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Temephos in Drinking-water: Use for Vector Control in Drinking-water Sources and Containers

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

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Preface

One of the primary goals of the World Health Organization (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 third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

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, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

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.

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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 fourth edition:

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Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
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Professor Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held on 19–23 June 2008. 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 at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, WHO Pesticide Evaluation Scheme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. 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 comments are greatly appreciated.

Acronyms and abbreviations used in the text

ADI	acceptable daily intake
ARfD	acute reference dose
CAS	Chemical Abstracts Service
FAO	Food and Agriculture Organization of the United Nations
GDWQ	*Guidelines for Drinking-water Quality*
IUPAC	International Union of Pure and Applied Chemistry
K_{ow}	octanol–water partition coefficient
LD_{50}	median lethal dose
MOE	margin of exposure
NOAEL	no-observed-adverse-effect level
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

Chemical Abstracts Service (CAS) Registry No.: 3383-96-8
Molecular formula: $C_{16}H_{20}O_6P_2S_3$

The International Union for Pure and Applied Chemistry (IUPAC) name for temephos is *O*,*O*,*O*',*O*'-tetramethyl *O*,*O*'-thiodi-*p*-phenylene bis(phosphorothioate).

1.2 Physicochemical properties

Some important physical and chemical properties of temephos are summarized in Table 1.

Table 1: Physicochemical properties of temephos (WHO, 2005)

Property	Value
Melting point	30–30.5 °C
Water solubility	30 µg/l at 25 °C
Log octanol–water partition coefficient (log K_{ow})	4.91 at 25 °C
Vapour pressure	8×10^{-6} Pa at 25 °C (extrapolated)

1.3 Major uses and sources in drinking-water

Temephos is a non-systemic organophosphorus insecticide, mainly used as a larvicide to control mosquitoes, including in domestic water containers and those used for storing drinking-water.

Two formulations of temephos have been evaluated by the WHO Pesticide Evaluation Scheme (WHOPES) for mosquito larviciding (WHO, 2006). WHO specifications for quality control and international trade have been published for the two formulations: emulsifiable concentration (EC) and granule (GR) formulations (WHO, 2008a). Only the granule formulation is used for mosquito larviciding in potable water at a dosage not exceeding 1 mg/l of the active ingredient.

WHO specifications for formulations, unless otherwise stated, encompass the products of all formulators legitimately able to certify that their products contain only active ingredient sourced from a manufacturer to whom the WHO specification for technical material/technical concentrate applies. Buyers and/or regulatory authorities should demand such certification and ensure both that it is valid and that the products fully comply with the physical and chemical requirements of the WHO specifications. The safety of the formulants used in making the final product should be considered by national authorities for products intended for use in potable water.

1.4 Environmental fate

Temephos has a relatively high log K_{ow} and, as would be expected, adsorbs to particles, sediment and the sides of containers (Bowman et al., 1968; Miles and Dale, 1975; Hughes et al., 1980). It appears to be rapidly degraded under field conditions

(Lacorte, Ehresmann & Barcelo, 1996). The primary means of degradation are sunlight and microbial action (USEPA, 2001). In order to extend the half-life of temephos in water in containers, it would therefore be appropriate to exclude sunlight. The major transformation products of temephos are temephos sulfoxide and temephos sulfone, which are more water soluble than temephos. Studies on granular formulations of temephos showed that water concentrations were very low when granules with percentage levels of Abate® or technical temephos were applied to water (Cilek, Webb & Knapp, 1991). In a field study of drinking-water in containers with temephos simply adsorbed onto sand, a temephos dose of 1 mg/l resulted in concentrations that did not appreciably increase above 0.5 mg/l through the trial period, even following retreatment at 3- and 6-week intervals (Laws et al., 1968).

2. HUMAN EXPOSURE

It is expected that exposure of the public through either food or drinking-water would be low. However, there is a potential for direct exposure through drinking-water when temephos is directly applied to drinking-water storage containers.

3. TOXICOLOGICAL SUMMARY[1]

When given to rats as an oral dose, temephos was rapidly absorbed. At least 40% of the administered dose was absorbed into the blood plasma. Clearance was rapid (mostly within 48 h), with about 40% of an orally administered dose being excreted in the urine and about 60% recovered in the faeces. Very little of the orally administered dose remained in tissues, but most (about 3% of the administered material) was in adipose tissue. Metabolism in rats is by *S*-oxidation to form the primary toxicant, temephos sulfoxide, and by carboxylesterase-mediated hydrolysis to form 4,4′-thiodiphenol. Temephos and these primary metabolites can undergo secondary metabolism by glucuronidation or sulfation to form conjugates.

Temephos was of low acute oral toxicity in rats (median lethal dose [LD_{50}], 4000–13 000 mg/kg body weight) and mice (LD_{50}, 2062 mg/kg body weight). Temephos did not cause irritancy to rabbits' eyes or to the skin of rabbits or guinea-pigs. It was not a skin sensitizer when tested on guinea-pigs in the Buehler test. In short-term studies with temephos administered in the diet or by gavage in rats (28–92 days), rabbits (30–35 days) and dogs (90–129 days), acetylcholinesterase activity in erythrocytes and, in some instances, in the brain was measured, and animals were observed for clinical signs. The overall no-observed-adverse-effect level (NOAEL) for clinical signs was 10 mg/kg body weight per day, as derived from a study in rats treated by gavage for 28 and 44 days and from a study in rabbits treated by gavage for 35 days. This NOAEL is supported by the absence of clinical signs at 5.4 and 30 mg/kg body weight per day, the highest doses tested, in the multigeneration study in rats and in a study of developmental toxicity in rabbits treated by gavage, respectively. Additional support is provided by the presence of mild signs in dogs given diets containing temephos at a concentration of 500 mg/kg diet for about 11 weeks, approximately equivalent to 25 mg/kg body weight per day. The NOAEL for biologically significant (i.e. 20% greater than control values) inhibition of brain

[1] After FAO/WHO (2006). The interested reader should consult WHO (2008b) for more detailed information and primary references.

acetylcholinesterase activity was 54 mg/kg diet (2.3 mg/kg body weight per day) in a 90-day dietary study in rats. In a 90-day dietary study in dogs, “marked” inhibition (no control values provided) in brain and >95% inhibition of erythrocyte acetylcholinesterase activity were reported after treatment at 500 mg/kg diet (25 mg/kg body weight per day), and there was no inhibition of erythrocyte acetylcholinesterase activity at 18 mg/kg diet (about 1 mg/kg body weight per day). The overall NOAEL for biologically significant (i.e. 20% greater than control values) inhibition of erythrocyte acetylcholinesterase activity was 1.8 mg/kg body weight per day in a 99-day dietary study in rats. Occasional and inconsistent reductions of erythrocyte acetylcholinesterase activity observed at lower doses in some studies in rats were not considered to be significant. The Meeting noted that between 80% and more than 90% inhibition of erythrocyte acetylcholinesterase activity was not associated with clinical signs of cholinergic toxicity in a 99-day dietary study in rats or in a limited 129-day dietary study in dogs, and this suggested that inhibition of erythrocyte acetylcholinesterase activity was not an appropriate indicator of inhibition of the activity of acetylcholinesterase in the peripheral nervous system. Consequently, the Meeting considered that the critical end-point for human risk assessment was inhibition of brain acetylcholinesterase activity, and the NOAEL was 2.3 mg/kg body weight per day.

In a study in human male volunteers who were prisoners, 10 men were given temephos at a dose of 1.1 mg/kg body weight per day for 4 weeks, and 9 men took temephos at a dose of 4.27 mg/kg body weight per day for 5 days. There was no inhibition of cholinesterase activity in the plasma or in erythrocytes.

This study in human volunteers who were prisoners was considered to be ethically acceptable according to the standards of the time it was performed (1967), although it would not be acceptable by current standards applied to new studies. The Meeting considered that the doses and the outcomes in this study in humans were not sufficiently well described for the results of this study to be used in isolation to set an acceptable daily intake (ADI) or an acute reference dose (ARfD).

Hepatotoxicity was inconsistently seen in a series of briefly reported experiments in rabbits. However, there was no evidence of any hepatotoxicity at doses of up to 30 mg/kg body weight per day in a well-conducted and well-reported study of developmental toxicity in rabbits. In a long-term combined study of toxicity and oncogenicity in rats, no adverse effects on neoplastic or non-neoplastic pathology were found at any dietary dose tested, up to the highest dose of 15 mg/kg body weight per day. Cholinesterase activities were not measured in this study.

Temephos gave uniformly negative results in an adequate range of tests for genotoxicity in vitro and in vivo. The Meeting concluded that temephos is unlikely to be genotoxic. Studies of reproductive toxicity in rats showed that temephos did not adversely affect reproduction when given as oral doses of up to 125 mg/kg diet (5.4 mg/kg body weight per day) for up to three generations. In a one-generation study, temephos at a dose of 500 mg/kg diet (22.5 mg/kg body weight per day) inhibited erythrocyte cholinesterase in mothers (90%) and in 21-day-old pups (30%), but other doses were not tested. There was no developmental toxicity or hepatotoxicity in rabbits given temephos at oral doses of up to 30 mg/kg body weight per day.

Studies in hens showed that temephos did not have the potential to cause organophosphate-induced delayed neuropathy and did not cause demyelination of nerves. Although, for the purposes of vector control, temephos is used at a concentration of up to 1 mg/l in drinking-water, only one report of an investigation of possible effects in exposed people was available. Approximately 2000 people were exposed to drinking-water containing temephos for 19 months without any adverse effects on plasma or erythrocyte cholinesterase activity. No illness attributable to the treatment was seen, and all eight babies born during the study period were normal. The drinking-water was treated monthly with temephos. The intended concentration of 1 mg/l was not achieved, and only one sample contained temephos at a concentration of more than 0.5 mg/l.

Temephos is recommended by WHO for addition to potable water as a larvicide treatment at an application rate not exceeding 1 mg/l. Assuming that an adult weighing 60 kg would consume 2 litres/day of drinking-water containing temephos at 1 mg/l, this would be equal to an oral exposure of 0.033 mg/kg body weight. However, given the limited solubility of temephos in water, incomplete dissolution in drinking-water would be expected, and this could result in actual exposures being appreciably less than this estimate. Consequently, 0.033 mg/kg body weight per day was regarded as a worst-case upper limit of exposure. Some of the studies that were critical to the assessment were of poor quality. The Meeting considered that the database was insufficiently robust to serve as the basis for establishing an ADI or an ARfD for temephos.

The Meeting concluded that the relevant NOAEL for human risk assessment is 2.3 mg/kg body weight per day on the basis of inhibition of brain acetylcholinesterase activity in rats. This NOAEL provides a margin of exposure (MOE) from the estimated oral exposure derived from drinking-water treated with temephos of about 70. The MOE for clinical signs and the (possibly secondary) effects on development and reproduction are in the range of >160 (highest dose tested in rat multigeneration study) to 900 (study of developmental toxicity in rabbits). In addition, reassurance is provided by the MOEs of 130 and 33 based on the absence of clinical signs and erythrocyte cholinesterase inhibition in the poorly described study in volunteers treated for 5 or 14 days, respectively.

In an early trial with temephos to control *Aedes aegypti* in drinking-water in containers, carried out with about 2000 persons, there were no apparent health effects in the volunteers over a period of 19 months, during which they were closely observed (Laws et al., 1968).[2]

4. PRACTICAL ASPECTS

4.1 Analytical methods and analytical achievability

Temephos can be extracted using liquid–liquid extraction or a solid-phase extraction method. Temephos is analysed by liquid chromatography and thermospray mass spectrometry coupled with online solid-phase extraction with a C18 cartridge. The limit of detection and the linear range of the calibration curve are 0.038 µg/l and

[2] This study was not included in FAO/WHO (2006).

0.050–2 µg/l, respectively (Lacorte & Barcelo, 1995). Temephos can also be analysed by high-performance liquid chromatography with either an ultraviolet detector or a triple-stage quadrupole mass spectrometry detector after condensation. Mass spectrometric detection is done using an electrospray ionization source in positive ionization mode. In this method, the limit of detection is 0.028 µg/l (Ontario Ministry of the Environment, 2008). Gas chromatography with a nitrogen–phosphorus detector is used for analysis of temephos (USEPA, 1995).

4.2 Removal from water

The proposed use is unlikely to result in contamination of public water supplies, although there may be a requirement to reduce levels in some storage containers. No specific information is available on removal of temephos during water treatment. However, the low aqueous solubility and high octanol–water partition coefficient (30 µg/l and 4.9, respectively; WHO, 2005) suggest that temephos should be removed by adsorption onto activated carbon and possibly removed during coagulation.

4.3 Use for vector control in drinking-water sources

Temephos is one of the compounds recommended by WHO for mosquito larvicide treatment in potable water at an application rate not exceeding 1 mg/l.

Formulations of temephos used for vector control in drinking-water in containers should always be those approved for such a use, and users should carefully follow the recommendations for use (WHO, 2005, 2006, 2008a).

5. CONCLUSIONS

It is not appropriate to set a formal guideline value for temephos used as a vector control agent in drinking-water. The NOAEL for human risk assessment for temephos is 2.3 mg/kg body weight per day, as determined by the Joint FAO/WHO Meeting on Pesticide Residues in 2006 (FAO/WHO, 2006), giving an acceptable daily intake (ADI) of 0.023 mg/kg body weight with an uncertainty factor of 100. Young animals do not appear to be significantly more sensitive than adults, and exposure from food is considered to be low. Where temephos is used for vector control in potable water, this will involve less than lifetime exposure. The maximum dosage in drinking-water of 1 mg/l would be equivalent to approximately 0.033 mg/kg body weight, compared with the ADI of 0.023 mg/kg body weight for a 60 kg adult drinking 2 litres of water per day. The exposure for a 10 kg child drinking 1 litre of water would be approximately 0.1 mg/kg body weight; for a 5 kg bottle-fed infant, the exposure would be approximately 0.15 mg/kg body weight, compared with the ADI of 0.023 mg/kg body weight. However, the low solubility and the high log K_{ow} of temephos indicate that it will not remain in solution at the maximum recommended applied dose, and the use of a slow-release formulation means that actual levels of exposure will be much lower than those calculated and are likely to be much less than half of the concentration if all the applied dose is in solution. This means that exposure is unlikely to exceed the ADI.

6. RECOMMENDATIONS

WHO specifications for formulations, unless otherwise stated, encompass the products of all formulators legitimately able to certify that their products contain only active ingredient sourced from a manufacturer to whom the WHO specification for technical material/technical concentrate applies. Buyers and/or regulatory authorities should demand such certification and ensure both that it is valid and that the products fully comply with the physical and chemical requirements of the WHO specifications. This is particularly important for pesticide formulations to be used in drinking-water in containers, in view of the importance of slow-release formulations and the direct exposure of humans.

National authorities, in approving products for use in drinking-water in containers, should ensure that any formulations are appropriate to deliver concentrations of active ingredient that are below the ADI, taking into account possible exposure from other sources, such as food, and that are maintained for the expected duration to be consistent with efficacy.

In setting local guidelines or standards, health authorities should take into consideration the potential for higher rates of water consumption in the area or region under consideration. Consideration should be given to using alternative sources of water for small children and bottle-fed infants for a period after an application of temephos, where this is considered appropriate and is practical. However, the ADI is unlikely to be exceeded, and, in the event of an exceedance, this does not necessarily mean that adverse effects will result. Indeed, the use of the slow-release formulation will result in much lower concentrations than the recommended dose of 1 mg/l and actual exposures lower than the theoretical exposures calculated above. The diseases spread by vectors are significant causes of morbidity and mortality. It is therefore important to achieve an appropriate balance between the intake of the pesticide from drinking-water and the control of disease-carrying insects.

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