Methoxychlor 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

The work of the following coordinators was crucial in the development of this background document for development of WHO Guidelines for Drinking-water Quality:

- J.K. Fawell, Water Research Centre, United Kingdom (inorganic constituents)
- U. Lund, Water Quality Institute, Denmark (organic constituents and pesticides)
- B. Mintz, Environmental Protection Agency, USA (disinfectants and disinfectant by-products)

The WHO coordinators were as follows:

**Headquarters:**
- H. Galal-Gorchev, International Programme on Chemical Safety
- R. Helmer, Division of Environmental Health

**Regional Office for Europe:**
- X. Bonnefoy, Environment and Health
- O. Espinoza, Environment and Health

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

The efforts of all who helped in the preparation and finalization of this document, including those who drafted and peer reviewed drafts, are gratefully acknowledged.

The convening of the experts meetings was made possible by the financial support afforded to WHO by the Danish International Development Agency (DANIDA), Norwegian Agency for Development Cooperation (NORAD), the United Kingdom Overseas Development Administration (ODA) and the Water Services Association in the United Kingdom, the Swedish International Development Authority (SIDA), and the following sponsoring countries: Belgium, Canada, France, Italy, Japan, Netherlands, United Kingdom and USA.
Acronyms and abbreviations used in the text

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>(p,p')-dichlorodiphenyltrichloroethane</td>
</tr>
<tr>
<td>DMDD</td>
<td>dimethoxydiphenyldichloroethane</td>
</tr>
<tr>
<td>DMDE</td>
<td>1,1-bis(4-methoxyphenyl)-2,2-dichloroethene</td>
</tr>
<tr>
<td>DMDT</td>
<td>1,1,1-trichloro-2,2-bis(4-methoxyphenyl)ethane</td>
</tr>
<tr>
<td>HSDB</td>
<td>Hazardous Substances Data Bank</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>IRIS</td>
<td>Integrated Risk Information System</td>
</tr>
<tr>
<td>LD(_{50})</td>
<td>median lethal dose</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>NADPH</td>
<td>reduced nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
</tr>
<tr>
<td>TDI</td>
<td>tolerable daily intake</td>
</tr>
</tbody>
</table>
Table of contents

1. GENERAL DESCRIPTION ...................................................................................... 1
   1.1 Identity ................................................................................................................. 1
   1.2 Physicochemical properties ................................................................................. 1
   1.3 Organoleptic properties ....................................................................................... 1
   1.4 Major uses ............................................................................................................ 1
   1.5 Environmental fate ............................................................................................ 1

2. ANALYTICAL METHODS ..................................................................................... 2

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE.................................. 2
   3.1 Air ........................................................................................................................ 2
   3.2 Water .................................................................................................................... 2
   3.3 Food ..................................................................................................................... 2
   3.4 Estimated total exposure and relative contribution of drinking-water................. 2

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS ...................................................................................................................... 3

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS.... 3
   5.1 Acute exposure ..................................................................................................... 3
   5.2 Short-term exposure ............................................................................................. 3
   5.3 Long-term exposure ............................................................................................. 3
   5.4 Reproductive toxicity, embryotoxicity, and teratogenicity.................................. 3
   5.5 Mutagenicity and related end-points .................................................................... 4
   5.6 Carcinogenicity .................................................................................................... 4

6. EFFECTS ON HUMANS .......................................................................................... 5

7. GUIDELINE VALUE ............................................................................................... 5

8. REFERENCES .......................................................................................................... 5
1. GENERAL DESCRIPTION

1.1 Identity

CAS No.: 72-43-5
Molecular formula: C_{16}H_{15}Cl_{3}O_{2}

Methoxychlor is the common name for 1,1,1-trichloro-2,2-bis(4-methoxyphenyl)ethane. Other names include methoxy-DDT and DMDT. Technical methoxychlor contains about 88% of the \( p,p' \)-isomer together with more than 50 structurally related contaminants, including 1,1,1,2-tetrachloro-2-\( p \)-(4-methoxyphenyl)ethane, \( o,o' \)-dimethoxydiphenyltrichloroethane, \( o,o' \)-dimethoxydiphenyldichloroethane, 1,1-bis(4-methoxyphenyl)-2,2-dichloroethene (DMDE) and \( o,p' \)-dimethoxydiphenyldichloroethene (1,2).

1.2 Physicochemical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical state</td>
<td>Light yellow crystals</td>
</tr>
<tr>
<td>Melting point</td>
<td>78 °C or 86–88 °C (dimorphisms)</td>
</tr>
<tr>
<td>Boiling point</td>
<td>Decomposes</td>
</tr>
<tr>
<td>Water solubility</td>
<td>0.1 mg/litre at 25 °C</td>
</tr>
<tr>
<td>Log octanol–water partition coefficient</td>
<td>3.05–4.30</td>
</tr>
<tr>
<td>Density</td>
<td>1.41 g/cm(^2) at 25 °C</td>
</tr>
</tbody>
</table>

1.3 Organoleptic properties

Methoxychlor has a light fruity smell (1). Its odour threshold in water is 4.7 mg/litre.\(^1\)

1.4 Major uses

Methoxychlor is used as an insecticide to protect vegetables, fruit, trees, fodder cereals, farm animals and pets against a variety of pests (3).

1.5 Environmental fate

Methoxychlor residues may persist in top soil for up to 14 months. Anaerobic biodegradation results mainly in dimethoxydiphenyltrichloroethane (DMDD) and the mono- and dihydroxy (demethylated) derivatives of methoxychlor and DMDD. Half-lives range from 1 week to 2 months. Aerobic degradation is much slower; half-lives are longer than 3 months. Methoxychlor may undergo indirect photolysis on the soil surface. The half-life for chemical hydrolysis in humid soils is about 1 year.\(^2\)

---

\(^1\) Hazardous Substances Data Bank (HSDB), Bethesda, MD, National Library of Medicine.
\(^2\) HSDB, Bethesda, MD, National Library of Medicine.
METHOXYCHLOR IN DRINKING-WATER

In water, methoxychlor can be degraded to DMDE by ultraviolet light (4). The main route of disappearance from the water phase is volatilization; the half-life for volatilization from shallow waters is 4.5 days.3 Methoxychlor is adsorbed onto suspended solids or sediment. In sediments, the same biodegradation products form under anaerobic conditions as in soil. Methoxychlor may be ingested by some aquatic organisms and bioaccumulated, except in fish, which quickly metabolize it (4).

2. ANALYTICAL METHODS

Methoxychlor is determined by a liquid–liquid extraction/gas chromatographic procedure. The sensitivity is 0.001–0.01 µg of methoxychlor per litre for single-component pesticides and 0.05–1.0 µg of methoxychlor per litre for multiple-component pesticides for a 1-litre sample and electron capture detection (5).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Methoxychlor has been detected at a concentration of 254 ng/m³ in the ambient air near a pesticide plant in southern California, USA.4

3.2 Water

Although methoxychlor is poorly soluble in water, it has been found in surface water, groundwater and drinking-water. Only 1 out of 71 groundwater samples from rural areas contained methoxychlor at 0.09 µg/litre, but concentrations of up to 50 µg/litre were detected in both surface water and groundwater close to agricultural areas where it was applied (5). Drinking-water in two rural areas in the USA was reported to contain methoxychlor at concentrations of up to 312 µg/litre (mean 33 ng/litre) and 100 µg/litre (mean 23 ng/litre), respectively.5

3.3 Food

In studies performed in the USA from 1982 to 1985, the estimated daily intake of methoxychlor from food was 99 ng for men aged 25–30 years (1).

3.4 Estimated total exposure and relative contribution of drinking-water

The estimated total exposure will generally be less than 1 µg/person per day. Significant contributions may be made by drinking-water, but this is rare.

3 HSDB, Bethesda, MD, National Library of Medicine.
4 HSDB, Bethesda, MD, National Library of Medicine.
5 HSDB, Bethesda, MD, National Library of Medicine.
4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Although methoxychlor is absorbed from the gastrointestinal tract, it does not accumulate in mammalian tissues (6). Body stores built up during periods of continuous exposure are cleared within a few weeks after cessation of exposure. Excretion in faeces exceeds that in urine (7).

In the presence of liver microsomes and NADPH, methoxychlor is oxidatively demethylated to form formaldehyde and phenolic metabolites (8–10). This reaction is not a precondition of the covalent binding of methoxychlor to the microsomal cytochrome P-450 (9). The phenolic metabolites competitively inhibit the binding of estradiol to its receptor; methoxychlor, like most of its technical impurities, is considered to be a proestrogen (1).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Reported LD₅₀s for mammals are generally higher than 2 g/kg of body weight (1). The main effects of single high exposures are disturbances of glycogen metabolism (11) and fatty degeneration of organs (12).

5.2 Short-term exposure

A NOAEL of 140 mg/kg of body weight per day for testicular atrophy was reported in a 30- to 45-day study on rats (13). In a 56-day study, a LOAEL of 25 mg of methoxychlor per kg of body weight per day increased pituitary prolactin levels in rats, an early effect of methoxychlor on the reproductive system (14).

5.3 Long-term exposure

Chronic toxicity tests on rats and mice exposed to technical-grade methoxychlor during a 78-week period revealed NOAELs of 70 and 450 mg/kg of body weight per day, respectively (15). In rats fed methoxychlor at up to 80 mg/kg of body weight per day for 2 years, tumours occurred at a similar frequency as in controls. The main effect observed at higher doses was growth retardation (16). Pigs and dogs seemed to be less sensitive than rats and mice (17).

5.4 Reproductive toxicity, embryotoxicity, and teratogenicity

Methoxychlor reduced the weight of testicles, prostate and seminal vesicles in rats (18) and disturbed spermatogenesis in sheep and rats (19,20). In a two-generation
METHOXYCHLOR IN DRINKING-WATER

study with rats, maternal toxicity and various effects on reproductive functions were seen after repeated exposure of dams to 50 mg of methoxychlor per kg of body weight per day (LOAEL) (21). Fetal effects (deformed ribs) occurred only at higher doses (22).

Methoxychlor accelerates the displacement of developed embryos from the ovaries to the uterus (23). This can occur in rats at exposures as low as 25 mg/kg of body weight per day (LOAEL) (24).

A tentative maternal NOAEL of 5 mg of methoxychlor per kg of body weight per day was established in pregnant rabbits that lost their litters and exhibited reduced weight gain at or above 35 mg/kg of body weight (25). The high incidence of lung agenesis in all fetuses of all dose groups was unusual.8

5.5 Mutagenicity and related end-points

Negative results were reported in various mutagenicity assays with or without metabolic activation.9 A weakly positive cell transformation response was obtained only with BALB/3T3 cells (7).

5.6 Carcinogenicity

Although increases in adenomas in rats (A.A. Nelson, O.G. Fitzburgh, personal communication, 1951) and in total tumour numbers in rats (16,26) have been reported, they were considered to be insignificant.10 A significant increase in hepatocellular carcinomas in male and female rats together with a significant increase in ovarian carcinomas was reported (27), but there is some doubt regarding the statistical evaluation (7). Studies on Osborne-Mendel rats and B6C3F1 mice may indicate the potential carcinogenicity of methoxychlor (15) but are inadequate because of the lack of satisfactory histopathological investigations.

Some positive evidence is provided by a 2-year study in which mice were given 750 mg of technical methoxychlor per kg of feed (27; K.J. Davis, personal communication, 1969). Higher incidences of liver tumours occurred compared with control animals. The males exhibited more testicular tumours and tumours of higher malignancy than the respective control animals.

Methoxychlor is likely to be a tumour promoter because it disturbs the metabolic cooperation between 6-thioguanidine-sensitive and -resistant V79-cells (28).

8 IRIS data file, Cincinnati, OH, US Environmental Protection Agency.
9 IRIS data file, Cincinnati, OH, US Environmental Protection Agency.
10 IRIS data file, Cincinnati, OH, US Environmental Protection Agency.
6. EFFECTS ON HUMANS

A single dose of 2 mg/kg of body weight was without effect on liver, testicles or small intestine (29). Doses of 0.5, 1.0 or 2.0 mg/kg of body weight per day administered orally to men and women over periods of 4–6 weeks (30) and 6–8 weeks (17) were without effect on body weight and several biochemical parameters. Tissue damage did not occur. The menstrual cycle and the volume of ejaculation were not affected, although a shortening of the neck of spermatozoa was observed in the first study (30).

7. GUIDELINE VALUE

In 1979, IARC assigned methoxychlor to Group 3 (31). Subsequent data suggest a carcinogenic potential of methoxychlor for liver and testis in mice, which may be due to the hormonal activity of proestrogenic metabolites of methoxychlor and may therefore have a threshold. The study, however, was inadequate because only one dose was used and because this dose may have been above the maximum tolerated dose (27). The genotoxic potential of methoxychlor appears to be negligible. It may be a tumour promoter.

The database for studies on long-term, short-term and reproductive toxicity is inadequate. A teratology study in rabbits reported a systemic NOAEL of 5 mg/kg of body weight per day (25), which is lower than the NOAELs and LOAELs from other studies. This NOAEL was therefore selected for use in the derivation of a TDI. Using this NOAEL and applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for concern for threshold carcinogenicity and the limited database), a TDI of 5 µg/kg of body weight can be calculated. Allocation of 10% of the TDI to drinking-water results in a guideline value of 20 µg/litre (rounded figure).

8. REFERENCES


11 Also based on data from IRIS data file, Cincinnati, OH, US Environmental Protection Agency.


