WHO/SDE/WSH/03.04/109
English only

Dialkyltins in Drinking-water

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

Preface

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

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

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

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

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

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

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

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

Acknowledgements

Dialkyltins in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document published in the second edition of the Guidelines. The update was prepared by T. Nishimura, National Institute of Health Sciences, Japan, to whom special thanks are due.

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

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

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
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Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

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

CPVC	chlorinated polyvinyl chloride
DBTCl	dibutyltin dichloride
DBTDA	dibutyltin diacetate
DMTCl	dimethyltin dichloride
FPD	flame photometric detection
GC	gas chromatography
LD_{50}	median lethal dose
MBTCl	(mono)butyltin trichloride
PVC	polyvinyl chloride

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1. GENERAL DESCRIPTION

1.1 Identity

The organotins are a large class of compounds that differ in their properties and applications. They can be divided into four groups with the general formulas R_4Sn, R_3SnX, R_2SnX_2 and $RSnX_3$, where R is usually an organic group and X is an anion (e.g., chloride, fluoride, oxide or hydroxide). In the case of the compounds used as heat stabilizers, the alkyl group can be methyl, butyl, octyl or dodecyl, and the most common are produced by the reaction of mono- and dialkyltin chlorides with mercaptoesters to give thioglycolates.

This document concentrates on the mono- and disubstituted compounds. Although the trisubstituted compounds are found in the environment, they are highly lipophilic, and those that reach drinking-water sources appear to be removed by the removal of particulate matter. There appears to be little evidence that they are found in drinking-water. The document is primarily concerned with those organotins used as stabilizers in plastic pipes that may come into contact with drinking-water, and most of these are dialkyltin compounds.

1.2 Major uses

Of the various organotins, the monosubstituted, disubstituted and trisubstituted compounds are the most widely used, the first two being employed as heat stabilizers in the manufacture of PVC and CPVC plastics, including water pipes and some food packaging materials, and the latter in the preservation of materials (wood, stone, textiles), as fungicides, miticides and disinfectants, as bactericides in cooling water and in antifouling paints.

2. ANALYTICAL METHODS

Dibutyltins can be determined by extraction followed by derivatization to form hexylbutyltins, which are measured by gas chromatography–mass spectrometry or gas chromatography with flame photometric detection (GC-FPD). A detection limit of 1 ng/litre is reported (Greaves & Under, 1988). Similar detection limits are obtained when organotins are measured by preconcentration using a tropolene-loaded silica column, followed by ethylation, separation and detection by capillary GC-FPD (Mueller, 1987). Flame atomic absorption spectrometry, which has a detection limit of 0.1 mg/litre, is a common method. Flameless atomic absorption spectrometry, using atomization in an electric furnace with graphite, is more sensitive and has a detection limit of 0.1–1.0 µg/litre (IPCS, 1990).

Dioctyltin reacts with sodium tetrahydridoborate at pH 5 to produce volatile hydrides. The volatile hydrides are extracted with methylene chloride, then identified by high-performance liquid chromatography–electrospray induction–mass spectrometry and measured by FPD using the quartz surface-induced tin emission. Detection limits of <10 pg of dioctyltin have been achieved (Jiang et al., 1999).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Unknown quantities of organotins may be released into air from factories that produce polyurethane or PVC resins in which they are used as stabilizers; however, there appear to be no analytical data to support this assumption.

3.2 Water

There is evidence that organotin stabilizers leach into water from plastic pipes, although usually at very low concentrations; a dibutyltin sulfide concentration of 100 µg/litre was reported after a plastic pipe had been in contact with static water (Mazaev & Slepnina, 1973). However, studies by Health Canada (Forsyth & Jay, 1997) found levels of monobutyltin and dibutyltin in potable water in PVC and CPVC pipes in the ng/litre range. Studies by Sadiki & Williams (1996) and Sadiki et al. (1996) found that levels in the great majority of samples were below the limit of detection of 0.5 ng/litre; in a study of the tap water from five municipalities, only one positive sample was found out of 22 dwellings sampled. In a later study in Canada (Sadiki & Williams, 1999) of recently installed PVC pipe, very few positive samples were found. The maximum concentrations detected were 28.5 ng/litre for monobutyltin and 53 ng/litre for dibutyltin. Studies of leaching from organotin-stabilized PVC in fixed laboratory tests in Japan showed that the highest concentrations encountered were for monomethyltin in samples that had been conditioned for the shortest period, 7 days, and after 16 h stagnation. Concentrations fell steadily as the conditioning period increased. Lower concentrations of octyltin and dioctyltin were observed in some samples, but all other organotin species were below the detection limit of 0.01 µg/litre (Y. Magara, personal communication, 2003).

3.3 Food

Although there are data in the public domain regarding the levels of tributyltins in foodstuffs, there appear to be no data on levels of the mono- and disubstituted organotins in foodstuffs.

3.4 Estimated total exposure and relative contribution of drinking-water

It is difficult to assess human exposure to these compounds; however, on the basis of the data given above, it would appear that human exposure is likely to be very low. The contribution from drinking-water would appear to be considerably less than 1 µg/day.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The available data suggest that organotins are poorly absorbed (Duncan, 1980); for example, it was reported that only 20% of dioctyltin dichloride was absorbed in rats

(Penninks et al., 1987). Organotins tend to be primarily distributed in the liver and kidney following oral administration to rodents (Evans et al., 1979; Mushak et al., 1982). Low levels of dioctyltin dichloride have been found in the adrena1, pituitary and thyroid glands (Penninks et al., 1987). The mercaptoesters and carboxylates would be expected to cleave hydrolytically on contact with stomach acid to give the respective chlorides.

It appears that alkyltins are metabolized by dealkylation (Iwai et al., 1982). *In vitro*, tributyltin was metabolized to dibutyltin, hydroxybutyltins, butanol and butene (Kimmel et al., 1977), whereas di-, tri- and tetraethyltin appeared to form ethene and ethane (Wiebkin et al., 1982). Carbon dioxide and butene were detected as metabolites of both dibutyltin diethanoate and tributyltin ethanoate in mice *in vivo* (Kimmel et al., 1977).

After oral administration, it appears that the principal route of excretion of organotins is in the faeces (Evans et al., 1979). Bile is also a significant route for some compounds, such as tetraalkyltins (Iwai et al., 1982). For others, significant amounts are expired as carbon dioxide (Kimmel et al., 1977).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Acute oral LD_{50}s of dioctyltins in rodents range from 880 to 8500 mg/kg of body weight (Klimmer, 1969; Pelikan et al., 1970). The acute oral LD_{50} of dibutyltin dichloride in rats has been reported to be 100 mg/kg of body weight (Klimmer & Nebel, 1960).

5.2 Short-term exposure

Rats were fed diets containing dioctyltin dichloride at 0, 50 or 150 mg/kg (equivalent to 0, 2.5 and 7.5 mg/kg of body weight per day) for 6 weeks. The principal effect was a reduction in thymus weight at both dose levels. Lymphocyte depletion was observed in the thymus and the thymus-dependent areas of the spleen and lymph nodes (Seinen & Willems, 1976). A weekly oral dose of 500 mg/kg of body weight for 8 weeks reduced thymus weight and induced immunodeficiency in mice, whereas a dose of 100 mg/kg of body weight did not cause such effects (Miller et al., 1986).

Dibutyltin dichloride was fed to rats at 0, 10, 20, 40 or 80 mg/kg of diet (equivalent to 0, 0.5, 1, 2 or 4 mg/kg of body weight per day) for 90 days. Reduction in food intake, depressed growth and mild anaemia were noted at the highest dose level, but no treatment-related effects were observed at lower doses (Gaunt et al., 1968). A reduction in thymus weight and immunocompetence was observed in rats fed diets containing dioctyltin dichloride at 75 mg/kg (about 3.8 mg/kg of body weight per day) for 8 or 12 weeks (Miller & Scott, 1985).

5.3 Reproductive and developmental toxicity

There are several studies on the reproductive and developmental toxicity of monomethyltin, dimethyltin, dioctyltin, monobutyltin and dibutyltin in the literature. After successful mating, female Wistar rats were given dibutyltin dichloride (DBTCl) by gavage at 0, 3.8, 7.6 or 15.2 mg/kg of body weight per day on days 0–3 of pregnancy (Ema & Harazono, 2000). Decreased body weight gain in female rats and an increase in implantation failure and pre-implantation embryonic loss were found at 7.6 mg/kg of body weight per day and higher. DBTCl caused the suppression of uterine decidualization and a decrease in serum progesterone levels in pseudopregnant rats at doses that induced implantation failure (Harazono & Ema, 2003). These findings suggested that a decline in progesterone levels caused the suppression of uterine decidualization and impairment of uterine function, and these effects were responsible for the DBTCl-induced implantation failure. DBTCl was given to female Wistar rats by gavage at 0, 2.5, 5.0, 7.5 or 10.0 mg/kg of body weight per day on days 7–15 of pregnancy (Ema et al., 1991). Maternal toxicity, decreases in body weight gain and decreases in food consumption were observed at 7.5 mg/kg of body weight per day and higher, and an increase in the incidence of fetuses with malformations, such as cleft jaw, ankyloglossia, defect of the mandible, fusion of the ribs and deformity of the vertebral column, was found at 5.0 mg/kg of body weight per day and higher. Following maternal exposure to DBTCl in rats, developing offspring were not susceptible to teratogenic effects of DBTCl on day 6; day 7 was the earliest susceptible period, day 8 was the highest susceptible period and day 9 was no longer a susceptible period for teratogenesis of DBTCl (Ema et al., 1992). However, Farr et al. (2001) reported that maternal toxicity, including decreased food consumption, body weight gain and thymus weight, but not a significant increase in the incidence of fetuses with malformations, was found at 10.0 mg/kg of body weight per day in Wistar rats after administration of DBTCl by gavage at 0, 1.0, 2.5, 5.0 or 10.0 mg/kg of body weight per day on days 6–15 of pregnancy. DBTCl had dysmorphogenic effects in rat embryos in a whole-embryo culture system (Ema et al., 1995a, 1996). Pregnant Wistar rats were treated orally with dibutyltin diacetate (DBTDA) at 0, 1.7, 5.0 or 15 mg/kg of body weight per day on days 0–19 of pregnancy (Noda et al., 1988). Decreased thymus weight in dams and an increased incidence of fetuses with malformations, such as mandible dysplasia, ankyloglossia and schistoglossia, were detected at 15 mg/kg of body weight per day. A critical pregnant day for teratogenesis from DBTCl was reported to be day 8 of pregnancy in rats (Noda et al., 1992a). After administration of DBTCl, DBTDA, dibutyltin maleate, dibutyltin oxide and dibutyltin dilaurate by gavage on day 8 of pregnancy in rats, no differences in the types of malformations or teratogenic potential were noted between the five dibutyltins with different anions (Noda et al., 1993). These data suggested the importance of the dibutyl group rather than the anionic group in the teratogenicity of dibutyltins. When dimethyltin dichloride (DMTCl) was given to Wistar rats by gavage at 0, 5, 10, 15 or 20 mg/kg of body weight per day on days 7–17 of pregnancy, DMTCl was maternally toxic, but not teratogenic, at 20 mg/kg of body weight per day (Noda & Morita, 1994). Although butyltin trichloride (MBTCl) did not show any signs of maternal or developmental toxicity when administered on days 7–17 of pregnancy by gavage at 400 mg/kg of body weight per day in rats (Noda et al., 1992b), MBTCl was

maternally, but not developmentally, toxic in rats when administered on days 7–8 of pregnancy by gavage at 1000 mg/kg of body weight per day (Ema et al., 1995b). In a study of the octyltin stabilizer ZK 30.424, which is a mixture of 80% dioctyltin diisothioglycolate and 20% monooctyltin triisooctylthioglycolate, administered by gavage to NMRI mice at 0, 20, 30, 45, 67 or 100 mg/kg of body weight per day on days 6–17 (plug = day 1) of pregnancy, Faqi et al. (2001) observed an increased incidence of embryonic resorptions and fetuses with cleft palate and reduced fetal weight at 67 mg/kg of body weight per day and higher and decreased weights of the liver and thymus in dams and increased incidence of fetuses with exencephaly at 100 mg/kg of body weight per day.

Noland et al. (1982) reported that monomethyltin trichloride given to female rats in drinking-water at 12, 40 or 120 mg/litre induced significant increases in extinction learning ability in pups at 11 days. At 120 mg/litre, the pups also displayed significantly increased acquisition time. At 21 days, pups displayed higher escape times than controls at 12 and 120 mg/litre but not 40 mg/litre.

5.4 Mutagenicity and related end-points

Dioctyltin dichloride gave negative results in the Ames test and in tests for the induction of unscheduled DNA synthesis in primary cultures of rat hepatocytes (Westendorf et al., 1986). No evidence of mutagenicity was found for dibutyltin diethanoate in the Ames test (Tennant et al., 1986). Sato et al. (1992) found positive results for DBTCl in the IMF test, SOS chromotest and rec assay, while DMTCl was positive only in the SOS chromotest. DBTCl and dioctyltin dichloride have been reported to give positive results in mammalian cell mutation assays *in vitro* in the absence of metabolic activation (Li et al., 1982; Westendorf et al., 1986), and dibutyltin sulfide increased the incidence of chromosomal aberrations in rat bone marrow cells *in vivo* (Mazaev & Slepnina, 1973). Dimethyltin and dibutyltin were reported not to induce aneuploidy in human peripheral lymphocytes *in vitro* (Jensen et al., 1991).

5.5 Carcinogenicity

F344 rats and B6C3F1 mice were fed diets containing dibutyltin diethanoate at 66.5 or 133 mg/kg (rats) and 76 or 152 mg/kg (mice) for 78 weeks. Non-significant increased incidences of hepatocellular adenomas in female mice and both hepatocellular adenomas and carcinomas in male mice were noted (NCI, 1979).

Rats were fed a mixture of octyltin trichloride and dioctyltin dichloride in the diet at doses equivalent to approximately 0.3, 0.7, 2.3 and 6.0 mg/kg of body weight per day for 2 years. A highly significant increased frequency of primary tumours of the thymus, especially thymic lymphomas, was noted in females in the highest dose group. The females also showed an increased incidence of generalized malignant lymphomas, as did the males in the two higher dose groups, although there seemed to be an unusually low incidence of such tumours in the control groups. In animals

treated at the lower dose levels, no increase in the incidence of primary thymic tumours or generalized malignant lymphomas was observed (US EPA, 1988).

6. EFFECTS ON HUMANS

There are no adequate studies of the effects of dialkyltins on humans.

7. CONCLUSIONS

The mono- and disubstituted compounds that may leach from PVC water pipes for a short time after installation are primarily immunotoxins; although they appear to be of low general toxicity, some are developmental toxins in rodents. The data available are insufficient to permit the proposal of guideline values for individual dialkyltins or the mono derivatives, although the concentrations observed in drinking-water are several orders of magnitude lower than the doses reported to cause developmental effects in rats and mice.

There appear to be no data on the removal of dialkyltins in water treatment. However, these are not normally considered to be raw water contaminants of significance. Leaching of dialkyltins and the mono derivatives used as stabilizers in PVC and CPVC is normally controlled by product specification.

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