Endosulfan 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

Acronyms and abbreviations used in the text

ADI	acceptable daily intake
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
CAS	Chemical Abstracts Service
FAO	Food and Agriculture Organization of the United Nations
IPCS	International Programme on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
NOAEL	no-observed-adverse-effect level
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	115-29-7
Molecular formula:	$C_9H_6Cl_6O_3S$

The chemical name of endosulfan is 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide. Technical endosulfan is a brown crystalline substance consisting of α- and β-isomers in the ratio of approximately 70:30. Endosulfan's chemical structure is shown below:
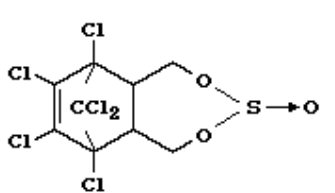
1.2 Physicochemical properties

Technical endosulfan is usually sold in the form of brown crystalline flakes.

Property	Value
Melting point	79–100 °C
Vapour pressure	1.3×10^{-3} Pa at 25 °C
Solubility in water	60–150 µg/litre; increases with decreasing pH

1.3 Major uses

Endosulfan is a contact and stomach poison that has been used to control insects such as the Colorado potato beetle, flea beetle, cabbageworm, peach tree borer and tarnished plant bug, as well as several species of aphid and leafhopper. It is used in countries throughout the world to control pests on fruit, vegetables and tea and on non-food crops such as tobacco and cotton. In addition to its agricultural use and its use in the control of the tsetse fly, endosulfan is used as a wood preservative and for the control of home garden pests (IPCS, 1984).

1.4 Environmental fate

Both endosulfan isomers undergo photolysis upon exposure to sunlight. The half-life is about 7 days. Endosulfan diol is the primary photolysis product; it is subsequently degraded to endosulfan α-hydroxy ether (ATSDR, 2000).

In water, endosulfan undergoes hydrolysis to endosulfan diol. The rate of hydrolysis is influenced by pH. Oxidative degradation also occurs. At pH 7, the half-lives for hydrolysis and oxidation were 23 and 25 days, respectively; at pH 5, the half-lives were 54 and 51 days, respectively (ATSDR, 2000).

Endosulfan released to soil is subject to biodegradation. Biodegradation in soil and water is dependent on climatic conditions and on the type of microorganisms present. Endosulfan sulfate is the major degradation product in soil and is persistent in the soil (ATSDR, 2000).

2. ANALYTICAL METHODS

The method of choice for the determination of endosulfan involves extraction from water with methylene chloride followed by gas chromatography combined with electron capture detection. In considering residue levels, the sum of the α- and β-isomers plus the endosulfan sulfate metabolite, which is similar in toxicity to the parent compound, have to be considered. Detection limits are 0.015 µg/litre for α-endosulfan, 0.024 µg/litre for β-endosulfan and 0.015 µg/litre for endosulfan sulfate (ATSDR, 2000).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Residues of α- and β-endosulfan have been detected in ambient air samples in the USA (Kutz et al., 1976). Between 1970 and 1972, α-endosulfan was found in 2.11% of samples tested in the USA at a mean concentration of 111.9 ng/m^3 and a maximum of 2256 ng/m^3. During the same period, β-endosulfan was present in 0.32% of the samples at a mean concentration of 22.0 ng/m^3 and a maximum of 54.5 ng/m^3. This information suggests that the α-isomer is more persistent in air. Both α- and β-endosulfan have been detected at levels up to 12 ng/litre in precipitation in the Great Lakes area of Canada and the USA (Strachan et al., 1980).

3.2 Water

Endosulfan contamination does not appear to be widespread in the aquatic environment, but endosulfan has been found in agricultural runoff and rivers in industrialized areas where it is manufactured or formulated (IPCS, 1984). Endosulfan (one or both of its isomers) has been identified in 24 surface water and 103 groundwater samples collected from 164 hazardous waste sites in the USA. Surface water samples in the USA generally contain less than 1 µg/litre (ATSDR, 2000).

3.3 Food

The main source of exposure of the general population is food, but residues have generally been found to be well below the FAO/WHO maximum residue limits (IPCS, 1984). These residue tolerances refer to the total residue of α- and β-endosulfan and endosulfan sulfate. Because of its use in tobacco farming, smoking may be an additional source of endosulfan exposure.

In a market basket survey conducted in the USA in 1986–1991, intakes of $2.3–3.8 \times 10^{-6}$ mg/kg of body weight for α-endosulfan and $6.5–9.9 \times 10^{-6}$ mg/kg of body weight for β-endosulfan were reported (ATSDR, 2000).

3.4 Estimated total exposure and relative contribution of drinking-water

With good agricultural practice, endosulfan residues in food should not be significant. Generally, endosulfan concentrations in air and water are very low and localized and accordingly of no significance as far as risk for the general population is concerned (IPCS, 1984). The most important routes of exposure to endosulfan for the general population are ingestion of food and the use of tobacco products with endosulfan residues remaining after treatment (ATSDR, 2000).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS[1]

More than 90% of an oral dose of endosulfan was absorbed in rats, with maximum plasma concentrations occurring after 3–8 h in males and about 18 h in females. Elimination occurs mainly in the faeces and to a lesser extent in the urine, more than 85% being excreted within 120 h. The highest tissue concentrations were in the kidneys. The metabolites of endosulfan include endosulfan sulfate, diol, hydroxy-ether, ether and lactone, but most of its metabolites are polar substances that have not yet been identified. Endosulfan would not be expected to accumulate significantly in human tissues.

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS[2]

A battery of tests for acute toxicity in several species with technical-grade endosulfan showed that it is highly toxic after oral or dermal administration, with respective LD_{50} values of 10–160 mg/kg of body weight and 45–135 mg/kg of body weight. The LC_{50} value for rats in a single study was 13 mg/m^3 in females and 35 mg/m^3 in males. Endosulfan, administered by any route, is more toxic to female than to male rats. Clinical signs of acute intoxication include piloerection, salivation, hyperactivity, respiratory distress, diarrhoea, tremors, hunching and convulsions. WHO (2001) has classified endosulfan as "moderately hazardous."

The kidney is the target organ for toxicity. The renal effects include increased renal weights and granular pigment formation after short-term administration and progressive, chronic glomerulonephrosis or toxic nephropathy after long-term exposure, although the observation of progressive glomerulonephrosis is complicated by the fact that this is a common lesion in aging laboratory rats and occurs at high incidence in control rats.

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[1] This section has been taken from FAO/WHO (1999).
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In a 90-day feeding study in rats, the cytoplasm of isolated cells in the renal proximal convoluted tubules had a yellowish colour, particularly in males, at all dietary concentrations from 10 mg/kg. The presence of this yellow pigmentation was largely reversible during a 4-week recovery period, and it did not appear to indicate nephrotoxicity. A darker, more particulate, granular and/or clumped pigment was also observed, predominantly in cells of the straight portions and occasionally in the proximal convoluted tubules, at dietary concentrations of 30 mg/kg and above. This darker pigment was more persistent than the yellow one, and urinalysis revealed darker urine and marginally more ketones at doses from 60 mg/kg and marginally more protein, particularly in males, indicating renal damage, at doses of 360 mg/kg and above. Similar findings emerged from a multigeneration study but not from a 2-year study of carcinogenicity in rats. The changes in pigmentation were considered to be due to the presence of endosulfan and/or its metabolites in the enlarged lysosomes. To test this hypothesis, a 4-week feeding study was conducted in which male rats were given dietary concentrations of 360 or 720 mg of endosulfan per kg. Light and electron microscopy of the kidneys of these animals clearly showed increases in the number of lysosomes and the size of cells in the convoluted tubule, probably as a result of accumulation of the test material and/or its metabolites. Lysosomal changes were not observed in either brain or liver, and the renal changes receded appreciably during a 30-day recovery period. Chemical analysis of the kidneys indicated the presence of α-endosulfan and, to a lesser extent, β-endosulfan sulfate and endosulfan lactone. The concentrations of the dominant α-endosulfan in the kidneys were about 50 times those in the liver. The concentrations in blood were usually below the level of detection. After the 30-day recovery period, renal α-endosulfan was detected only in traces and β-endosulfan not at all. Similar analysis of tissues from rats in the 2-year study of toxicity and carcinogenicity did not reveal the presence of these substances in the kidney, although measurable α-endosulfan was found in the liver at 75 mg/kg. The yellow colour therefore indicates the presence of endosulfan and/or its metabolites, rather than either a stage in the pathogenesis of nephropathy or an independent expression of toxicity. It was postulated that in longer studies, its removal from lysosomes is accelerated by enzyme induction, which has not been investigated.

Groups of 50 Sprague-Dawley rats of each sex were fed diets containing endosulfan at concentrations of 0, 3, 7.5, 15 or 75 mg/kg, equal to 0, 0.1, 0.3, 0.6 and 2.9 mg/kg of body weight per day for males and 0, 0.1, 0.4, 0.7 and 3.8 mg/kg of body weight per day for females, for 104 weeks. Reductions in body weights and body weight gains were observed in males and females at 75 mg/kg, but no clinical signs of poisoning were seen at any dose. No increase in mortality rates was observed in treated groups. Increased incidences of enlarged kidneys in females and of aneurysms and enlarged lumbar lymph nodes in males were seen at 75 mg/kg. Histopathological examination showed that males at 75 mg/kg had an increased incidence of aneurysm and marked progressive glomerulonephrosis. The most common neoplasms were pituitary tumours in males and females and mammary tumours in females, but the increased incidences did not appear to be related to treatment. The NOAEL was 15 mg/kg, equal to 0.6 mg/kg of body weight per day, on the basis of reduced body weights and pathological findings at higher doses.

Groups of 50 B6C3F1 mice of each sex were fed diets containing technical-grade endosulfan at time-weighted average concentrations of 3.5 or 6.9 mg/kg for males and 2 or 3.9 mg/kg for females for 78 weeks. There were no clear compound-related effects on appearance or behaviour in the treated groups, and the body weights of both males and females were unaffected by treatment. The mortality rate of males at the high dose was increased early in treatment, whereas the mortality rates of female mice were not affected by treatment. No treatment-related clinical signs were recorded, and no treatment-related neoplastic lesions were seen in the females. Owing to the high early mortality rates, no conclusion could be drawn about the carcinogenic potential of endosulfan in males. None of the non-neoplastic changes seen in the kidneys and sex organs of male and female mice could be attributed to treatment. The NOAEL for female mice was 3.9 mg/kg, equal to 0.58 mg/kg of body weight per day.

Groups of six beagle dogs of each sex were fed diets containing technical-grade endosulfan at concentrations of 0, 3, 10 or 30 mg/kg for 1 year, calculated to be equivalent to 0, 0.23, 0.77 and 2.3 mg/kg of body weight per day. Some animals given endosulfan at 30 mg/kg throughout the 12-month study had violent contractions of the abdominal muscles (without vomiting), and males at this dose had reduced body weight gains throughout the study and slightly reduced body weights in the latter stages of the study, in comparison with control animals. Cholinesterase activity was measured in serum, erythrocytes and brain, but difficulty appears to have been experienced in measuring these activities, and there were large variations within groups for the brain enzyme, the group mean of which was increased in dogs at 30 mg/kg. No other effects related to treatment were observed, and no increase in the incidence of neoplastic or non-neoplastic lesions was observed in treated animals. The NOAEL was 10 mg/kg, calculated to be equivalent to 0.77 mg/kg of body weight per day, on the basis of clinical signs and reductions in body weight.

In a 78-week study, exposure of rats to endosulfan at a high dose of 20 mg/kg of body weight per day resulted in testicular atrophy, characterized by degeneration and necrosis of the germinal cells lining the seminiferous tubules. In addition, decreased sperm counts accompanied by an increased incidence of sperm abnormalities have been reported in mice, again at high doses of endosulfan. Reductions in the activities of some testicular xenobiotic-metabolizing enzymes and some hormones that are necessary for normal testicular function were also seen in a 30-day study in rats at 10 mg/kg of body weight per day, but not at 7.5 mg/kg of body weight per day. The functional significance of these findings was not clear, as studies of reproductive and developmental toxicity in rats and rabbits showed neither impaired fertility nor any increase in the incidence of defects or abnormalities in offspring. Given the high doses at which these testicular effects were observed, it would appear that they are of little human significance.

No genotoxic activity was observed in an adequate battery of tests for mutagenicity and clastogenicity *in vitro* and *in vivo*. The JMPR Meeting concluded that endosulfan is not genotoxic.

No carcinogenic effect was observed in mice at 18 mg/kg for 24 months, in female rats at 445 mg/kg for 78 weeks in one study or in male or female rats at 75 mg/kg or 100 mg/kg for 2 years in two other studies. The JMPR Meeting noted the differences in the dietary concentrations used in these studies, but non-neoplastic responses were seen even at the lower doses.

Endosulfan at dietary concentrations of 0, 3, 15 or 75 mg/kg did not affect reproductive performance or the growth or development of the offspring of rats over the course of a two-generation study. The NOAEL was 75 mg/kg, the highest dose tested, equal to 5 mg/kg of body weight per day for males and 6.2 mg/kg of body weight per day for females. The NOAEL for parental toxicity was 15 mg/kg, equal to 1 mg/kg of body weight per day for males and 1.2 mg/kg of body weight per day for females, on the basis of increased liver and kidney weights at 75 mg/kg.

In two studies of developmental toxicity in rats given oral doses of 0, 0.66, 2 or 6 mg/kg of body weight per day, the NOAEL for maternal toxicity was 0.66 mg/kg of body weight per day in one study and 2 mg/kg of body weight per day in the other. In the first case, the basis was decreased body weight gain at 2 mg/kg of body weight per day and decreased body weight gain and clinical signs of toxicity at 6 mg/kg of body weight per day; in the second case, the basis was mortality, clinical signs of toxicity and decreased body weight gain at 6 mg/kg of body weight per day. In both studies, the NOAEL for developmental toxicity was 2 mg/kg of body weight per day, in the first case on the basis of delayed development and a low incidence of skeletal variations seen at 6 mg/kg of body weight per day and in the second on the basis of an increased incidence of fragmented thoracic vertebral centra seen at 6 mg/kg of body weight per day. In neither study was there any treatment-related major malformation.

In a study of developmental toxicity in rabbits given oral doses of 0, 0.3, 0.7 or 1.8 mg/kg of body weight per day, the NOAEL for maternal toxicity was 0.7 mg/kg of body weight per day on the basis of clinical signs of toxicity at 1.8 mg/kg of body weight per day. The NOAEL for developmental toxicity was 1.8 mg/kg of body weight per day, the highest dose tested.

Several recent studies have shown that endosulfan, alone and in combination with other pesticides, may bind to estrogen receptors and may perturb the endocrine system. The available studies show only very weak binding to hormone receptors *in vitro*, and the evidence for their relevance to adverse physiological effects *in vivo* is extremely limited. Long-term assays of toxicity and studies of reproductive and developmental toxicity in experimental mammals did not indicate that endosulfan induces functional aberrations that might result from loss of endocrine homeostasis.

The absence of immunotoxic effects in a large number of bioassays with endosulfan suggested that it does not have an adverse effect on the immune function of laboratory animals. However, in two studies, rats given endosulfan in the diet at 30 or 50 mg/kg for 6 weeks or 20 mg/kg for 22 weeks had reduced serum titres of tetanus toxoid antibody, reduced immunoglobulins G and M and inhibition of migration of both leukocytes and macrophages. These findings have not been confirmed.

6. EFFECTS ON HUMANS[3]

In a summary of case reports of human poisoning incidents, the lowest reported dose that caused death was 35 mg/kg of body weight. Higher doses caused death within 1 h. The clinical signs in these patients were dominated by tonic-clonic convulsions, consistent with the observations in experimental animals.

7. CONCLUSIONS

An ADI of 0.006 mg/kg of body weight was established on the basis of the NOAEL of 0.6 mg/kg of body weight per day in the 2-year dietary study of toxicity in rats and using a safety factor of 100. The ADI is supported by similar NOAEL values in the 78-week dietary study of toxicity in mice (0.58 mg/kg of body weight per day), the 1-year dietary study of toxicity in dogs (0.77 mg/kg of body weight per day) and the study of developmental toxicity in rats (0.66 mg/kg of body weight per day for maternal toxicity).

A health-based value of 20 µg/litre can be calculated on the basis of the ADI of 0.006 mg/kg of body weight, with an allocation of 10% of the ADI to drinking-water, and with the assumption that a 60-kg adult consumes 2 litres of drinking-water per day. However, endosulfan usually occurs at concentrations in drinking-water well below those at which toxic effects can be expected to occur, and it is therefore not considered necessary to derive a guideline value for endosulfan in drinking-water.

8. REFERENCES

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