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Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade
Chemical Review Committee
First meeting
Geneva, 11–18 February 2005
Item 7 (b) of the provisional agenda*

Inclusion of chemicals in Annex III of the Rotterdam Convention: review of notifications of final regulatory actions to ban or severely restrict a chemical: endosulfan

Endosulfan: supporting documentation from Norway

Note by the secretariat

The secretariat has the honour to provide, in the annex to the present note, the supporting documentation provided by Norway in support of its final regulatory action on endosulfan. This supporting documentation was previously considered by the interim Chemical Review Committee at its fifth session.

* UNEP/FAO/RC/CRC.1/1.

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Annex

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Interim Chemical Review Committee
Fifth session
Geneva, 2 – 6 February 2004
Item 5(a) of the provisional agenda*

INCLUSION OF CHEMICALS IN THE INTERIM PRIOR INFORMED CONSENT PROCEDURE - SUPPORTING DOCUMENTATION

Endosulfan

Note from the Secretariat

1. Annexed to this note is the documentation provided by Norway in support of their notification of final regulatory action on endosulfan.

* UNEP/FAO/PIC/ICRC.5/1

List of Documentation Annexed to UNEP/FAO/PIC/ICRC5/10/Add.3

Supporting documentation on endosulfan from Norway:

Environmental Health Criteria – 40 – endosulfan (1984)
Endosulfan Health and Safety Guide 17 – endosulfan (1988)
English summary of Swedish report on endosulfan, 1990

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 40

ENDOSULFAN

Published under the joint sponsorship of
the United Nations Environment Programme,
the International Labour Organisation,
and the World Health Organization

Draft prepared by Professor D. Beritc-Stahuljak and Professor F. Valic (University of Azgreb, Croatia) using texts made available by Dr R. Millischer (ATOCHEM, Paris, France),

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World Health Orgnization
Geneva, 1984

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR ENDOSULFAN

Following the recommendations of the United Nations Conference on the Human Environment held in Stockholm in 1972, and in response to a number of World Health Resolutions (WHA23.60, WHA24.47, WHA25.58, WHA26.68), and the recommendation of the Governing Council of the United Nations Environment Programme, (UNEP/GC/10, 3 July 1973), a programme on the integrated assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, has been implemented with the support of the Environment Fund of the United Nations Environment Programme. In 1980, the Environmental Health Criteria Programme was incorporated into the

International Programme on Chemical Safety (IPCS). The result of the Environmental Health Criteria Programme is a series of criteria documents.

A WHO Task Group on Environmental Health Criteria for Organochlorine Pesticides other than DDT (Endosulfan, Quintozene, Tecnazene, Tetradifon) was held at the Health Protection Branch, Department of National Health and Welfare Ottawa from 28 May - 1 June, 1984. The meeting was opened by Dr E. Somers, Director-General, Environmental Health Directorate, and Dr K.W. Jager welcomed the participants on behalf of the three co-sponsoring organizations of the IPCS (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria document and made an evaluation of the health risks of exposure to endosulfan.

The drafts of this document were prepared by Dr D.C. Villeneuve of Canada and Dr S. Dobson of the United Kingdom.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

Partial financial support for the publication of this criteria document was kindly provided by the United States Department of Health and Human Services, through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA - a WHO Collaborating Centre for Environmental Health Effects.

1. SUMMARY AND RECOMMENDATIONS

1.1. SUMMARY

1.1.1. Identity, analytical methods, and sources of exposure

Technical endosulfan (6,7,8,9,10, 10-hexachloro-1,5,5a,6,9,9a, hexahydro 6,9-methano-2,4,3-benzodioxathiepin, 3-oxide) is a brown crystalline substance consisting of alpha- and beta-isomers in the

ratio of approximately 70:30. It is used in a formulated form as a broad-spectrum contact and stomach insecticide mainly in agriculture and, in some countries, in public health.

The method of choice for its determination is gas chromatography combined with electron capture detection. In considering residue levels, the sum of the alpha- and beta-isomers plus the endosulfan sulfate metabolite, which is similar in toxicity to the parent compound, have to be considered.

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. Because of its use in tobacco farming, smoking may be an additional source of endosulfan exposure.

1.1.2. Environmental concentrations and exposures

Both endosulfan isomers are fairly resistant to photo-degradation, but the metabolites endosulfan sulfate and endosulfan diol are susceptible to photolysis. Its half-life in water is estimated to be 4 days, but anaerobic conditions and/or a low pH will lengthen the half-life. In water, it is mainly degraded to endosulfan diol. Fish are extremely sensitive to endosulfan and fish kills have been reported as a result of the discharge of endosulfan into rivers. Agricultural run-off has not caused such a problem.

In soil, the alpha-isomer disappears more rapidly than the beta-isomer. Endosulfan sulfate is the major degradation product in soil. These compounds are not prone to leaching.

Biodegradation in soil and water is dependent on climatic conditions and on the type of microorganisms present.

1.1.3. Kinetics and metabolism

Endosulfan can be absorbed following ingestion, inhalation, and skin contact. Following oral or parenteral dosing, it is rapidly excreted via faeces and urine. Following acute over-exposure, high endosulfan concentrations can temporarily be found in the liver;

the concentration in plasma decreases rapidly. The major metabolities are endosulfan sulfate and endosulfan diol.

1.1.4. Studies on experimental animals

Endosulfan is moderately to highly toxic according to the scale of Hodge & Sterner (1956). The oral LD_{50} in the rat ranges from 18 to 355 mg/kg body weight. WHO (1984) classified endosulfan in Class II: technical products moderately hazardous. One of its metabolites, endosulfan sulfate, has the same order of toxicity as endosulfan.

Signs of acute intoxication include neurological manifestations, such as hyperactivity, muscular twitching, and convulsions, sometimes followed by death.

In rats, induction of hepatic mixed-function oxidases was observed after administration of endosulfan for 7 days at 2.5 mg/kg body weight per day. At higher doses (100 mg/kg in the diet for 104 weeks), testicular atrophy and renal tubular damage with interstitial nephritis were observed. The long-term, no-observed-adverse-effect level in rats was 30 mg/kg of diet (1.5 mg/kg body weight) and 0.75 mg/kg body weight in dogs. Protein-deficient rats are more sensitive to acute toxic effects of endosulfan.

Adequate data were not available on effects on reproduction, or teratogenic or embryotoxic effects. Negative or conflicting results were obtained in short-term tests for genetic activity. Carcinogenicity studies on mice and rats were difficult to evaluate because of inadequate reporting or early death in males; however, there was no indication of carcinogenic activity in females.

1.1.5. Effects on man

Several cases of accidental and suicidal poisoning have been reported. In fatal cases, death occurred within a few hours of ingestion. Signs of poisoning included vomiting, restlessness, irritability, convulsions, pulmonary oedema, and cyanosis. EEG changes have been reported in occupationally overexposed persons. Cases of poisoning in production workers have been reported, but

occurred only when safe handling procedures were neglected.

1.1.6. Effects on the environment

Endosulfan is not readily bioaccumulated and it is not persistent in biological tissues. It is hazardous as an acute poison for some aquatic species, particularly fish, even at application rates recommended for wetland areas. It is moderately toxic for honey bees. It is moderately to highly toxic for birds in a laboratory setting, but no poisonings have been reported under field conditions.

1.2. Recommendations

1. Precautions should be taken to avoid contamination of surface and drinking-water supplies during spraying. Where necessary, residue levels of endosulfan in drinking-water should be reduced by proper water treatment.

2. In countries where endosulfan is used for tsetse fly control, exposed populations should be monitored for potential adverse health effects.

3. Research is required to determine whether biological monitoring can be used as an early warning of endosulfan exposure.

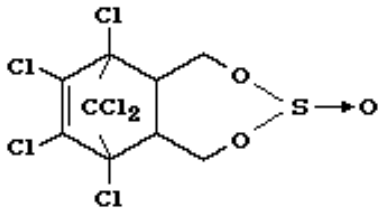
4. Further research is required to investigate possible reproductive, teratological, and embryotoxic effects.

5. An adequate carcinogenicity study should be carried out.

2. IDENTITY, ANALYTICAL METHODS AND SOURCES OF EXPOSURE

2.1. Identity

Chemical structure:



Molecular formula:	$C_9H_6Cl_6O_3S$
CAS chemical name:	6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a -hexahydro-6,9-methano-2,4,3-benzo-dioxa-thiepin-3-oxide
Common trade names:	Benzoepin, Beosit, Chlorthiepin, Cyclodan, FMC 5462, Insectophene, Kop-thiodan, HOE 2671, Malix, NCI-C00566, NIA 5462, Thifor, Thimul, Thiodan, Thiofor, Thiomul, Thionex, Thiosulfan, Tionel, Tiovel. Formulations under other trade names may also exist.
CAS registry number:	115-29-7
Relative molecular mass:	406.9

Endosulfan was developed and introduced in the mid 1950s (Maier-Bode, 1968). Technical endosulfan is obtained through the Diels-Alder addition of hexachlorocylopentadiene and cis-butene-1,4-diol, followed by reaction of the addition-product with thionyl chloride (Canada, National Research Council, 1975). Technical endosulfan consists of a mixture of alpha- and beta-isomers in the approximate ratio of 70:30.

2.2. Properties and Analytical Methods

2.2.1. Physical and chemical properties

Technical endosulfan is usually sold in the form of brown crystalline flakes with a terpene odour (Maier-Bode, 1968). It has a melting point of 79 - 100°C (Canada, National Research Council, 1975) and a vapour pressure of 1 x 10^{-5} mm Hg at 25°C. Its solubility in water is low: 60 - 150 µg/litre (Canada, National Research Council, 1975), and increases with decreasing pH (Shuttleworth, 1971). Solubility in other solvents varies from 5 - 65% (Maier-Bode, 1968; Canada, National Research Council, 1975).

Endosulfan is available as a wettable powder, granules, emulsifiable concentrates, dusts, and as ultra-low-volume (ULV) formulations.

2.2.2. Analytical methods

Methods for the clean-up and determination of endolsulfan have been summarized by Maier-Bode (1968), Canada, National Research Council (1975), and Goebel et al., (1982), but the sensitivities and recoveries for the various methods are not always given. Although colorimetric techniques, thin-layer chromatography, and bio-assays have been used for the determination of endosulfan, the most recent method involves a combination of gas chromatography with electron capture detection (GC-EC).

The sensitivity of assays in water ranged from 0.01 - 2.0 g/litre with recoveries generally greater than 90% (Wegman & Greve, 1978; 1980; Frank et al., 1979a). In soil and sediment, assays were not as sensitive, ranging from 0.001 to 0.1 mg/kg with recoveries between 80 - 110% but usually less than 90% (Miles & Harris, 1973; Frank et al., 1976; Carey et al., 1979). Biological samples such as animal and plant tissues, milk, etc., normally require more extensive clean-up procedures (i.e., column methods). Sensitivities from 0.2 to 10 µg/kg were usual with most recoveries greater than 90% (Cheng & Braun, 1977; Chopra & Mahfouz, 1977; Frank et al., 1979a; Zanini et al., 1980). Samples with a high sugar content gave erroneous results, but methods have been developed to overcome the problem (Shuttleworth, 1971). Clean-up methods employing high-pressure liquid chromatography (HPLC) have been used, which reduce the time involved in the preparation of such samples (Demeter & Heyndrickx, 1979).

It should be noted that detection limits for the alpha- and beta-isomers of endosulfan usually differ, the alpha-isomer being easiest to detect (Goebel et al., 1982). At low concentrations, the identification of endosulfan residues can be hampered by a variety of other pesticides or plant components. Endosulfan residues in environmental samples can only be considered to be valid if alpha- and beta-together with endosulfan sulphate are found simultaneously. Validation can be achieved by methods summarized by Goebel et al. (1982).

3. USES, ENVIRONMENTAL SOURCES, TRANSPORT AND DISTRIBUTION

3.1. 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 (Canada, National Research Council, 1975). It is used in countries throughout the world to control pests on fruit, vegetables, tea, and on non-food crops such as tobacco and cotton (FAO/WHO, 1968). Depending on the type of crop and the area in which it is grown, application rates usually range between 0.45 kg ai and 1.4 kg/ha, but both smaller and larger doses have occasionally been used. Minimum time intervals between the last application and harvesting are prescribed in most countries and vary between 0 and 42 days, depending on the crop, type of formulation used, the mode of application, tolerances, and agronomic needs (Hoechst, 1977).

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 (Canada, National Research Council, 1975). A list of uses together with respective quantities used in some countries appear in Table 1.

Figures for world production are not available but, after DDT was banned, the use of endosulfan in Canada increased quite rapidly until the mid 1970s (Canada, National Research Council, 1975). At present, world production might be in the order of 10 000 tonnes per year.

An estimated several tens of thousands of drums containing chemical waste including endosulfan, which have been found in and along the North Sea, are a potential source of pollution (Greve, 1971b).

3.2. Transport and Distribution

Air

Endosulfan is most frequently applied using air-blast equipment or boom sprayers with a resulting potential for local drift and air pollution. Keil et al. (1972) included 4-metre guard rows between treated and control plots. The day after treatment, endosulfan levels of 0.091 - 0.529 mg/kg were found in the control plots, indicating a considerable drift of the insecticide between the plots. Eighteen days after treatment, an endosulfan level of 0.037 mg/kg was still detectable in the control plots. Endosulfan was also found in the water and sediments of streams adjacent to sprayed crops (Canada, National Research Council, 1975).

Table 1. Usage data for endosulfan from selected countries[a]

Area	Quantity	Year	Uses
Colombia	21 834 kg 15 918 kg 16 868 kg	1982 1981 1980	agricultural insecticide recommended in the growth of cotton, rice, corn, cabbage, sorghum
Malaysia			insecticide
Sweden	2000 kg	1981	horticultural use against insects and mites
Tanzania	2130 tonne	1980-83	applied to various crops to control chewing, mining, and sucking pests
Thailand	63 420 kg 114 800 kg 99 550 kg	1982 1981 1980	insecticide

	27 587 kg	1979	
	24 519 kg	1978	
	18 482 kg	1977	
	1540 kg	1976	
United Kingdom	27.58 tonne per year	1975-79	insecticide and acaricide
USA	511-704 tonne	1980	insecticide on various crops;
	454 tonne	1971	insecticide on potatoes, tobacco, and fruits

[a] From: IRPTC, personal communication, 1984.

Residues of alpha- and beta-endosulfan have been detected in ambient air samples in the USA (Alabama, Arkansa, Illinois, Kansas, Kentucky, Louisiana, Maine, Montana, New Mexico, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee), though not frequently (Kutz et al., 1976). Between 1970 and 1972, alpha-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, beta-endosulfan was present in 0.32% of the samples at a mean of 22.0 ng/m^3 and a maximum concentration of 54.5 ng/m^3. This information suggests that the alpha-isomer is more persistent in air. Both alpha- and beta-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).

Water

Endosulfan contamination does not appear to be widespread in the aquatic environment but has been found in agricultural run-off and rivers in industrialized areas where it is manufactured or formulated. Estimates for the aquatic half-life of both isomers of endosulfan range from 4 days in river water subjected to municipal and industrial runoff (Eichelberger & Lichtenberg, 1971) to 7 days

(Greve, 1971a) in normal water (pH 7, with normal oxygen saturation). However, the half-life was profoundly affected by pH and oxygen content; a drop in either of these two parameters

inhibited endosulfan degradation. Under anaerobic conditions at pH 7, the half-life increased to approximately 5 weeks, and at pH 5.5, the half-life was nearly 5 months (Greve, 1971a). More than 80% of the endosulfan present can be removed from water by filtration and almost all by treatment with activated charcoal (Greve, 1971a).

Studies of endosulfan in agricultural run-off, in the USA, indicate that, if rain follows within 4 days of application (0.35 kg/ha), residues can average 16 µg/litre run-off (Epstein & Grant, 1968).

A widespread fish kill was observed in 1969, when an estimated quantity of 30 kg of endosulfan was discharged into the section of the Rhine river that runs through the Federal Republic of Germany (Sievers et al., 1972). Annual monitoring of endosulfan (drinking water, ground water, rain water, surface water) since 1969 in the Netherlands has revealed that maximum levels have dropped approximately 3 orders of magnitude, with maximum concentrations in 1977 of 0.03 µg/litre (Wegman & Greve, 1980).

Endosulfan was found only once in rivers draining orchard areas in Ontario, during 2-week sampling periods in 1973 at levels ranging from 0.47 to 0.083 µg/litre (Frank, unpublished data, 1973). Studies on water samples from Lake Erie, Ontario, and the St. Lawrence River showed that approximately 15% of the samples contained endosulfan at levels ranging from 0.005 to 0.060 µg/litre (Natural Research council, 1975). In recent work in Western Canada, endosulfan was found (0.011 µg/litre) in one out of 1400 surface water samples, indicating that water contamination by this insecticide was not widespread (Gummer, 1980).

No alpha- or beta-endosulfan or endosulfan sulfate residues were detected (method sensitivity, 10 µg/litre) in well waters located near treated fields in Wisconsin and Florida, USA, 282 and 100 days, respectively, after the last endosulfan application. The treated fields in Wisconsin received seven foliar applications of endosulfan at 0.56 kg/ha (2 in 1966 and 5 in 1969), while the fields in Florida were treated with 10 - 16 foliar applications of endosulfan at 1.12 kg/ha over a 5-year period (Niagara Chemical Division, 1971).

Soil

Early work by Byers et al. (1965) indicated that the alpha-isomer dissipated more rapidly in the soil than the beta-isomer. The authors suggested that the latter was more strongly adsorbed on soil than the former. The results of field studies have since confirmed that the alpha-isomer has a shorter half-life (60 days) than the beta-isomer (900 days) (Steward & Cairns, 1974).

It was also suggested that endosulfan sulfate (the major degradation product in soil) accumulated at a rate comparable to the rate of loss of alpha- and beta-endosulfan. Endosulfan sulfate tended to be more stable than either of the 2 endosulfan isomers, but none of the 3 compounds was prone to leaching in soil (Stewart & Cairns, 1974).

The degradation of endosulfan, which was substantially reduced when the compound was incorporated into soil, halted during winter months (Niagara Chemical Division, 1966, Stewart & Cairns, 1974). A survey of agricultural soils in North America showed that endosulfan residue levels were typically below 1 mg/kg, with a few exceptions (4.78 mg/kg, 4.93 mg/kg) (Frank et al., 1976; Harris et al., 1977). A study from Italy revealed endosulfan soil residues ranging from 0.23 to 3.88 mg/kg (Sanna et al., 1979). Endosulfan has been detected in the sediments of drainage ditches (Miles & Harris, 1971; Niagara Chemical Division, 1971), rivers (Miles, 1976), and lakes (Canada, National Research Council, 1975). Concentrations ranged from trace amounts to 0.64 mg/kg dry weight (Miles et al., 1971).

Degradation of endosulfan appears to be different in sediments and in soil. Martens (1977) studied soil samples under a variety of conditions, including flooding, and demonstrated that the percentage of endosulfan diol was increased in the flooded soil samples and that a lower percentage of the sulfate was observed. Carbon dioxide production was measured in all samples and was highest under aerobic condition (Martens, 1977).

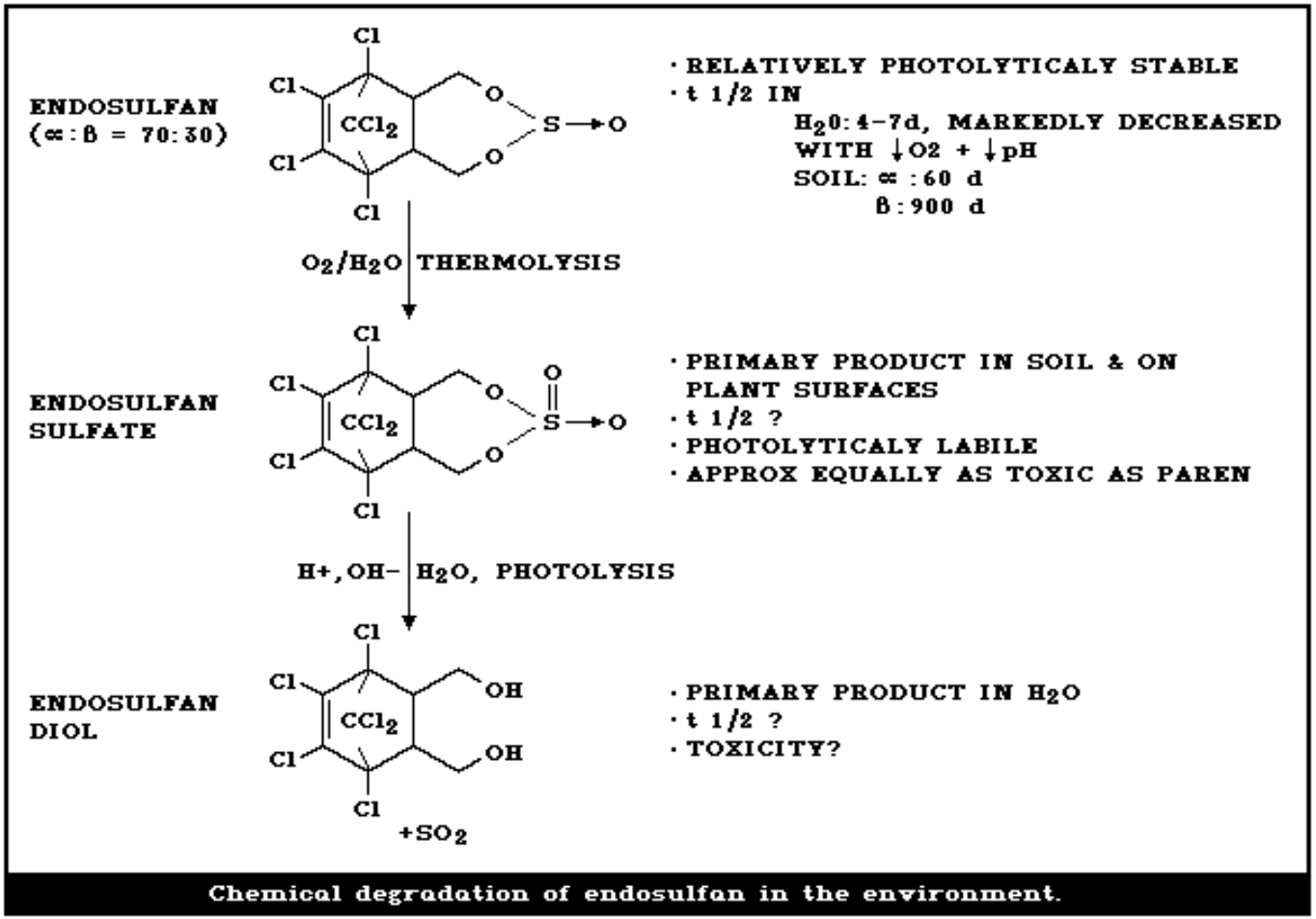
Abiotic degradation and bioaccummulation

Both alpha- and beta-endosulfan are fairly resistant to photodegradation (Schumacher et al., 1971; Schuphan et al., 1972), but the 2 dominant break-down products, endosulfan sulfate and endosulfan diol, are susceptible to photolysis (Fig. 1) (Schuphan et al., 1972). Technical endosulfan is sensitive to moisture, acids, and alkali and will undergo slow hydrolyses producing sulfur dioxide ($S0_2$) and endosulfan alcohol via the intermediate endosulfan sulfate (FAO/WHO, 1968; Martens, 1977).

In soil and on plant surfaces, endosulfan sulfate is the primary degradation product of endosulfan (Cassil & Drummond, 1965; Martens, 1977) with lesser amounts of endosulfan diol and endosulfan lactone being produced. Although sunlight may be involved in the initiation of sulfate production, Archer et al. (1972) felt that thermolysis was the principle formation mechanism.

In aquatic environments (water and sediment), endosulfan diol was present together with smaller amounts of the sulfate and other compounds (Eichelberger & Lichtenberg, 1971; Martens, 1977).

Martens (1972) demonstrated the production of endosulfan and endosulfan diol by fungi, but the role that these and other microorganisms play in environmental degradation is not clear.



Chemical degradation of endosulfan in the environment.

As a result of the higher solubility in water of endosulfan compared with most other organochlorine pesticides, it does not have the affinity for lipids that most related compounds have. Consequently, biomagnification and accumulation of endosulfan in food chains is less likely to occur. The typical response for most organisms exposed to endosulfan at below lethal levels, is to accumulate the compound up to a plateau, but clear the residues fairly rapidly once the source of contamination is removed. The higher the exposure level, the longer it takes to reach a plateau and the higher the plateau is. This response was demonstrated in mussels (Roberts, 1972), fish (Schoettger & Bier, 1970; Oeser & Knauf, 1973), and algae (Oeser & Knauf, 1973). An estimate of the half-life of endosulfan in fish was 3 days (Oeser & Knauf, 1973). Similar results have been found in mammals; summaries of data have

been made by Maier-Bode (1968), Goebel et al. (1982), and US EPA (1982). Endosulfan sulfate was generally the only compound detected in tissues of animals exposed to endosulfan. In cattle (FAO/WHO, 1967), the concentration factors were small (0.5 in milk, 0.05 in muscle tissue, and 0.15 in fat), and residues cleared quite rapidly when endosulfan was removed from the diet. Other diet studies have produced similar results in sheep (Maier-Bode, 1968) and dogs (FMC Corp., unpublished data, 1963). No reports of endosulfan residues in human adipose tissue or breast milk were available.

In plants sprayed with endosulfan, initial residues on fruits and vegetables can vary from about 1 to 100 mg/kg; after 1 week, residues generally decrease to 20% or less of the initial amount (Canada, National Research Council, 1975).

3.3. Levels of Exposure

Air

Human exposure during endosulfan spraying for tsetse fly control using a helicopter in the Ivory Coast was assessed by means of exposure pads worn over or under light overalls (Copplestone et al., 1979). Three male volunteers were positioned within a village and three more in the area deliberately being sprayed. The men walked in the area during spraying and for 1 h afterwards. The application rate of the compound is not stated. Five cm square sections of 7 pads, 6 worn over and 1 worn under clothing, were analysed from each volunteer and the total exposure to endosulfan calculated assuming that all endosulfan measured on the pads was absorbed into the body, irrespective of clothing. An addition of 10% was made to the calculation as an estimate of respiratory absorption. Calculated values were compared with the dermal LD_{50} for rat of 74 mg/kg body weight. The men outside the village received 0.27% and those in the village 0.007% of the rat LD_{50}. The exposure calculated was an overestimate as it assumed that clothing offered no protection. The authors showed that the cotton overalls reduced the dose of endosulfan by the pads by a factor of at least 20.

Endosulfan has been shown to be released from a wood preservative into a room atmosphere over a 1-year period of observation (Zimmerli et al., 1979).

It is well-known that the respiratory route is a potential route of exposure to endosulfan (Oudbier et al., 1974; Wolfe, 1976), and a TLV has been established at 0.1 mg/m^3 (ACGIH, 1982).

Food

In the USA, endosulfan has been reported to be present in the market basket survey since 1967. Between the 1967 and the 1974-75 studies, the level of contamination decreased, but the proportion of food samples containing endosulfan increased. Endosulfan (alpha-, beta-isomer and the sulfate derivative) was present in 3 out of 360 food samples in the 1967-68 survey, at a concentration range of 0.008 - 0.134 mg/kg and was found in 1 sample of each of 3 food groups: garden fruits, leafy vegetables, and oils and fats (Corneliussen, 1969). The 1968-69 survey revealed that endosulfan was present in 16 out of 360 food samples with a range from 0.01 to 0.042 mg/kg. It was present in 7 out of 20 food samples, but only in 2 food groups, leafy vegetables and garden fruits (Johnson & Manske, 1977). Similar results for the above food groups were found in Canada (Canada, National Research Council, 1975).

Endosulfan sulfate was also present in cow's milk from tobacco farming areas at levels of up to 0.010 mg/litre (Frank et al., 1970, 1979). Beck et al. (1966) reported that endosulfan could not be detected in the milk of cows that had been fed forage containing endosulfan at 0.41, 0.70, or 2.35 mg/kg for 21 days.

No endosulfan residues have been reported in market basket surveys from other countries and there are no reports of the daily human intake of endosulfan exceeding the FAO/WHO temporary ADI of 0.008 mg/kg body weight (FAO/WHO, 1982).

In general, endosulfan residues in food are well below the tolerance levels established for various food types by the FAO/WHO (1975a) (Table 2). These residue tolerances refer to the total residue of alpha- and beta-endosulfan and endosulfan sulfate.

Table 2. Endosulfan tolerances in food[a]

Food	FAO/WHO tolerance[b]
Tea (dry, manufactured)	30 mg/kg
Fruits and vegetables (other than exceptions noted)	2 mg/kg
Carrots, potatoes, sweet potatoes, bulb onions	0.2 mg/kg
Cottonseed	1.0 mg/kg
Cottonseed oil (crude)	0.4 mg/kg
Rice (in husk)	0.1 mg/kg
Milk and milk products (fat basis)	0.5 mg/kg
Fat and meat	0.2 mg/kg

[a] From: FAO/WHO (1975a).

[b] Calculated as the total of alpha- and beta-endosulphan plus endosulfan sulfate.

High endosulfan residues have been found in tobacco leaves in both Canada and the USA. Pyrolysis studies on tobacco indicate that the alpha- and beta-isomers, the sulfate derivative, and a variety of other products are present in contaminated tobacco smoke (Chopra et al., 1978). Levels as high as 30.9 and 20 µg/m^3 were detected in Canada and the USA, respectively (Dorough, 1973; Cheng & Braun, 1977). Residues seem to consist primarily of endosulfan sulfate followed by the beta-isomer, then the alpha-isomer (Cheng & Braun, 1977).

Relative importance of different sources

With good agricultural practice, endosulfan residues in food should not be significant. Its use in tobacco farming has been discouraged (Cheng & Braun, 1977) but, if not regulated, could provide a significant route of exposure. As a rule, endosulfan concentrations in air and water are very low and localized, and accordingly of no significance as far as risk for general population is concerned.

No reports of endosulfan in breast milk have appeared in the literature. However, since endosulfan is used as a wood preservative and garden pesticide in some countries, direct exposure of infants and children remains a possibility.

Occupational exposure

Only 2 reports on occupational exposure were found; both involved workers who filled sacks with endosulfan powder. A total of 11 people were poisoned, all of whom experienced difficulties in concentration, vertigo, followed by epileptiform convulsions or stupor (FAO/WHO, 1975b). No further information on workers exposed during the production or spraying of endosulfan was available.

4. KINETICS AND METABOLISM

4.1. Animal Studies

Five days after a single oral administration (by gavage) of ^{14}C-labelled alpha-endosulfan in corn oil at 2 mg/kg body weight to female albino rats, totals of 75% and 13% of the dose were eliminated in the faeces and urine, respectively. With the same dose of ^{14}C-labelled beta-endosulfan, and under the same conditions, the values were 68% and 18.5%, respectively. When radio-labelled endosulfan was fed to rats at 5 mg/kg diet for 14 days, 56% was eliminated in the faeces and 8% in the urine. Maximum residues of endosulfan, which occurred in the kidney and liver, were 3 and 1 mg/kg, respectively. Metabolism studies using alpha- and beta-endosulfan did not reveal any appreciable differences in the fate of the 2 isomers in the rat (Dorough et al., 1978). Endosulfan was metabolized in rats to endosulfan diol, endosulfan hydroxyethers, endosulfan lactone, endosulfan sulfate, and some unidentified polar metabolites (Dorough et al., 1978). Similar metabolites of endosulfan were identified in mice (Deema et al., 1966; Schuphan et al., 1968).

Sheep given daily doses of endosulfan at 15 mg/kg body weight for 28 days, eliminated 20% of the dose in the faeces as the unchanged compound; only a small amount of endosulfan diol was

detected in the urine. Endosulfan sulfate (0.1 mg/kg) was found in perirenal and mesenteric adipose tissues (Gorbach, 1965).

In rabbits, after a single intravenous (iv) injection of endosulfan at 2.0 mg/kg, the concentration in plasma declined rapidly. Thirty-seven percent of the dose was excreted in the urine as alpha-endosulfan and 11% as beta-isomer in the first 5 days (Gupta & Ehrnebo, 1979).

The distribution pattern of endosulfan in the plasma and brain was studied when rats were administered daily doses of 5 or 10 mg/kg body weight in peanut oil by gavage (approximately 1/20 and 1/10 LD_{50}) (2 alpha-:1 beta-isomer ratio) for 15 days (Gupta, 1978). On day 16, the rats that were dosed with 5 mg/kg had the following concentrations of the alpha-isomer in the brain: cerebrum, 3.76 mg/kg, cerebellum, 2.04 mg/kg; remaining parts of the brain, 2.66 mg/kg. The concentrations of the beta-isomer were 0.06 mg/kg in the cerebrum and 0.02 mg/kg in the cerebellum; no beta-isomer was detected in the other parts of the brain (Gupta, 1978). When the rats were fed the higher dose level the same pattern of isomers and metobolite was found, the only difference being that the concentrations were higher than in rats receiving the lower dose. Distribution of endosulfan was also investigated in the cat brain. Following a single iv administration of 3 mg/kg body weight, groups of animals were sacrificed at selected time intervals and analysed for endosulfan content. The cerebrum had the highest concentration followed by the spinal cord, cerebellum, and the brain stem (Khanna et al., 1979).

4.2. Human Studies

Some human data were obtained following the analysis of a case of suicide in which an unknown amount of endosulfan was ingested (Demeter et al., 1977) in combination with alcohol. The individual died within 6 h after ingestion of the chemical. The tissue distribution of endosulfan is given in Table 3. It could not be concluded that death was due solely to the effects of endosulfan.

Table 3. Tissue distribution of endosulfan

Tissue	alpha-endosulfan (mg/kg)	beta-endosulfan (mg/kg)
Liver	12.4	5.2
Kidney	2.48	1.8
Blood	0.06	0.015
Urine	1.78	0.87
Stomach content	2610	1900
Small intestinal content	190	99

5. STUDIES ON EXPERIMENTAL ANIMALS

The toxicity and the residue data on endosulfan have been reviewed by the Joint Meeting on Pesticide Residues (JMPR) in 1965, 1967, 1968, 1971, 1974, and 1982 (FAO/WHO, 1965, 1968, 1969, 1972, 1975a, 1983). For their conclusion, refer to section 8. We refer to these reports, which contain more detailed information on the toxicity studies and residue data than the present report. Moreover, several unpublished studies have been evaluated and reported there.

5.1. Short-Term Exposures

5.1.1. Single exposure

The LD_{50} of endosulfan varied widely depending on the route of administration, species, vehicle, and sex of the animal. The available acute toxicity data are summarized in Table 4. The clinical signs of toxicity include hyperactivity, tremors, and convulsions, followed by death (Boyd, 1972; Gosselin et al., 1976; Gupta, 1976).

Limited short-term studies on the dog showed that as little as 30 mg/kg body weight could be fatal (Canada, National Research Council, 1975), and 2.5 mg/kg body weight per day for 3 days induced toxic symptoms (FAO/WHO, 1968). The 2 stereoisomers have comparable LD_{50} values for the rat (Lindquest & Dahm, 1957).

Male rats given a single oral dose of endosulfan at 40 mg/kg body weight displayed acute neurotoxic manifestations and showed a significant increase in blood glucose, blood ascorbic acid, and blood and brain glutathione (Garg et al., 1980). There have been no published data on skin irritation or sensitization.

5.1.2. Repeated exposures

Endosulfan sulfate was fed to rats in the diet for 3 months at levels as high as 500 mg/kg (Canada, National Research Council, 1975); no effects were detected other than increased liver or kidney weight.

The same compound was administered to dogs for 3 months at levels ranging from 0.75 to 2.5 mg/kg body weight per day. The lowest dose did not have any effect, but the highest dose was not tolerated and the 1.5 mg/kg dose induced occasional signs of toxicity. It was concluded that endosulfan sulfate appeared to have the same order of toxicity as endosulfan (Canada, National Research Council, 1975).

Table 4. Acute toxicity of endosulfan in different animal species

Species	Sex	Route	Vehicle	LD_{50} (mg/kg body weight)	Reference
Rat	NS	oral	olive oil	64	Truhaut et al. (1974)
Rat	NS	oral	95% alcohol	40 - 50	FAO/WHO (1968)
Rat	M	oral	peanut oil	43	Gaines (1969)
Rat	M	oral	cottonseed oil	121	Boyd (1972d)
Rat	F	oral	peanut oil	18	Gaines (1969)

Rat	NS	oral	NS	355	Boyd & Dobos (1969)
Rat	NS	ip	95% alcohol	8	FAO/WHO (1965)
Rat	N	dermal	xylene	130	Gaines (1969)
Rat	F	dermal	xylene	74	Gaines (1969)
Rat	NS	dermal	cottonseed oil	681	Gupta & Gupta (1979)
Rat	NS	inhalation	NS	350 (mg/m^3)[a]	Gupta & Gupta (1979)
Mouse	F	ip	95% alcohol	7.5	Gupta (1976)
Mouse	F	ip	alcohol & peanut oil	13.5	Gupta (1976)
Mouse	M	ip	95% alcohol	6.9	Gupta (1976)
Mouse	M	ip	alcohol & peanut oil	12.6	Gupta (1976)
Rabbit	NS	dermal	cottonseed oil	147	Gupta & Gupta (1979)
Rabbit	NS	percutan-aneous	cottonseed oil	360	Gupta & Gupta (1979)
Rabbit	NS	dermal	oil solvent	359	Martin (1968)

Table 4. (contd.)

Species	Sex	Route	Vehicle	LD_{50} (mg/kg body weight)	Reference

Rabbit	NS	dermal	chloroform	187	Gupta & Chandra (1975)
Guinea-pig	NS	dermal	cottonseed oil	1000	Gupta & Gupta (1979)
Hamster	NS	oral	olive oil	118	Truhaut et al. (1974)

[a] Value represents the LC_{50} in mg/m^3 for a 4-h exposure period.
NS = Not stated.
M = Male.
F = Female.

When rats were treated with daily oral doses of endosulfan at 1.6 - 3.2 mg/kg body weight, for 12 weeks, no effects were observed on growth-rate (FAO/WHO, 1967). Administration of dietary levels of endosulfan ranging from 2 to 200 mg/kg to male rats for 2 weeks, resulted in changes in mixed-function oxidase activity (Den Tonkelaar et al., 1974). Endosulfan at the highest level (200 mg/kg, approximately 10 mg/kg body weight per day) was found to induce mixed-function oxidases activity (aniline hydroxylase and aminopyrine demethylase).

Endosulfan was administered to female rats at daily oral doses of 1.0, 2.5, or 5.0 mg/kg body weight for 7 or 15 days (Gupta & Gupta, 1977). No changes were observed in body, ovary, or adrenal weights. Liver weight increased and pentobarbital sleeping time decreased at the 2 highest dose levels and both time intervals. The results of subsequent studies (Agarwal et al., 1978) showed that the 2 highest levels resulted in induction of aminopyrine demethylase and aniline hydroxylase activities as well as a dose-related increase in amino-transferase activity and spontaneous lipid peroxidation.

Male rats were dosed by oral intubation with endosulfan at levels of 5 or 10 mg/kg body weight per day for 15 days (Gupta, 1978). A reduction in body weight gain was observed at the higher dose, and 3 out of 12 animals died during testing.

In a separate study (Garg et al., 1980), male rats were dosed orally with endosulfan at 0.625, 5.0, or 20 mg/kg body weight, 6 days per week, for 7 weeks. Animals receiving the highest dose showed a slight increase in blood glucose and a decrease in plasma calcium levels.

Endosulfan was administered orally to 4 dogs for 3 days at 2.5 mg/kg body weight (FAO/WHO, 1967). Vomiting was observed in one dog and vomiting, tremors, convulsions, rapid respiration, and mydriasis in the 3 remaining animals. Three other groups of dogs, 2 males and 2 females per group, were administered endosulfan orally at levels of 0.075, 0.25, or 0.75 mg/kg body weight for 6 days a week over a 1-year period (FAO/WHO, 1968). No signs of toxicity were observed. At autopsy, gross and microscopic examination of the tissues did not reveal any differences between treated and control animals.

When endosulfan was administered to cats (Misra et al., 1980) at levels of 2, 3, or 4 mg/kg body weight, muscular twitching was observed in all treatment groups, followed by convulsions. At the 2 higher dose levels, there was a marked rise in blood glucose levels after 15 and 30 min with a gradual fall up to 4 h. Adrenalectomy prevented this rise. Cats were fasted for 1 - 2 h before this study and were then injected with a single intravenous dose of endosulfan (2, 3, or 4 mg/kg) through a cannula inserted into the femoral vein. Blood was drawn from the femoral vein after 0, 15, and 30 min, and 1, 2, and 4 h.

Endosulfan is able to inhibit sodium-, potassium-, and magnesium-dependent ATPase enzymes in rainbow trout brain (Davis & Wedemeyer, 1971).

5.2. Long-Term Exposures

Groups of 25 male and 25 female rats received technical grade endosulfan at 10, 30, and 100 mg/kg diet for 104 weeks (FAO/WHO, 1968). Survival of the female rats in the 10 and 30 mg/kg groups was lower than that in the female control group, during the second year of exposure. In the 100 mg/kg female group, survival was significantly lower after 26 weeks and abnormalities were observed

in weight gain and haematological parameters. At autopsy, the relative weight of the testes in the 10 mg/kg male group was significantly lower than in the control group. Significant histopathological findings were apparent only in the 100 mg/kg male group. In these animals, the kidneys were enlarged and there were signs of renal tubular damage with interstitial nephritis. Hydropic changes were seen in liver cells. The tumor incidence in all test groups was within the range of the control group.

In a study reported by the Commission of European Communities (CEC, 1981), male and female dogs were dosed with endosulfan (by capsule), 6 days a week for 10 months. The dose levels ranged from 0.075 to 0.75 mg/kg body weight. No gross or microscopic evidence of toxicity was noted.

The Joint Meeting on Pesticide Residues (JMPR) reviewed the toxicity data on endosulfan in its 1982 meeting (FAO/WHO, 1983) and concluded that the following levels did not cause any toxicological effects:

rat: 30 mg/kg diet, equivalent to 1.5 mg/kg body weight; and

dog: 0.75 mg/kg body weight per day (administered by capsules)

5.3. Reproduction Studies

Adequate data are not available.

5.4. Mutagenicity

Endosulfan was not mutagenic in *E. coli* or *S. typhimurium* (Fahrig, 1974; Moriya et al., 1982). It did not induce mitotic conversion in *Saccharomyces cerevisae* (Fahrig, 1974). However, in one study, technical grade endosulfan was reported to induce reverse mutations, cross overs, and mitotic gene conversions in *Saccharomyces cerevisiae* (Yadav et al., 1982).

Endosulfan did not induce chromosomal abberations in bone

marrow cells or spermatogonia of male rats treated with 5 daily oral doses of 11 - 55 mg/kg body weight (Dikshith & Datta, 1978).

An increased number of micronuclei induced in the bone marrow erythrocytes of mice treated with endosulfan in the drinking-water (43.3 mg/litre) for 2 consecutive days was not statistically significant (Usha Rani et al., 1980). Negative results were observed in a dominant lethal test in mice (Canada, National Research Council, 1975).

5.5. Teratogenicity

Adequate data are not available.

5.6. Carcinogenicity

The carcinogenicity of technical grade endosulfan was tested using Osborne-Mendel rats and B6C3F1 mice (NCI Tech. Series, 1978). The time-weighted average high and low endosulfan concentrations in the diet for male rats were 952 and 408 mg/kg; for female rats 445 and 223 mg/kg; for male mice 6.9 and 3.5 mg/kg; and for female mice 3.9 and 2.0 mg/kg. Testing of high-dose male rats was terminated during week 82 and low dose male rats during week 74.

Female rats were administered endosulfan for 78 weeks followed by a 33-week observation period. Mice were administered the chemical for 78 weeks and observed for an additional 14 weeks. A high early mortality rate in male rats and mice precluded any conclusions concerning carcinogenicity. Under the conditions of the assay, it was concluded that endosulfan was not carcinogenic for female Osborne-Mendel rats or female B6C3F1 mice.

In a large scale screening study, 2 strains of male and female hybrid mice [(C57BL/6 x C3H/Anf)F_1] and [(C57BL/6 x AKR)F_1] were given 2.15 or 3.0 mg/kg body weight endosulfan by oral intubution on days 7 - 28 of age followed by the feeding of diets containing concentrations of 3 or 6 mg/kg diet for 78 weeks (Innes et al., 1969). Although no conclusion could be drawn about its carcinogenic potential, endosulfan was reported as being one of the

compounds requiring further study.

5.7. Factors Influencing Toxicity

Rats subjected to protein-deficient diets were more susceptible to the acute toxic effects of endosulfan (Boyd, 1972). The LD_{50} for rats on normal lab chow was reported to be 121 mg/kg body weight, compared with 5 mg/kg for rats on a protein-deficient diet.

6. EFFECTS ON MAN

6.1. Poisoning Incidents

A report from Bulgaria described the circumstances, clinical symptoms, and morphological changes in 5 cases associated with endosulfan poisoning (Terziev et al., 1974). These cases comprised 2 suicides and 3 accidental poisonings. Death generally followed a few hours after ingestion. The clinical symptoms included vomiting, agitation, convulsions, cyanosis, dyspnoea, foaming at the mouth, and noisy breathing.

Another report lists the findings on 2 cases (apparently suicides) of men who died after ingesting endosulfan (Demeter & Heyndrickx, 1978). Again, death was noted to occur within a few hours of ingestion, and significant post-mortem findings included congested and oedematous lungs and cyanosis. Tissue analysis for residues indicated the possible synergistic effect of endosulfan and alcohol in one patient (Demeter et al., 1977) and endosulfan, alcohol, and dimethoate, an organophosphorous insecticide, in the second.

6.2. Occupational Exposure

Three cases of poisoning in workers employed in a chemical factory have been reported (Israeli et al., 1969; Tiberin et al., 1970). Poisoning occurred when the men filled bags with insecticide without wearing protective clothing and masks. Symptoms developed after 3 weeks, 1 month, and 18 months, respectively, following daily exposure, and consisted of headaches, restlessness, irritability, vertigo, stupor, disorientation, and

epileptiform convulsive seizures.

Electroencephalogram changes were noted. Endosulfan has been shown to persist on the hands of pest control operators for up to 31 days after exposure. No clinical symptoms were observed (Kazen et al., 1974).

6.3. Treatment of Poisoning

In case of overexposure, medical advice should be sought immediately.

If the pesticide has been ingested, gastric lavage should be performed with 2 - 4 litres of tap water followed by saline purgatives (30 g sodium sulfate in 250 ml of water). Barbiturates or diazepam should be given intraveneously in sufficient dosage to control restlessness or convulsions. Mechanical respiratory assistance with oxygen may be required. Calcium gluconate (10% in 10 ml) should be injected 4-hourly. Contraindications are oily purgatives, epinephrine, and other adrenergic drugs and central stimulants of all types (FAO/WHO, 1975b).

7. EFFECTS ON THE ENVIRONMENT

7.1. Toxicity for Aquatic Organisms

The most representative studies on the toxicity of endosulfan for aquatic organisms are summarized in Table 5. A more comprehensive table, listing different conditions and exposure times, is available on request from IRPTC, Geneva, Switzerland.

Ramachandran et al. (1981) looked at the effects of a low concentration of endosulfan (50 µg/litre) on photosynthesis and respiration in some common seaweeds. The red alga *Gracilaria verrucosa* showed the highest tolerance to endosulfan. Photosynthesis was 96.2% of control levels and respiration was stimulated to 112.32%. The 3 other algal species *Gratiloupia, Enteromorpha intestinalis*, and *Cheatomorpha linum* showed photosynthetic rates of 80.4, 83.6, and 84.6% of control levels and respiration rate of 107.38, 86.97, and 93.6%, respectively. The respiration to photosynthesis ratio was lower than control levels

for all 4 species.

The toxic effects of endosulfan, determined for 1 freshwater and 2 seawater species of crustacea, are summarized in Table 5. McLeese & Metcalfe (1980) studied the effects of including sediment in test vessels. For the shrimp *Crangon*, 96-h LC_{50} values for endosulfan increased from 0.2 µg/litre to 6.9 µg/litre with the inclusion of sediment. The mortality rate estimate of Butler (1963) for the brown shrimp included animals immobilized by the material and showing no clear signs of life. Twenty-four- and 48-h LC_{50} values for the freshwater scud *Gammarus lacustris* were 9.2 and 6.4 µg/litre, respectively (Sanders, 1969).

McLeese et al. (1982) tested the toxicity of endosulfan for the ragworm *Nereis virens* with and without sediment in the test vessels. The LC_{50} for endosulfan in 288-h tests were 100 µg/litre with sea water and 340 µg/kg with sediment. Symptoms of stress in the worms included eversion of the proboscis, lost equilibrium, and immobilization. Stressed worms in sediment tests emerged from the sediment and subsequently did not burrow, even after the sediment was changed.

Table 5. Toxicity of endosulfan for aquatic organisms

Organism	Size/ age	Grade	Temp (°C)	pH	Stat/ flow	Sal (^{0}/00)	Effect	Parameter	Conc. (µg/litre)	Reference
eastern oyster *(Crassostrea virginical)*			28			22	decrease in shell growth	96-h EC_{50}	65	Butler (1963)
polychaete worm *(Nereis nereis)*	adult		9-10		stat		death	12-day LC_{50}	100	McLeese et al. (1982)
	adult		9-10		stat		death	12-day LC_{50}	340[a]	McLeese et al. (1982)
Cladoceran			10	7.4		45[b]	death	96-h LC_{50}	52.9	Schoettger

(Daphnia magna)					38[c]				(1970)
shrimp	adult		20		stat	death	96-h LC_{50}	0.2	McLeese & Metcalfe (1980)
(Crangon septemspinosa)	adult		10		stat	death	96-h LC_{50}	6.9[a]	McLeese & Metcalfe (1980)
blue crab *(Callinectes sapidus)*	juv.		30		stat	death or loss of equilib-rium	24-h EC_{50} 48-h EC_{50}	55 35	Butler (1963) Butler (1963)
freshwater mite *(Hydrachna trilobata)*	adult	tech	25-31	7.8-8	stat	immobil-isation	48-h EC_{50}	2.8	Nair (1981)
stonefly *(Pteronarcys californica)*	nymph		15.5	7.1	stat	death	96-h LC_{50}	2.3	Sanders & Cope (1968)
rainbow trout *(Salmo gairdneri)*	1.3g	tech 96%				death	96-h LC_{50}	1.4	Johnson & Finley (1980)
fathead minnow	0.7g	tech 96%				death	96-h/LC_{50}	1.5	Johnson & Finley (1980)

Table 5. (contd.)

Organism	Size/ age	Grade	Temp (°C)	pH	Stat/ flow	Sal ($^0/_{00}$)	Effect	Parameter	Conc. (µg/litre)	Reference
channel catfish *(Ictalurus punctatus*	1.7g	tech 96%					death	96-h LC_{50}	1.5	Johnson & Finley (1980)
catfish	6-10g	35%	18.2	6.9-	stat		death	96-h LC_{50}	0.67	Verma et al.

(Mystusvittatus)	80-100mm	EC		7.4						(1980)
	6-10g	35%	18.2	6.9-7.4	stat		death	96-h LC_0	0.06	Verma et al. (1980)
	80-100mm	EC								
	6-10g	35%	18.2	6.9-7.4	stat		death	96-h LC_{50}	3.50	Verma et al. (1980)
	80-100mm	EC		8.4	flow	152[b] 330[c]	death	96-h LC_{50}	2.2	Rao & Murty (1982)
catfish *(Heteropneustes fossilis)*				8.4	flow	152[b] 330[c]	death	96-h LC_{50}	1.1	Rao & Murty (1982)
	41.8± 4.7g 197± 8mm	35% EC		7.8	stat	120[c]	death	96-h/LC_{50}	14.7	Singh & Narain (1982)
	11.3± 1.6g 102± 5mm	35% EC		7.8	stat	120[c]	death	96-h/LC_{50}	7.3	Singh & Narain (1982)
catfish *(Mystuscavasius)*				8.4	flow	152[b] 330[c]	death	96-h LC_{50}	1.9	Rao & Murty (1982)
catfish *(Ophiocephalus punctatus)*	40-55g 90-100mm	35% EC	18.2	6.9-7.4	stat		death	96-h LC_{50}	22	Verma et al. (1981)

[a] Sediment present in test vessel.

[b] Hardness mg CO_3/litre.

[c] Alkalinity mg HCO_3-/litre.

Nair (1981) tested endosulfan toxicity with a range of concentrations from 2.6 and 2.9 µg/litre on the freshwater mite

Hydrachna trilobata viets and reported a 48-h LC_{50} value of 2.8 µg/litre. The small difference between the no-effect and lethal dosages of endosulfan is typical for many different aquatic organisms. A 96-h LC_{50} of 1890 µg/litre was reported by Holcombe et al. (1983) for adult freshwater snails *Aplexa hypnorum.* Roberts (1972) reported that endosulfan at a concentration of 1000 µg/litre delayed the onset of spawning and prolonged the spawning period for the common mussel *Mytilus edulis.* At a lower dose of 100 µg/litre, a slight reduction in the length of the spawning period was considered by the author to reflect the experimental tank conditions rather than the endosulfan treatment.

Endosulfan has a high acute toxicity for fish. There have been studies on many species of teleosts with 96-h LC_{50} values ranging from 0.67 µg/litre to 4.8 µg/litre. Where commercial preparations of endosulfan have been used, it is not always clear how the dose is presented. Where LC_{50} values exceed 4.8, it seems clear that the values given are for a preparation that usually contains only 35% endosulfan.

Singh & Narain (1982) looked at variations in LC_{50} values in 96-h tests on the catfish *Heteropneustes fossilis* in relation to season, and size and weight of the fish. Tolerances of the fish to the Thiodan preparation (35% endosulfan) showed a significant seasonal variation. Fish were more tolerant to endosulfan during the colder months of the year. The toxicity of endosulfan was directly proportional to the length and weight of fish; LC_{50} values increased from 5 to 4.7 µg/litre with an increase in fish weight from 4.8 to 41.8 g and an increase in length from 6.2 to 19.7 cm. The relative toxicity of technical endosulfan, endosulfan isomers, and formulations, was investigated in the freshwater fish *Labeo rohita* by Rao et al. (1980), and in *Channa punctata,* a catfish, by Devi et al. (1981). In *Labeo rohita,* endosulfan-A was 3.33 times and endosulfan-B 0.16 times more toxic than technical endosulfan; the alpha-isomer was 30 times and the beta-isomer 0.7 times more toxic than technical material in *Channa punctata.* Rao & Murty (1982) demonstrated in 3 species of catfish that the relative toxicity between species could not be determined using LC_{50} values alone. The slopes of endosulfan toxicity curves

were different for different species. The same authors (Rao & Murty, 1980), reported that endosulfan metabolites were eliminated mainly with faeces and urine, the principal sites of detoxification of endosulfan being the liver and kidney. Using the freshwater catfish *Saccobranchus fossilis,* Verma et al. (1982a) calculated the safe levels of 2 preparations of endosulfan to be 0.14 µg/litre (Thiotox) and 0.23 µg/litre (Thiodan). Verma et al. (1980) looked for synergism and antagonism between endosulfan, dichlorvos and carbofuran on the test fish *Mystus vittatus* and *Ophiocephalus punctatus,* but did not find any evidence of either.

Histopathological, biochemical, and physiological changes in fish after exposure to endosulfan have been reported in a large number of studies. Gopal et al. (1981a) measured blood glucose levels in catfish during 96-h of exposure to endosulfan at 10 µg/litre. A marked rise, at 4 h, of 66.4% over control levels increased to a peak of 101.6% at 48 h compared with control levels and then declined to match control levels at 72 h. At the end of the study, after 95 h, the glucose level was not significantly different from controls. Singh & Srivastava (1981) exposed Indian catfish to a high sublethal concentration of endosulfan of 1.5 µg/litre (representing 75% of the 96-h LC_{50} for the species). The average mortality rate for all fish groups was 5% over the 96-h experimental period. Muscle glycogen was depressed for most of the experimental period. Liver glycogen was the least affected of all the variables measured. Blood glucose was significantly elevated at 3, 6, 48, and 96 h of exposure, but not at 12 h. Blood pyruvate was elevated at 6 and 48 h only, whereas blood lactate was significantly elevated for the first 6 h of exposure and significantly depressed for the remainder of the observation period. Endosulfan was shown by Sastry & Siddiqui (1982) to reduce intestinal uptake of glucose by the fish *Channa punctatus* at doses of 1 mg/litre and above. Using endosulfan concentrations of between 0.17 and 2.3 µg/litre on 3 species of Indian catfish, Verma et al. (1983) found elevation of blood glucose ranging from 67.31% to 98.36%. The concentrations of endosulfan used represent 25% of the 96-h LC_{50} for each species. Murty & Devi (1982) demonstrated that changes in tissue protein, glycogen, and lipid levels in the fish *Channa punctatus* were greater with exposure to the alpha- than to the beta-isomer of endosulfan.

A clear dose-related reduction in both oxygen consumption and total nitrogen excretion was shown by Rao et al. (1981) in the fish *Macrognathus aculeatum* with endosulfan concentrations ranging from 1 to 15 µg/litre. Verma et al. measured the activity of 3 phosphatases in the liver, brain, and gills of *Saccobranchus fossilis* after 30 days exposure to endosulfan at concentrations from 0.63 µg/litre. The depression in the activity of these enzymes was increased by the addition of ascorbic acid to the food of the fish. Dalela et al. (1979) reported that acute (5 h of exposure) and short-term exposure (up to 32 days) of the fish *Channa gachua* to endosulfan at respectively 11.76 and 3.5 µg/litre produced histological changes in the gills. On acute exposure to 11.76 µg/litre, there was separation of the respiratory gill epithelium from the basement membrane, pronounced hyperaemia, necrosis, fusion of adjacent gill lamellae, erosion at the distal end of gill filaments, and loss of cell membrane. With exposure to a sub-lethal dose of 3.5 µg endosulfan/litre, damage to the gill was not as severe after 8 days, but was found to be progressively more pronounced with increasing exposure time.

A detailed field study was conducted in relation to tsetse fly control operations in the Okavango delta region of Botswana. Fox & Matthiessen (1982) reported that in laboratory studies, 24-h LC_{50} values for Okavango fish ranged from 1.2 to 7.4 µg/litre, depending on species. Field concentrations of endosulfan after spraying at 9.5 g/ha ranged between 0.2 and 4.2 µg/litre. The authors

determined pre-spraying population densities and, thereby, the apparent mortality rate in a variety of fish species after spraying. Estimated mortality rates ranged from 0.2 to 4.3% for individual species with an overall estimate of 0.9%. Matthiessen & Roberts (1982) reported pathological changes in the liver and brain of fish exposed to endosulfan spray, and Matthiessen (1981) reported a significant elevation in blood cell counts during spraying.

7.2. Toxicity for Terrestrial Organisms

The toxicity of endosulfan for terrestrial organisms is

summarized in Table 6.

7.2.1. Plants

Some phytotoxic effects of endosulfan have been reported. Gentile et al. (1978) reported that 24% endosulfan reduced the germination of cucumber pollen to 54.6% of control levels at a concentration of 1000 mg ai/litre, half the recommended concentration for field use. At the same concentration, pollentube length was only 8.1% of controls. Morey & Singh (1980) examined the effects of endosulfan on several species of *Cucurbitae* and found that it was phytotoxic to all but one species and moderately phytotoxic to the latter. Concentrations ranged from 0.035 to 0.14%. Phytotoxicity was estimated by necrotic spots on leaves. Agarwal & Beg (1982a) studied the effects of endosulfan on the germination and seedling growth of *Cicer arietinum.* They found reduced viability and delayed germination with endosulfan treatment. Inhibition, at lower concentrations of 0.01, 0.1, and 1 mg/litre in an agar bed used as the germination medium, was reversed as germination progressed, whereas at 10 mg/litre inhibition persisted. Endosulfan affected all major stages of germination and seedling growth. The results of a simple *in vitro* experiment suggested that endosulfan changed the permeability of root membranes. Gupta & Gupta (1977) examined 4 concentrations of endosulfan between 0.35 g/kg and 3 g/kg for effects on Green Gram, *Vigna radiata.* Toxic effects were dose-dependent. At 0.35 g/kg and 0.7 g/kg, no adverse effects were observed in any of the parameters studied, but, at higher concentrations of 1.5 g/kg and 3 g/kg, symptoms of toxicity were visible. These included coiling of the radical, inhibition of root growth, stunting of shoots, and burning of the tips and margins of leaves. Plants were dwarfed and chlorotic, having damaged pollen grains and low productivity. Agarwal & Beg (1982b) reported that exposure of germinating *Cicer arietinum* seeds to endosulfan resulted in a fall in the pectin, hemicellulose, and cellulose contents of cell walls at all stages of germination compared with untreated controls. It must be stated that these were very isolated phytotoxic effects. In normal usage, endosulfan has not been shown to be significantly toxic to plants.

Table 6. Toxicity of endosulfan for terrestrial organisms

Organism	Size/ age	Grade	Temp (°C)	Route	Parameter	Concentration (mg/kg)[a]	Reference
braconoid parasite *(Apanteles ornigis)*	adult	technical	24	contact	24-h LC_{50}	494 mg/litre	Hagley et al. (1981)
ladybird beetle	adult	technical		contact	72-h LC_{83}	200 mg/litre	Makar & Jadhav (1981)
(Menochilus sexmaculatus)	1-day-old larva 3rd instar	technical		contact	72-h LC_{78}	200 mg/litre	Makar & Jadhav (1981)
honey bee, worker *(Apis mellifera)*		95%		contact oral	LD_{50} LD_{50}	7.1 g/bee 6.9 g/bee	Stevenson et al. (1978)
mallard (*Anas platyrhynchos*)	36 h	96%		oral	acute LD_{50}	27.8 (22.8-33.8)	Hudson et al. (1972)
	7 day	96%		oral	acute LD_{50}	6.47 (5.19-9.05)	Hudson et al. (1972)
	30 day	96%		oral	acute LD_{50}	7.89 (5.77-10.8)	Hudson et al. (1972)
	3-4 month	96%		oral	acute LD_{50}	33 (23.8-45.8)	Tucker & Crabtree (1970)
	6 month	96%		oral	acute LD_{50}	34.4	Hudson et al. (1972)
	16 day	96%		diet	5-day LC_{50}	1053 (781-1540)	Hill et al. (1975)
	young	35%[b]		diet	< 10-day LC_{50}	1000	DeWitt et al. (1963)
	adult	35%[b]		diet	< 10-day LC_{50}	> 5000	DeWitt et al. (1963)
	adult	35%[b]		diet	< 100-day LC_{50}	1000	DeWitt et al. (1963)

Table 6. (contd.)

Organism	Size/ age	Grade	Temp (°C)	Route	Parameter	Concentration (mg/kg)[a]	Reference
ringnecked pheasant *(Phasianus colchicus)*	10 day	96%		diet	5-day LC_{50}	1275 (1098-1482)	Hill et al. (1975)
	young	35%[b]		diet	< 10-day LC_{50}	500	DeWitt et al. (1963)
	young	35%[b]		diet	< 100-day LC_{50}	> 300	DeWitt et al. (1963)
	adult	35%[b]		diet	< 100-day LC_{50}	1000	DeWitt et al. (1963)
Japanese quail *(Coturnix coturnix japonica)*	14-day	96%		diet	5-day LC_{50}	1250	Hill et al. (1975)
bobwhite quail *(Colinus virginianus)*	9-day	96%		diet	5-day LC_{50}	805 (690-939)	Hill et al. (1975)
	young	35%[b]		diet	< 10-day LC_{50}	300	DeWitt et al. (1963)
	young	35%[b]		diet	< 100-day LC_{50}	100	DeWitt et al. (1963)
	adult	35%[b]		diet	< 100-day LC_{50}	> 250	DeWitt et al. (1963)
cowbird		35%[b]		diet	10-day LC_{50}	1000	DeWitt et al. (1963)

[a] Concentrations are mg/kg body weight for oral dosing and mg/kg diet for dietary dosing.
[b] Preparation used is "thiodan", which is a 35% formulation of endosulfan.

7.2.2. Honey bees

Endosulfan is considered of moderate or low toxicity for honey bees. Stevenson et al. (1978) reported a contact LD_{50} of 7.1 µg/bee and an oral LD_{50} of 6.9 µg/bee for endosulfan. Endosulfan has never

been implicated in episodes of poisoning of bees investigated in Great Britain (Stevenson et al., 1978).

7.2.3. Birds

The toxicity of endosulfan for birds is summarized in Table 6. Hudson et al. (1972) examined the effects of age of mallard ducks on their sensitivity to endosulfan. The acute oral LD_{50}s for ducks at 36 h, 7 days, 30 days, and 6 months of age were 27.8, 6.47, 7.89, and 34.4 mg/kg body weight, respectively.

Field studies on birds in the Okavango delta of Botswana related to endosulfan sprays for tsetse fly control failed to show any change in bird numbers or species diversity (Douthwaite, 1980). Douthwaite (1982) looked specifically at kingfishers that fed on fish killed or incapacitated by the spray. The feeding rates of kingfishers were greatly increased by the availability of debilitated fish, but these rates fell when spraying ended. The kingfisher population in the study area survived and numbers at a communal roost were steady.

7.3. Toxicity for Microorganisms

Endosulfan is toxic for a wide variety of microorganisms. Srivastava & Misra (1981) found a dose-related increase in oxygen consumption by the yeast *Rhodotorula gracilis* at concentrations of endosulfan between 10 and 200 mg/litre medium. Further increases in dose up to 400 mg/litre did not show any increased effects. The authors suggested that endosulfan affects membrane components. Butler (1963) reported that endosulfan (thiodan) at a concentration of 1 mg/litre, decreased productivity in a natural phytoplankton community by 86.6% during a 4-h exposure. The bacterial insecticide, *Bacillus thuringiensis,* was reported by Kahlon et al. (1981) to show reduced viable count and spore count on incubation with solutions of endosulfan at 0.5 or 1 µg/litre. Endosulfan was the most effective inhibitor of sporulation of the 3 insecticides tested. Tarar & Salpekar (1980) reported that endosulfan was the most toxic of 6 organochlorines for soil algae. Of algal species present in the soil (18 species present in the control soil), 17 were eliminated by endosulfan concentrations of 2 g/kg. Only 1

species survived endosulfan at 4 and 6 g/kg. This species, *Chlorococcum humicolo,* was unaffected by any of the organochlorines with which the soil was treated. El Beit et al. (1981) examined the microbial metabolism of pesticides and effects of the pesticides on the growth of bacterial and actinomycete colonies. Endosulfan either as the alpha- or beta-isomer applied at 4000 mg/litre prevented the growth of any bacterial or actinomycete colonies from any soil type tested. Alpha-endosulfan seemed to be broken down by both bacteria and fungi whereas the beta-isomer was degraded more by bacteria than by fungi. Results suggest that

while both isomers can be degraded by microbial organisms, the degradation materials released counteract the growth of the microorganisms.

7.4. Bioaccumulation

In aquatic ecosystems, endosulfan residues tend to reach a plateau level in tissues. Schoettger (1970) exposed western white suckers to water containing ^{14}C-labelled endosulfan at 29 µg/litre for 12 h. In the tissues concentrating the most endosulfan, a plateau level of the compound was reached within 12 h. A plateau was maintained over a prolonged period in studies on goldfish exposed to endosulfan solutions at 7 µg/litre. Residue levels in muscle were 2.54 mg/kg after 5 days and 1.09 mg/kg after 20 days (Schoettger, 1970). Accumulation appeared to be transitory, because endosulfan disappeared rapidly in mussels (Roberts, 1972) and goldfish after the source was removed (Schoettger, 1970). Oeser & Knauf (1973) calculated the half-life for the elimination of endosulfan from goldfish to be 2 - 3 days. This followed a 5-day exposure to 1 µg of the pesticide/litre, during which time residues reached a mean level of 0.35 mg/kg. Little accumulation of endosulfan seems to have been reported in the field. The mean residue level in fish living in endosulfan-contaminated natural surface water was 0.4 mg/kg (Gorbach & Knauf, 1971).

Roberts (1972) reported concentration factors of 17, 11, and 8.1 after exposing mussels to 0.1, 0.5, and 1.0 mg endosulfan/litre, respectively, for 112 days. Although the mussels assimilated more pesticide at higher dose levels, the greatest concentration factors

were achieved with the lowest dose of 0.1 mg/litre, a maximum BCF of 22.5 being reached after 70 days. Roberts (1972) found that the major storage site for endosulfan in scallops was the digestive gland. He suggested this would also be the case for mussels and other bivalves.

In a study by Ernst (1977) on the uptake and elimination of endosulfan, a somewhat higher BCF value of 600 was measured in mussels, with an initial concentration of endosulfan in the water of 2.05 µg/litre. The concentration factor is based on a steady state concentration of 0.14 µg endosulfan/litre water. If the BCF is calculated on the initial concentration, a BCF of 41, a more typical value for aquatic organisms, is obtained. Bioaccumulation data are summarized in Table 7.

Table 7. Bioaccumulation of endosulfan

Organism	Grade	Temp (°C)	Organ	Exposure time	Concentration factor BCF	Dose (µg/litre)	References
green alga (*Chlorella* sp.)			WB[c]	initial BCF	2500		Oeser et al. (1971)
mussel			WB	112 day	17	100	Roberts (1972)
(*Mytilus edulis*)			WB	112 day	11	500	Roberts (1972)
			WB	112 day	8.1	1000	Roberts (1972)
	alpha-isomer		WB		600[a] (41)[b]	0.14[a] (2.05)[b]	Ernst (1977)
goldfish			liver	11-20 day	781	7	Schoettger (1970)
(*Carassius auratus*)			muscle	5-20 day	314	7	Schoettger (1970)
western white		19	muscle	12 h	65	20	Schoettger (1970)
sucker		19	muscle	9 h	55	20	Schoettger (1970)
(*Catostomus*		19	liver	12 h	550	20	Schoettger (1970)
commersoni)		19	liver	9 h	695	20	Schoettger (1970)

[a] Higher BCF based on steady state concentration of endosulfan.
[b] Values in () based on original concentration of endosulfan (static test).
[c] WB = whole body.

Koeman et al. (1974) measured residues in animal species in Java, following BIMAS programmes for the control of paddy-stem borer that had continued over several years. No residues were found (detection limit 0.03 mg/kg); animals used included fish, molluscs, crabs, and shrimps. Matthiessen et al. (1982) studied the accumulation of endosulfan in fish and their predators following aerial spraying to control the tsetse fly in Botswana. Residue levels in fish predators, birds, and crocodiles, were similar to those in their prey. Risk to predators was consequently deemed to be low. Although endosulfan residues in insects were not measured, low residues in insectivorous birds suggested rapid degradation and little accumulation. According to Matthiessen et al. (1982), lean fish have a lower survival rate than fat ones at subacute concentrations of endosulfan in the water.

There do not seem to be any accumulation data available for wild mammals.

8. PREVIOUS EVALUATIONS OF ENDOSULFAN BY INTERNATIONAL BODIES

The Joint Meeting on Pesticide Residues (JMPR) have reviewed residues and toxicity data on endosulfan on several occasions in the past: 1965, 1967, 1968, 1971, 1974, and 1982 (FAO/WHO, 1965, 1968, 1969, 1972, 1975a, 1983).

In 1982, the estimate of a temporary acceptable daily intake for man was made at 0 - 0.008 mg/kg body weight (total of alpha- and beta-endosulfan and endosulfan sulfate). This was based on no-observed-adverse-effect levels of:

rat: 30 mg/kg diet, equivalent to 1.5 mg/kg body weight; and

dog: 0.75 mg/kg body weight per day (administered by capsules).

The FAO/WHO (1975b) in its series of "Data sheets on chemical pesticides" issued one on Endosulfan. Based on a brief review of use, exposure, and toxicity, practical advice is given on labelling, safe-handling, transport, storage, disposal, decontamination, selection, training, and medical supervision of workers, and first aid and medical treatment.

WHO (1984), classified endosulfan in the list of technical products being moderately hazardous.

Regulatory standards established by national bodies in 12 different countries (Argentina, Brazil, Czechoslovakia, Federal Republic of Germany, India, Japan, Kenya, Mexico, Sweden, the United Kingdom, the USA, and the USSR) and the EEC can be found in the IRPTC (International Register of Potentially Toxic Chemicals) Legal file (IRPTC, 1983).

9. EVALUATION OF HEALTH RISKS FOR MAN AND EFFECTS ON THE ENVIRONMENT

9.1. Evaluation of Health Risks for Man

Endosulfan toxicity

Endosulfan is moderately to highly toxic according to the scale of Hodge & Sterner (1956). The oral LD_{50} in the rat ranges from 18 - 355 mg/kg body weight, depending on such parameters as sex, strain, and vehicle used.

WHO (1984) classified endosulfan in the category of technical products that are moderately hazardous.

Endosulfan can be absorbed following ingestion, inhalation, and skin contact. It is readily metabolized and excreted and does not accumulate in the body.

On acute intoxication, neurological manifestations may occur, such as irritability, restlessness, muscular twitchings, and convulsions. Lung oedema and cyanosis may precede death.

Endosulfan was negative or produced conflicting results in

short-term tests for genetic activity. It showed no carcinogenic activity in mice or rats but studies were limited by inadequate reporting or survival.

Several cases of suicidal and occupational poisoning have been reported, the latter resulting, in most cases, from neglect of safety precautions.

Exposure to endosulfan

Food is the main source of exposure of the general population to endosulfan. Endosulfan residues in food (the sum of its alpha- and beta-isomers and endosulfan sulfate) have been found to be generally well below FAO/WHO maximum residue limits.

In occupationally-exposed persons, both skin contact and inhalation can be important routes of absorption when adequate safety precautions are not taken.

Hazard assessment

The main hazard associated with endosulfan is acute intoxication through overexposure. Such situations may be due to intentional or accidental overexposure or to gross negligence in occupational situations.

In all other exposure situations, especially as far as the general population is concerned, the toxicity profile and the present exposure pattern do not indicate any appreciable hazard.

9.2. Evaluation of Overall Environmental Effects

Degradation of endosulfan in soil and water by photolysis, chemical reactions, and biotransformation is governed by a wide range of climatic factors and the type of microorganisms present.

Endosulfan does not appear to be a problem with regard to persistence. It is not readily bioaccumulated. In aquatic organisms, loss soon balances uptake and a fairly low plateau level of residues is achieved.

Endosulfan is hazardous in acute overexposure for some aquatic species, especially fish. There has been large-scale field experience with endosulfan without any long-term adverse effects on the environment.

Careful application to avoid overexposure of non-target organisms does not eliminate kills in local fish populations when endosulfan is applied to wetland areas at recommended rates. Because there is little or no biomagnification, endosulfan, when applied at recommended rates, is not hazardous to terrestial animals. Toxicity for bees is low to moderate.

The reported toxicity of endosulfan for microorganisms in the laboratory is low; it is unlikely to have an appreciable effect in the field.

9.3. Conclusions

1. The general population does not appear to be at risk from endosulfan residues in food. Exposure of the general population via air and drinking-water is generally low.

2. Occupational exposure has resulted in some incidents of poisoning. These appear however, only to have occurred when adequate safety precautions were not taken.

3. In terms of the general environment, endosulfan is highly toxic for some aquatic species, particularly fish. Endosulfan is moderately toxic for honey bees.

4. Endosulfan does not accumulate in food chains and is excreted from the body rapidly.

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See Also:
Toxicological AbbreviationsEndosulfan (HSG 17, 1988)Endosulfan (PDS)Endosulfan (PIM 576) Endosulfan (FAO Meeting Report PL/1965/10/1)Endosulfan (FAO/PL:1967/M/11/1)Endosulfan (FAO/PL:1968/M/9/1) Endosulfan (WHO Pesticide Residues Series 1)Endosulfan (WHO Pesticide Residues Series 4)Endosulfan (WHO Pesticide Residues Series 5)Endosulfan (Pesticide residues in food: 1982 evaluations)Endosulfan (Pesticide residues in food: 1989 evaluations Part II Toxicology)Endosulfan (JMPR Evaluations 1998 Part II Toxicological)

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Health and Safety Guide No. 17

ENDOSULFAN
HEALTH AND SAFETY GUIDE

UNITED NATIONS ENVIRONMENT PROGRAMME

INTERNATIONAL LABOUR ORGANISATION

WORLD HEALTH ORGANIZATION

WORLD HEALTH ORGANIZATION, GENEVA

This is a companion volume to Environmental Health Criteria 40: Endosulfan

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welcomes such applications.

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CONTENTS

INTRODUCTION

The Environmental Health Criteria (EHC) documents produced by the International Programme on Chemical Safety include an assessment of the effects on the environment and on human health of exposure to a chemical or combination of chemicals, or physical or biological agents. They also provide guidelines for setting exposure limits.

The purpose of a Health and Safety Guide is to facilitate the application of these guidelines in national chemical safety programmes. The first three sections of a Health and Safety Guide highlight the relevant technical information in the corresponding EHC. Section 4 includes advice on preventive and protective measures and emergency action; health workers should be thoroughly familiar with the medical information to ensure that they can act efficiently in an

emergency. Within the Guide is an International Chemical Safety Card which should be readily available, and should be clearly explained, to all who could come into contact with the chemical. The section on regulatory information has been extracted from the legal file of the International Register of Potentially Toxic Chemicals (IRPTC) and from other United Nations sources.

The target readership includes occupational health services, those in ministries, governmental agencies, industry, and trade unions who are involved in the safe use of chemicals and the avoidance of environmental health hazards, and those wanting more information on this topic. An attempt has been made to use only terms that will be familiar to the intended user. However, sections 1 and 2 inevitably contain some technical terms. A bibliography has been included for readers who require further background information.

Revision of the information in this Guide will take place in due course, and the eventual aim is to use standardized terminology. Comments on any difficulties encountered in using the Guide would be very helpful and should be addressed to:

The Manager
International Programme on Chemical Safety
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World Health Organization
1211 Geneva 27
Switzerland

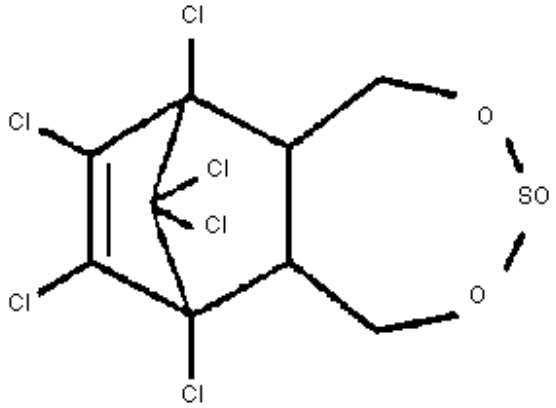
THE INFORMATION IN THIS GUIDE SHOULD BE CONSIDERED AS A STARTING POINT TO A COMPREHENSIVE HEALTH AND SAFETY PROGRAMME

1. PRODUCT IDENTITY AND USES

1.1 Identity

Common name: Endosulfan (ISO, BSO, ANSI, ESA), benzoepin (JMAF)

Chemical structure:



Molecular formula:	$C_9H_6Cl_6O_3S$
CAS chemical name:	6,7,8,9,10,10-hexachloro-1,5,5a,6, 9,-9a-hexahydro-6,9-methano-2,4, 3-benzodioxathiepin-3-oxide.
Trade names:	Beosit, Malix, Thiodan, Thiofor, Thiomul, Thionex, Thimul Formulations under other trade names may also exist
Development codes:	HOE 002671, NIA 5462
CAS registry number:	115-29-7
RTECS registry number:	RB 9275000
Relative molecular mass:	406.9

Technical endosulfan is a brown crystalline substance consisting of alpha- and beta-isomers in the ratio of approximately 70:30. Its purity is 94-96%.

1.2 Physical and Chemical Properties

Pure grade endosulfan is a colourless crystalline solid. Its solubility in water is low, being less than 0.5 mg/litre at 20°C, but increases with decreasing pH. Solubility in other solvents varies from 5-65%.

Technical endosulfan is usually sold in the form of brown crystalline

flakes with a faint odour of sulfur dioxide. It is stable to sunlight, sensitive to moisture, unstable in alkaline media, and subject to slow hydrolysis.

Endosulfan is available as an emulsifiable concentrate, water dispersible powder, dispersion, dust, granules, and as an ultra-low-volume (ULV) formulation.

Some physical and chemical properties of pure and technical endosulfan are listed in the International Chemical Safety Card on pages 22-25.

1.3 Analytical Methods

Standard analytical methods for the determination of endosulfan in the technical product, and in formulations, include saponification and titration of the sulfur dioxide formed with iodine, or gas chromatography. The method of choice for the determination of residues is gas chromatography with electron capture detection. In considering residue levels, the sum of the alpha- and beta-isomers plus the metabolite endosulfan sulfate, which is similar in toxicity to the parent compound, have to be considered.

1.4 Production and Uses

Present world production of technical grade endosulfan is estimated to be of the order of 10 000 tonnes per year.

Endosulfan is used in a formulation as a non-systemic contact and stomach insecticide, mainly in agriculture, in the control of the tsetse fly, and in the control of home garden pests.

Endosulfan controls a wide range of sucking and chewing insect pests, notably of the orders of Lepidoptera, Coleoptera, Heteroptera, Homoptera, Thysanoptera, Diptera, and some species belonging to the order of Acarina. It is especially used on non-food crops, such as cotton and tobacco, and on food crops, such as vegetables, fruits, corn, cereals, oilseeds, potatoes, tea, and coffee. It is also used on numerous other crops.

2. SUMMARY AND EVALUATION

2.1 Endosulfan toxicity

WHO (1986) classified endosulfan in the category of technical products that are moderately hazardous, based on an oral LD_{50} in the rat of 80 mg/kg body weight.

Endosulfan can be absorbed following ingestion, inhalation, or skin contact. It is readily metabolized and eliminated and does not accumulate in the body.

Acute intoxication may result in neurological manifestations, such as irritability, restlessness, muscular twitchings, and convulsions that may end in death.

The long-term, no-observed-adverse-effect level in rats was 30 mg/kg diet (equivalent to 1.5 mg/kg body weight) and 0.75 mg/kg body weight in dogs. At higher dose levels, testicular and renal damage occurred in the rat.

Endosulfan was essentially negative in short-term tests for genetic activity. It did not show any carcinogenic activity in mice or rats, but studies were limited by inadequate reporting or survival.[a]

Several cases of suicidal and occupational poisoning have been reported, the latter resulting, in most cases, from neglecting safety precautions.

2.2 Human exposure to endosulfan

Food is the main source of exposure of the general population to endosulfan. Endosulfan residues in food (the sum of its alpha- and beta-isomers and endosulfan sulfate) have been found to be generally well below FAO/WHO maximum residue limits.

In occupationally-exposed persons, both skin contact and inhalation can be important routes of absorption, when adequate safety precautions are not taken.

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[a] Adequate proprietary data on reproductive toxicity, teratogenicity, and neurotoxicity have become available since this evaluation was made in 1984; new carcinogenicity studies on the rat and the mouse are in progress.

2.3 Evaluation of Health Risks for Man

The main hazard associated with endosulfan is acute intoxication through overexposure. Such situations may be due to intentional or accidental overexposure or to gross negligence in occupational situations.

In all other exposure situations, especially as far as the general population is concerned, the toxicity profile and the present exposure pattern do not indicate any appreciable hazard.

2.4 Fate in the Environment

Both endosulfan isomers are fairly resistant to photodegradation, but the metabolites endosulfan sulfate and endosulfan diol are susceptible to photolysis. The half-life of endosulfan in water is estimated to be 4 days, but anaerobic conditions and/or a low pH will lengthen the half-life. In water, it is mainly degraded to endosulfan diol.

In soil, the alpha-isomer disappears more rapidly than the beta-isomer. Endosulfan sulfate, the major degradation product in soil, is relatively persistent. These compounds are not prone to leaching.

Biodegradation in soil and water is dependent on climatic conditions and on the types of microorganism present.

2.5 Evaluation of Effects on the Environment

Endosulfan does not appear to be a problem with regard to persistence in biota. It is not readily bioaccumulated. In aquatic organisms, loss soon balances uptake and a fairly low plateau level of residues is achieved.

Fish are extremely sensitive to endosulfan and the killing of fish has been reported as a result of the discharge of endosulfan into rivers. Agricultural run-off has not caused such a problem. However, application of endosulfan to wetlands at recommended rates may well result in the killing of fish. Large-scale field experience with endosulfan has not resulted in any long-term adverse effects on the environment.

Because there is little or no biomagnification, endosulfan applied at recommended rates is not hazardous for terrestrial animals. Toxicity for bees is low to moderate. Toxicity for birds is high in a laboratory setting, but no poisonings have been reported under field conditions.

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

(a) The general population does not appear to be at risk from

endosulfan residues in food. Exposure of the general population via air and drinking-water is generally low.

(b) Occupational exposure has resulted in some incidents of poisoning. These appear to have occurred, however, only when adequate safety precautions were not taken.

(c) In terms of the general environment, endosulfan is highly toxic for some aquatic species, particularly fish. Endosulfan is moderately toxic for honey bees.

(d) Endosulfan does not accumulate in food-chains and is eliminated rapidly from the body.

3.2 Recommendations

(a) Precautions should be taken to avoid contamination of surface and drinking-water supplies during spraying. Where necessary, residue levels of endosulfan in drinking-water should be reduced by proper water treatment.

(b) In countries where endosulfan is used for tsetse fly control, exposed populations should be monitored for potential adverse health effects.

4. HUMAN HEALTH HAZARDS, PREVENTION AND PROTECTION, EMERGENCY ACTION

4.1 Main Human Health Hazards, Prevention and Protection, First Aid

Endosulfan is an organochlorine insecticide. It is toxic and can be hazardous for human beings if incorrectly or carelessly handled. It is therefore essential that the correct precautions are observed in handling and use. For details see the International Chemical Safety Card on pages 22-25.

4.1.1 Advice to Physicians

4.1.1.1 Symptoms of poisoning

Endosulfan is hazardous by mouth, by skin contact (especially liquid formulations) and, to a lesser extent, by inhalation. It acts as a stimulant of the central nervous system.

Following accidental ingestion or gross overexposure, symptoms may include headache, dizziness, nausea, vomiting, weakness in the legs,

and convulsions, sometimes leading to death.

4.1.1.2 Medical advice

Medical treatment is largely symptomatic and supportive and directed against convulsions and anoxaemia.

If endosulfan is swallowed, vomiting should not be induced and emetics are contraindicated, because many liquid formulations contain hydrocarbons and there is a risk of aspiration pneumonia. Instead, the stomach should be emptied as soon as possible by careful gastric lavage (with a cuffed endotracheal tube already in place), avoiding aspiration into the lungs. This should be followed by intragastric administration of 3-4 tablespoons of activated charcoal and 30 g magnesium or sodium sulfate in a 30% aqueous solution. Oily purgatives are contraindicated. No fats, oils, or milk should be given.

If convulsions occur, anticonvulsants should be given immediately, e.g., 10 mg of diazepam, slowly, intravenously (children 1-5 mg), repeated as necessary; or thiopental sodium or hexobarbital sodium slowly, intravenously, in a dose of 10 mg/kg with a maximum total dose of up to 750 mg for an adult, or paraldehyde 5 ml by intramuscular injection. These short-acting anticonvulsants should always be followed by phenobarbital given orally at 3 mg/kg (up to 200 mg for an adult), or phenobarbital sodium given intramuscularly at 3 mg/kg (also up to 200 mg for an adult).

Morphine and its derivatives, epinephrine, and noradrenaline should never be given.

An unobstructed airway must be maintained. Respiratory inadequacy, which may be accentuated by barbiturate anticonvulsants, should be corrected and oxygen and/or artificial ventilation may be needed.

4.1.2 Health Surveillance Advice

A complete medical history and physical examination of regularly exposed workers should be made on an annual basis.

4.2 Safety in Use

Handling liquid formulations:	Wear protective neoprene or PVC gloves, cotton overalls, rubber boots, and face shield.
Handling powder formulations:	Avoid raising a dust cloud. Wear

	protective gloves and dust mask. Follow the advice relating to personal hygiene.
Application in the field	
Aerial application:	Ensure that flag-men (markers) do not stand in the spray-path of the aircraft; do not spray over surface waters and avoid spraying over ditches, canals, rivers, streams, ponds, or lakes.
Ground spraying:	Wear suitable protective clothing (i.e., cap or hat, cotton overalls or long-sleeved cotton shirt and long trousers, boots or shoes); when spraying tall crops or when there is a risk of accidental contamination by the spray, also wear impermeable hood and jacket; at all times avoid exposure to the spray mist; do not spray into the wind.
Hand-held ULV application:	Wear suitable protective clothing (i.e., cap or hat, cotton overalls or long-sleeved cotton shirt and long trousers, boots or shoes; read and observe the instructions that apply to the equipment being used; pay proper attention to wind speed and direction; always spray in a down-wind direction; do not spray if there are other people immediately down-wind.
After application:	Take off heavily splashed or contaminated clothing; wash hands and exposed skin before eating, drinking, or smoking; wash overalls, boots, hat, and other protective clothing thoroughly, especially the inside of gloves; keep application equipment in good condition, and free from leaks and external contamination; keep

contents tightly closed in original labelled container when not fully used; do not reuse empty container for any other purpose; keep container in a safe place away from food, children, and animals; empty containers must be washed out and disposed of as advised in sections 4.4.1 and 4.6.2.

4.3 Explosion and Fire Hazards

4.3.1 Explosion hazards

The explosion hazard will depend on the solvent used in the formulation, or on the characteristics of the dust.

4.3.2 Fire hazards

Liquid formulations containing organic solvents may be flammable. Extinguish fires with alcohol-resistant foam, carbon dioxide, or powder. With sufficient burning or external heat, endosulfan will decompose, emitting toxic fumes. Fire-fighters should be equipped with self-contained breathing apparatus, eye protection, and full protective clothing.

The use of water spray should be confined to the cooling of unaffected stock, thus avoiding the accumulation of polluted run-off from the site.

4.4 Storage

Products should be stored in locked buildings -- preferably buildings dedicated to insecticides.

Keep the products out of reach of children and unauthorized personnel. Do not store near foodstuffs or animal feed.

4.4.1 Leaking containers in store

Take precautions and use appropriate personal protection (section 4.2). Empty any product remaining in damaged/leaking containers into a clean empty drum, which should then be tightly closed and suitably labelled.

Sweep up spillage with sawdust, sand, or earth (moisten for powders), and dispose of safely.

After emptying, the leaking containers should be rinsed with at least 1 litre water per 20-litre drum. Swirl round to rinse the walls, empty, and add the rinsings to the sawdust or earth. Puncture the container to prevent reuse.

4.5 Transport

Comply with any local requirements regarding movement of hazardous goods. Do not transport in the same compartment as foodstuffs. Check that containers are sound and labels undamaged before despatch.

4.6 Spillage and Disposal

4.6.1 Spillage

Before dealing with any spillage, precautions should be taken as required, and appropriate personal protection should be used (section 4.2).

4.6.1.1 Solid products

Sweep up and absorb remaining spilled product with moist sawdust, sand, or earth, and transfer the sweepings in a suitable container to a safe place for disposal.

4.6.1.2 Liquid products

Prevent the liquid from spreading or contaminating other cargo, vegetation, or waterways, by making a barrier of the most suitable available material, e.g., earth or sand.

Absorb spilled liquid with sawdust, sand, or earth, sweep up and place it in a closeable container for later transfer to a safe place for disposal.

4.6.1.3 All products

As soon as possible after the spillage and before reuse, cover all contaminated areas with damp sawdust, sand, or earth. Sweep up and place in a closeable container for later transfer to a safe place for disposal. Since this insecticide is highly toxic for fish, care should be taken to avoid run-off into water courses.

4.6.2 Disposal

Any surplus product, contaminated absorbents, and containers should be

disposed of in an appropriate way. Waste material should be burned in a proper incinerator designed for organochlorine waste disposal (1000°C and 30 min residence time with effluent gas scrubbing). If this is not possible, bury in an approved dump or landfill where there is no risk of contamination of surface or ground water. Comply with any local legislation regarding disposal of toxic wastes. Puncture container to prevent reuse.

5. HAZARDS FOR THE ENVIRONMENT AND THEIR PREVENTION

Endosulfan is highly toxic for fish and some other aquatic organisms, and moderately toxic for honey bees. It is not readily bioaccumulated and it does not persist in the environment.

Industrial discharges from manufacture, formulation, and technical applications should not be allowed to pollute the environment and should be properly treated (section 4.6.2).

Any spillage or unused product should be prevented from spreading to vegetation or waterways and should be treated and disposed of properly.

6. INTERNATIONAL CHEMICAL SAFETY CARD

This card should be easily available to all health workers concerned with, and users of, endosulfan. It should be displayed at, or near, entrances to areas where there is potential exposure to endosulfan, and on processing equipment and containers. The card should be translated into the appropriate language(s). All persons potentially exposed to the chemical should also have the instructions on the chemical safety card clearly explained. Space is available on the card for insertion of the National Occupational Exposure Limit, the address and telephone number of the National Poison Control Centre, and for local trade names.

ENDOSULFAN

CAS chemical name: 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide
Molecular formula: $C_9H_6Cl_6O_3S$
RTECS registry number: RB 9275000 CAS Registry number: 115-29-7

PHYSICAL PROPERTIES OTHER CHARACTERISTICS

Pure substance:		
Melting point of alpha-isomer	109.2°C	Endosulfan is a non-systemic contact and stomach insecticide effective against a wide range of sucking and
of beta-isomer	213.3°C	
Relative density at 20°C	1.745	chewing insect pests in agriculture, and public health
Vapour pressure	<0.1 µPa at 20°C <1.4 µPa at 40°C	and technical fields of applications
Relative molecular mass	406.9	
Solubility in water	0.5 mg/litre at 20°C	Formulations include:
in most organic solvents	5-65 g/100 ml at 20°C	emulsifiable concentrates water dispersible powders, dispersions, dusts, granules, and ultra-low-volume formulations
Technical grade:		
Melting point	80°C	
Appearance	brown crystalline flakes	
Odour	faint odour of sulfur dioxide	
Ratio of isomers	alpha- to beta-endosulfan approx. 70:30	

HAZARDS/SYMPTOMS	PREVENTION AND PROTECTION	FIRST AID
SKIN: may cause poisoning in contact with skin immediately	Avoid contact with skin; wear suitable protective clothing and gloves	After contact with skin, wash immediately with plenty of water and soap; remove all contaminated clothing
EYES: may cause irritation to eyes	Avoid contact with eyes; wear eye protection	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
INHALATION: dusts may cause poisoning by inhalation	Do not breathe dusts or sprays	
INGESTION: unlikely occupational hazard	Do not eat, drink or smoke during work; wash hands before eating,	

	drinking or smoking	
Accidental or intentional ingestion may cause poisoning		If swallowed, seek medical advice immediately and show container or label; do not induce vomiting where organic solvents are present in emulsifiable concentrates; keep at rest, lying face downwards, and ensure a clear airway
ENVIRONMENT: Dangerous for aquatic life, particularly fish	Do not contaminate surface waters	

SPILLAGE	STORAGE	FIRE AND EXPLOSION
Take appropriate personal precautions; prevent liquid from spreading or contaminating other cargo, vegetation, or surface waters and drainage systems, with a barrier of most suitable material, e.g., earth or sand	Products should be stored in locked buildings preferably dedicated to insecticides; keep out of reach of children; keep away from food, drink and animal feeding stuffs	Liquid products containing organic solvents may be flammable. Extinguish fires with alcohol-resistant foam, CO2 or powder. With sufficient burning or external heat endosulfan will decompose, emitting toxic fumes. Fire-fighters should be with self-contained breathing apparatus, eye protection, and full protective clothing; confine the use of water spray to cooling of unaffected stock, thus avoiding the accumulation of polluted run-off from the site
Absorb spilled liquid with sawdust, sand, or earth; sweep up and place it in a closeable container for later safe disposal. Since this insecticide is dangerous for fish, care should be taken to		

avoid run-off into water courses

WASTE DISPOSAL	NATIONAL INFORMATION	
Endosulfan waste material should be burned in a proper incinerator designed for organochlorine waste disposal; if this is not possible, bury in an approved dump or landfill where there is no risk of contamination of surface or ground water; comply with any local legislation regarding disposal of toxic wastes	National Occupational Exposure Limit: National Poison Control Centre: Local Trade Names:	UN No. 2761, 2762, 2995, 2996

Giftig
Giftig
Τοξικό
Toxic
Toxique
Tossico
Vergiftig

7. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

The information given in this section has been extracted from the International Register of Potentially Toxic Chemicals (IRPTC) legal file and other UN sources. Its intention is to give the reader a representative but non-exhaustive overview of current regulations, guidelines, and standards.

The reader should be aware that regulatory decisions about chemicals taken in a certain country can only be fully understood in the framework of the legislation of that country.[a]

7.1 Previous Evaluations by International Bodies

The FAO/WHO Joint Meeting on Pesticide Residues (JMPR) has reviewed residues and toxicity data on endosulfan on several occasions in the past: 1965, 1967, 1968, 1971, 1974, 1975, 1978, 1982, and 1985.

The 1985 meeting discussed the situation with regard to endosulfan and found it to be unsatisfactory. The meeting concluded that a complete reevaluation was necessary, which should be based on current use patterns, with toxicological data obtained following up-to-date protocols and residue data obtained using the present analytical methods. The reevaluation should also take into account the relevant information in the Environmental Health Criteria document on endosulfan. The required data should be submitted for study by the 1989 JMPR. Nevertheless, because of the absence of any indications of potential major adverse toxicological effects in man, the temporary acceptable daily intake (TADI) of 0.008 mg/kg body weight was extended.

WHO (1975) issued a data sheet on endosulfan (No. 15) in its series of "Data sheets on chemical pesticides" Based on a brief review of use, exposure, and toxicity, practical advice is given on labelling, safe-handling, transport, storage, disposal, decontamination, selection, training, and medical supervision of workers, and first aid and medical treatment.

WHO has classified endosulfan as moderately hazardous (WHO, 1986).

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[a] The regulations and guidelines of all countries are subject to change and should always be verified withe appropriate regulatory authorities before application.

7.2 Exposure Limit Values

Some exposure limit values are shown in the table on pages 28-31.

When no effective date appears in the IRPTC legal file, the year of the reference from which the data are taken is indicated by (r).

7.3 Specific Restrictions

The use of endosulfan is permitted with certain restrictions in Argentina, Canada, Czechoslovakia, Finland, Japan, Norway, Portugal, the USSR, the United Kingdom, Venezuela, and Yugoslavia.

Absorption through the skin is indicated as a potentially hazardous route in the regulatory documents of Argentina, Australia, Belgium, Canada, Finland, the Netherlands, Switzerland, the United Kingdom, and the USA.

7.4 Labelling, Packaging and Transport

The United Nations Committee of Experts on the Transportation of Dangerous Goods classifies endosulfan in:

Hazard Class 6.1: poisonous substance

Packing Group II: substances and preparations presenting a serious risk of poisoning, when the content of active ingredient is 80-100%.

Packing Group III: substance presenting a relatively low risk of poisoning in transport, when the content of active ingredient is 20-80% (solid) or 8-80% (liquid).

EXPOSURE LIMIT VALUES

Medium	Specification	Country/ organization	Exposure limit description	Value	Effective date
AIR	Work-place	Argentina	Maximum permissible concentration		1979
			- time-weighted average (TWA)	0.1 mg/m^3	
			- short-term exposure limit (STEL)	0.3 mg/m^3	
		Australia	Threshold limit value (TLV)		
			- time-weighted average (TWA)	0.1 mg/m^3	
		Bulgaria	Maximum permissible concentration	0.1 mg/m^3	
		Finland	Occupational exposure limit		
			- time-weighted average (TWA)	0.1 mg/m^3	1981
			- short-term exposure limit	0.3 mg/m^3	1981
		Netherlands	Maximum limit		
			- time-weighted average (TWA)	0.1 mg/m^3	

		Switzerland	Maximum worksite concentration (MAK) - time-weighted average (TWA)	0.1 mg/m^3
		United Kingdom	Recommended limit - time-weighted average (TWA) - short-term exposure level (STEL) (10 min - TWA)	0.1 mg/m^3 0.3 mg/m^3
		USA	Threshold limit value (TLV) - time weighted average (TWA) - short term exposure limit (STEL)	0.1 mg/m^3 0.3 mg/m^3
		USSR	Maximum allowable concentration (MAC) - ceiling value (CLV) (vapour + aerosol)	0.1 mg/m^3
1977				

Medium	Specification	Country/ organization	Exposure limit description	Value	Effective date
AIR	Ambient	USSR	Maximum allowable concentration (MAC)		1984
			- (1x/day)	0.017 mg/m^3	
			- (av/day)	0.0017 mg/m^3	
FOOD	Intake from	FAO/WHO	Acceptable daily intake (ADI)	0.008 mg/kg body weight	
		USSR	Acceptable daily intake (ADI)	0.002 mg/kg	1983
FOOD	Plant	Argentina	Maximum limit	0.5-2 mg/kg	1969
		Brazil	Acceptable limits	0.01-2 mg/kg	
		FAO/WHO	Maximum residue limit	0.02-30 mg/kg	1987
		Germany,	Maximum residue limit	0.2-30.0 mg/kg	1984

		Federal Republic of		
		Finland	Maximum residue limit	0.5-1.0 mg/kg 1987
		Netherlands	Maximum residue limit	0.05-30 mg/kg 1987
		EEC	Maximum residue limit	1 mg/kg 1984
			(Root vegetables)	0.2 mg/kg 1976
		India	Maximum tolerable concentration	0.2-2.0 mg/kg
		Kenya	Maximum limit	0.1-30.0 mg/kg
		Sweden	Maximum tolerable concentration	0.2-0.5 mg/kg 1985

Medium	Specification	Country/ organization	Exposure limit description	Value	Effective date
FOOD		USA	Acceptable residue limit (in dried tea)	24 mg/kg	
			Acceptable residue limit	0.1-2 mg/kg	
		USSR	Maximum residue limit for food products exported and imported by CMEA countries	0.1-1.0 mg/kg	1984
		USSR	Pesticide is prohibited in some food products		1983
WATER	Ambient	Mexico	Maximum permissible concentration (coastal)	0.0002 mg/litre	1973
			(estuarine)	0.002 mg/litre	1973

SOIL	USSR	Permissible limit	0.1 mg/kg

The label should be as follows:

Class II

Symbol (skull and crossbones): black
Background: white

Class III:

The bottom half of the label should bear the inscriptions
HARMFUL
Stow away from foodstuffs
Symbol (St Andrew's Cross over an ear of wheat): black
Background: white

The FAO specifications for plant protection products containing endosulfan specify the composition and purity of the technical product and its formulations. They also advise on methods for checking this. The endosulfan content should be stated and may not differ by more

than 2% from this for the technical product (and up to 10% for some formulations). The isomeric composition of the total endosulfan should be:

64-67% alpha-isomer and 29-32% beta-isomer.

In the WHO interim specifications for endosulfan technical and endosulfan emulsifiable concentrate, similar specifications and checking methods are given for its use in public health.

The WHO specifications include the following provisions:

(a) Technical endosulfan shall consist essentially of a mixture of the alpha- and beta-isomers (same isomeric composition as above for FAO) of endosulfan, together with related manufacturing compounds, and shall be in the form of beige to dark brown flakes with the tendency to agglomeration, free from extraneous impurities and added modifying agents.

(b) Technical endosulfan shall be packed in suitable, clean containers, as specified in the order.

All packages shall bear, durably and legibly marked on the container the following:

Manufacturer's name
Endosulfan to Interim Specification WHO/IS/1.0205-1
Batch or reference number, and date of test
Net weight of contents
Date of manufacture

and the following minimum cautionary notice:

Endosulfan is a sulfurous acid ester of a chlorinated cyclic diol. It is poisonous if swallowed or inhaled as dusts or mists. Avoid eye and skin contact; wear safety goggles, protective gloves, clean protective clothing, and a respirator when handling the material. Wash thoroughly with soap and water after using. Keep the material out of reach of children and well away from foodstuffs, animal feed, and their containers. If poisoning occurs, call a physician. Endosulfan is highly toxic to fish. Keep the material and the emptied containers away from ground and surface water.

(c) The emulsifiable concentrate shall consist of technical endosulfan dissolved in suitable solvents, with other necessary formulants added. It shall be in the form of a stable liquid, free from suspended matter

and sediment. The technical endosulfan used in the manufacture of the concentrate shall comply with the requirements of Interim Specification WHO/IS/1.0205-1.

(d) Endosulfan emulsifiable concentrate shall be packed in suitable, clean containers, as specified in the order. All packages shall bear, durably and legibly marked on the container, the following:

Manufacturer's name
Endosulfan emulsifiable concentrate to Interim Specification WHO/IS/3.0205-1
Endosulfan, ... g/kg
Batch or reference number and date of test
Net weight of contents
Instructions for dilution
Date of formulation

and the same minimum cautionary notice as for the technical material.

The European Community legislation requires labelling as a dangerous substance using the symbol:

Giftig
Giftig
Τοξικό
Toxic
Toxique
Tossico
Vergiftig

The label must read:

toxic by inhalation, in contact with skin and if swallowed; irritating to eyes and skin; keep out of reach of children; keep away from food, drink and animal feeding stuffs; if you feel unwell, seek medical advice (show the label where possible).

The European Community legislation on labelling of pesticide preparations classifies endosulfan in Class I/b for the purpose of determining the label for preparations containing endosulfan and other active ingredients.

7.5 Waste Disposal

In the USA, any non-domestic waste containing endosulfan must be treated as a hazardous waste. Specific instructions are given for notification and incineration. Under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), as amended, unless in compliance with a specified permit or procedure, owners/operators of vessels or onshore or offshore facilities must notify the USA government (National Response Center) of any release of endosulfan in or on navigable waters, adjoining shorelines, in the contiguous zone or beyond the contiguous zone or to any other environmental media (air, land or groundwater) in an amount equal to or greater than one pound (0.454 kg).

In Finland, any waste containing endosulfan is classified as hazardous waste and must be treated according to specific instructions.

7.6 Other Measures

The European Community legislation requires that Member States shall prescribe that cereals (wheat, rye, barley, oats, paddy rice, buckwheat, millet, grain sorghum, triticale) may not contain (in and on cereals), from the time they are put into circulation, levels of residues of endosulfan (sum of alfa- and beta-isomers and of endosulfan sulfate, expressed as endosulfan) greater than maximum 0.1 mg/kg, and, in and on maize, levels of residues greater than 0.2 mg/kg (applicable latest by June 1988).

The European Community legislation requires that Member States shall prescribe that fruit and vegetables may not contain, from the time they are put into circulation, levels of residues of endosulfan (sum of alfa- and beta-isomers and of endosulfan sulfate, expressed as endosulfan) greater than 0.2 mg/kg for root vegetables and root fruits, and greater than 1 mg/kg for leaf vegetables.

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See Also:

Toxicological AbbreviationsEndosulfan (EHC 40, 1984)Endosulfan (PDS)Endosulfan (PIM 576)Endosulfan (FAO Meeting Report PL/1965/10/1)Endosulfan (FAO/PL:1967/M/11/1)Endosulfan (FAO/PL:1968/M/9/1)Endosulfan (WHO Pesticide Residues Series 1)Endosulfan (WHO Pesticide Residues Series 4)Endosulfan (WHO Pesticide Residues Series 5)Endosulfan (Pesticide residues in food: 1982 evaluations)Endosulfan (Pesticide residues in food: 1989 evaluations Part II Toxicology)Endosulfan (JMPR Evaluations 1998 Part II Toxicological)

Landbrukstilsynet

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Supporting documentation on endosulfan

I refer to your letter dated Sept.18th 2003 requesting for supporting documentation on endosulfan.

Endosulfan has never been manufactured within Norway. The last preparation with an approval in Norway was Thiodan 35. This preparation was permitted sold on the Norwegian marked until Dec. 31st 1997. Import of endosulfan was permitted until Dec. 31st 1996.

The risk assessment was mainly based on data submitted by the manufacturer, and this data has been returned to the manufacturer. Enclosed is an English summary of Swedish report from 1990 which was used in the toxicological evaluation of endosulfan.
Our notification document provided quite a detailed assessment, please refer to this for the information needed for a focused summary of the information used in support of the regulatory action. The Norwegian Agricultural Inspection Service has no further information on this chemical.

Hopefully this information is useful to the Interim Chemical Review Committee.

Yours Sincerely

Reidunn Stokke

Reidunn Stokke
Senior executive officer (ecotoxicologist)

Swedish report, 1990

VII ENGLISH SUMMARY

The objective of this document is to present a comprehensive survey and evaluation of available toxicological data of endosulfan. These data are primarily based on original reports listed in the reference section.

Endosulfan is the common name for 1,4,5,6,7,7-hexachloro-8,9,10-trinorborn-5-en-2,3-ylendimethylsulphite and is the active ingredient in the formulation Cyclodan from Hoechst AG which is used against insects and mites.
Technical endosulfan is a mixture of two isomers, α- and ß-endosulfan (2:1), with different chemical and physical properties. Technical endosulfan is lipofilic, a crystal at room temperature and not so volatile. Technical endosulfan has a melting point of about 80 °C. The purity of the technical grade has been reported to be not less than 94 % and the substance is most stable at acid conditions.

The toxicokinetic data indicate that endosulfan is well absorbed in the gastrointestinal tract. Furthermore, toxicological data suggest that this compound is also well absorbed by the skin and by the lungs. Endosulfan is primarely distributed to the liver, kindeys and adipose tissue. The compound has also been observed in the testicles and in the brain.
The absorbed compound is highly metabolized, primarily to endosulfan-sulphate and endosulfan-diol, and to a less extent to endosulfan-ether or rather endosulfan-α-hydroxy ether and endosulfan-lacton.
Endosulfan is excreted by the urine and the feces. A significant amount of the absorbed compound is excreted via the bile, mainly as metabolites.

The acute toxicity of endosulfan is high to very high.

Peroral studies of subacute and subchronic toxicity have shown that endosulfan is primarily affecting the liver and the kidneys as well as the central nervous system (CNS). Immunosuppression has

also been observed. These effects were observed att doses between 1-10 mg/kg/day. Mice seem to be more sensitive than rats. After dermal administration of 10 mg/kg/day to rats, effects on the liver and CNS was noticed, indicating that systemic effects cannot be excluded by this type of exposure. In an inhalation study on rats signs of CNS intoxication was observed at an air concentration of 2.0-6.5 mg/m^3.

In peroral studies of chronic toxicity endosulfan has caused effects on the liver and the kidneys.

The carcinogenic properties of endosulfan have been debated since structural related compound like chlordane and heptachlor have such properties.
Endosulfan has not been carcinogenic in any of the studies available. Unfortunately, only a mouse study fulfill the guidelines of OECD. A new rat study will be finished 1990.

The genotoxic properties of endosulfan is quite well investigated. Available data indicate that endosulfan has no or a very low genotoxic potential.

Available data have not shown any embryo-/fetotoxic or impaired fertility at doses where no maternal intoxication was observed.

Available studies indicate that technical endosulfan has no or a low skin irritating potential and no sensitization properties.

Endosulfan is a weak inducer of cytochrome P-450 dependent monooxygenases in the liver.

Experience from human exposure indicates that endosulfan is distributed mainly to the liver and the kidneys and to a less extent to the brain. High and acute doses of endosulfan have been shown to affect the CNS and to give symtoms like impaired memory and coordination. Furthermore, cyonosis, dyspnoe and convulsions have also been observed.