methoxyacetic, acetic, glycolic, glyoxylic and oxalic) and the mono- and diformate esters of 1,2-ethanediol (Stefan & Bolton, 1988). A removal of 90% was achieved after 5 min of treatment, although complete mineralization required about 60 min. Effective removal can be achieved by light irradiation in the presence of titanium dioxide, hydrogen peroxide or peroxodisulfate (Maurino et al., 1997).

1,4-Dioxane is not effectively oxidized by ozone alone, but the rate can be increased by addition of hydrogen peroxide. Practically total removal was achieved from a 200 mg/litre solution with an absorbed ozone dose of 336 mg/litre and a peroxide:ozone ratio of 0.5 (Adams & Scanlan, 1993). Ozone plus hydrogen peroxide treatment causes an increase in BOD, indicating an increase in biodegradability of the treated solution (Adams et al., 1994; Suh & Mohseni, 2004). Neither ozone nor hydrogen peroxide alone had any effect on 1,4-dioxane concentrations (Adams et al., 1994).

7. GUIDELINE VALUE

1,4-Dioxane caused hepatic and nasal cavity tumours in rodents in most long-term oral studies conducted. Tumours in the peritoneum, skin and mammary gland were also observed in rats given a high dose. Lung tumours were specifically detected after intraperitoneal injection. Although cohort studies of workers did not reveal any elevation in the incidence of death by cancer, a significant increase in liver cancer was found in a comparative mortality study. However, the evidence is inadequate for human carcinogenicity assessment because of small samples or lack of exposure data. IARC (1999) has classified 1,4-dioxane as Group 2B (possibly carcinogenic to humans).

Although only a possible weak genotoxic potential has been suggested for 1,4-dioxane, the compound clearly induces multiple tumours in various organs. Based on

calculations using the linearized multistage model for estimating cancer risk for the most sensitive sites found in rats exposed to 1,4-dioxane in drinking-water — nasal carcinomas (NCI, 1978) and hepatic tumours (Yamazaki et al., 1994) — drinking-water concentrations of 88 and 54 µg/litre, respectively, were found to be associated with an upper-bound excess lifetime cancer risk of 10^{-5} without body surface correction.

On the other hand, if it is considered that 1,4-dioxane is not genotoxic in humans at low doses, the TDI approach can be used for derivation of the guideline value. For a non-cancer end-point (including renal tubular epithelial and hepatocellular degeneration and necrosis), a TDI of 96 µg/kg of body weight per day can be calculated by applying an uncertainty factor of 100 (for inter- and intraspecies variation) to a NOAEL of 9.6 mg/kg of body weight per day from a long-term drinking-water study in rats (Kociba et al., 1974). For a cancer end-point (hepatocellular tumours), a TDI of 16 µg/kg of body weight per day can be calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation, 10 for non-genotoxic carcinogenicity) to the NOAEL of 16 mg/kg of body weight per day from a long-term drinking-water study in rats (Yamazaki et al., 1994). The equivalent concentration in drinking-water is calculated to be 48 µg/litre based on 10% allocation of the lower TDI from the cancer end-point.

As similar values of 54 and 48 µg/litre were derived with two different approaches, a rounded figure of 50 µg/litre is considered to be the appropriate guideline value for 1,4-dioxane. This guideline value should be both analytically and technically achievable.

8. REFERENCES

Abe A (1997) [Determination method for 1,4-dioxane in water samples by solid phase extraction–GC/MS.] *Journal of Environmental Chemistry*, 7:95–100 (in Japanese).

Abe A (1999) Distribution of 1,4-dioxane in relation to possible sources in the water environment. *The Science of the Total Environment*, 227:41–47.

Adams CD, Scanlan PA (1993) Biodegradability enhancement and mineralization of 1,4-dioxane by the hydrogen peroxide/ozone advanced oxidation process. In: *Proceedings of the 11th Ozone World Conference*. Vol. 1. Scottsdale, AZ, International Ozone Association, pp. S-3-60 – S-3-75.

Adams CD, Scanlan PA, Secrist ND (1994) Oxidation and biodegradability enhancement of 1,4-dioxane using hydrogen peroxide and ozone. *Environmental Science and Technology*, 28:1812–1818.

Anon. (1970) *Product use patterns*. New York, NY, Union Carbide Corporation.

Budavari S et al., eds. (1996) *The Merck index*, 12th ed. Whitehouse Station, NJ, Merck & Co., Inc., p. 3358.

Buffler P et al. (1978) Mortality follow-up of workers exposed to 1,4-dioxane. *Journal of Occupational Medicine*, 20:255–259.

DeRosa CT et al. (1996) Health evaluation of 1,4-dioxane. *Toxicology and Industrial Health*, 12:1–43.

ECETOC (1983) *1,4-Dioxane.* Brussels, European Chemical Industry Ecology and Toxicology Centre (Joint Assessment of Commodity Chemicals No. 2).

Fairley A, Linton EC, Ford-Moore AH (1934) The toxicity to animals of 1:4 dioxane. *Journal of Hygiene*, 34:486–501.

Galloway SM et al. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environmental and Molecular Mutagenesis*, 10:1–175.

Giavini E, Vismara C, Broccia ML (1985) Teratogenesis study of dioxane in rats. *Toxicology Letters*, 26:85–88.

Goldsworthy TL et al. (1991) Examination of potential mechanisms of carcinogenicity of 1,4-dioxane in rat nasal epithelial cells and hepatocytes. *Archives of Toxicology*, 65:1–9.

Hansen J (1993) *The industrial use of selected chemicals and risk of cancer 1970–1984*. Copenhagen, National Institute of Occupational Health.

Harris LE, Budde WL, Eichelberger JW (1974) Direct analysis of water samples for organic pollutants with gas chromatography–mass spectrometry. *Analytical Chemistry*, 46:1912–1917.

Haworth S et al. (1983) *Salmonella* mutagenicity test results for 250 chemicals. *Environmental Mutagenesis*, 5(Suppl. 1):1–142.

Hellmér L, Bolcsfoldi G (1992) An evaluation of the *E. coli* K-12 uvrB/recA DNA repair host-mediated assay. I. *In vitro* sensitivity of the bacteria to 61 compounds. *Mutation Research*, 272:145–160.

IARC (1987) *1,4-Dioxane*. Lyon, International Agency for Research on Cancer, pp. 272–274 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Suppl. 7).

IARC (1999) *Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide*. Lyon, International Agency for Research on Cancer, pp. 589–602 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 71).

Inamori Y (1999) [Removal character of trace chemical contaminants in landfill leachate by biological treatment.] *Japanese Journal of Water Treatment Biology*, 19(Suppl.):52 (in Japanese).

Japan Ministry of the Environment (1999) *Outline of 1998 study results on designated chemicals*. Tokyo, Ministry of the Environment, Planning and Coordination Bureau, pp. 26–37.

Khudoley VV, Mizgireuv I, Pliss GB (1978) The study of mutagenic activity of carcinogens and other chemical agents with *Salmonella typhimurium* assays: testing of 126 compounds. *Archiv für Geschwulstforschung*, 57:453–462.

King ME, Shefner AM, Bates RR (1973) Carcinogenesis bioassay of chlorinated dibenzodioxins and related chemicals. *Environmental Health Perspectives*, 5:163–170.

Kitchin KT, Brown JL (1990) Is 1,4-dioxane a genotoxic carcinogen? *Cancer Letters*, 53:67–71.

Kociba RJ et al. (1974) 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. *Toxicology and Applied Pharmacology*, 30:275–286.

Lundberg I et al. (1987) Three industrial solvents investigated for tumor promoting activity in the rat liver. *Cancer Letters*, 36:29–33.

Magara Y et al. (1998) [*Comprehensive approaches to the management of surfactants and related chemicals in water sources and drinking water treatment processes*.] Tokyo, National Research Institutes of Government Ministries and Agencies, pp. 8.1–8.33 (Environmental Research in Japan No. 1) (in Japanese).

Maronpot RR et al. (1986) Strain A mouse pulmonary tumor test results for chemicals previously tested in the National Cancer Institute carcinogenicity tests. *Journal of the National Cancer Institute*, 76:1101–1112.

Marzulli NF, Anjo DM, Maibach HI (1981) *In vivo* skin penetration studies of 2,4-toluenediamine, 2,4-diaminoanisole, 2-nitro-*p*-phenylenediamine, *p*-dioxane and *N*-nitrosodiethanolamine in cosmetics. *Food and Cosmetics Toxicology*, 19:743–747.

Maurino V et al. (1997) Light-assisted 1,4-dioxane degradation. *Chemosphere*, 35(11):2675–2688.

McFee AF et al. (1994) Results of mouse bone marrow micronucleus studies on 1,4-dioxane. *Mutation Research*, 322:141–150.

McGregor DB et al. (1991) Responses of the L5178Y mouse lymphoma cell forward mutation assay. V: 27 coded chemicals. *Environmental and Molecular Mutagenesis*, 17:196–219.

Mikheev MI, Gorlinskaya YeP, Solovyova TV (1990) The body distribution and biological action of xenobiotics. *Journal of Hygiene, Epidemiology, Microbiology, and Immunology*, 34:329–336.

Mirkova ET (1994) Activity of the rodent carcinogen 1,4-dioxane in the mouse bone marrow micronucleus assay. *Mutation Research*, 322:141–150.

NCI (1978) *Bioassay of 1,4-dioxane for possible carcinogenicity*. Bethesda, MD, Department of Health, Education and Welfare, National Institutes of Health, National Cancer Institute (Technical Report Series 80; DHEW Publication No. 78-1330).

Reitz RH et al. (1990) Development of a physiologically based pharmacokinetic model for risk assessment with 1,4-dioxane. *Toxicology and Applied Pharmacology*, 105:37–54.

RTECS (2000) *Registry of Toxic Effects of Chemical Substances database*. Cincinnati, OH, National Institute for Occupational Safety and Health.

Sheu CW et al. (1988) *In vitro* BALB/3T3 cell transformation assay of nonoxynol-9 and 1,4-dioxane. *Environmental and Molecular Mutagenesis*, 11:41–48.

Song D, Zhang S (1997) Rapid determination of 1,4-dioxane in water by solid-phase extraction and gas chromatography–mass spectrometry. *Journal of Chromatography A*, 787:283–287.

Stefan MI, Bolton IR (1988) Mechanism of the degradation of 1,4-dioxane in dilute aqueous solution using the UV/hydrogen peroxide process. *Environmental Science and Technology*, 32:1588–1596.

Stoner GD et al. (1986) Comparison of two routes of chemical administration on the lung adenoma response in strain A/J mice. *Toxicology and Applied Pharmacology*, 82:19–31.

Stott WT, Quast JF, Watanabe PG (1981) Differentiation of the mechanisms of oncogenicity of 1,4-dioxane and 1,3-hexachlorobutadiene in the rat. *Toxicology and Applied Pharmacology*, 60:287–300.

Suh JH, Mohseni M (2004) A study on the relationship between biodegradability enhancement and oxidation of 1,4-dioxane using ozone and hydrogen peroxide. *Water Research*, 38(10):2596–2604.

Thiess AM, Tress E, Fleig I (1976) Results from an occupational medical investigation of employees exposed to dioxane. *Arbeitsmedizin, Sozialmedizin, Praeventivmedizin*, 11:36–46.

Tinwell H, Ashby J (1994) Activity of 1,4-dioxane in mouse bone marrow micronucleus assays. *Mutation Research*, 322:141–150.

Torkelson TR et al. (1974) 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. *Toxicology and Applied Pharmacology*, 30:287–298.

Yamazaki K et al. (1994) Two-year toxicological and carcinogenesis studies of 1,4-dioxane in F344 rats and BDF1 mice. In: *Proceedings of the Second Asia-Pacific Symposium on Environmental and Occupational Health*. Kobe, Japan, Kobe University, pp. 193–198.

Young JD et al. (1977) Pharmacokinetics of 1,4-dioxane in humans. *Journal of Toxicology and Environmental Health*, 3:507–520.

Young JD, Braun WH, Gehring PJ (1978) Dose-dependent fate of 1,4-dioxane in rats. *Journal of Toxicology and Environmental Health*, 4:709–726.

Zenker MJ, Borden RC, Barlaz MA (2003) Occurrence and treatment of 1,4-dioxane in aqueous environments. *Environmental Engineering Science*, 20(5):423–431.