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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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SUBJECT: Endosulfan (Thiodan) Registration Standard

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Attached are the Topical Discussion, Toxicology Profile, Toxicology Hazard Assessment and Tables of Data Requirement for Endosulfan.

ENDOSULFAN

Registration Standard

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Introduction

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 mixture of two geometric isomers of a synthetic chlorinated cyelodiene was introduced in 1956 as an experimental broad spectrum pesticide.

Endosulfan is an insecticide/acaricide registered for use on a large number of agricultural and ornamental crops. The estimated annual use of endosulfan is between 1.5 million and 2 million pounds active ingredient. Approximately 60-80% of the pesticide is used on fruit trees (predominantly apples, peaches, pears, and cherries) and vegetables (predominantly potatoes, tomatoes, green beans, lettuce and sweet corn). Other uses include cotton, alfalfa and tobacco.

In 1971 farmers in the United States used roughly one million pounds of endosulfan. About 20% of this quantity was used on Irish potatoes, with substantial application on other vegetables, tobacco, apples and other fruits, and nuts. By 1973, when endosulfan was registered for use on 59 agricultured crops, California alone used over 0.8 million pounds. Endosulfan residue in 1973 ranged from trace amounts to 0.439 ppm in over 8 percent of all food composites sampled during that year.

Endosulfan is formulated into dusts (2%, 4% and 5% ai), granules (3% ai), wettable powder (50% ai), emulsifiable concentrates (9%, 22-24%, and 33-34%), pressurized liquid (aerosol, 10% ai), and an impregnated material (pressure fumigant, 15% ai). Applications of the emulsifiable concentrate and wettable powder formulations are generally foliar with aircraft or ground equipment.

Topical Discussion

The topical discussions listed below correspond to the number of the sections in the proposed guidelines (40CFR, Part 163, August 1978) which explains the minimum data required by the Agency to assess a pesticide's toxicity.

Technical Chemical:

Acute oral toxicity - 163.81-1.
Acute dermal toxicity - 163.81-2.
Acute inhalation toxicity - 163.81-3.
Acute delayed neurotoxicity - 163.81-7.
Subchronic oral toxicity - 163.82-1.
Subchronic dermal toxicity - 163.82-2, -3.
Subchronic inhalation toxicity - 163.82-4.
Subchronic neurotoxicity - 163.82-5.
Chronic feeding studies - 163.82-1.
Oncogenicity - 163.83-2.
Teratogenicity - 163.83-3.
Reproduction - 163.83-4.
Mutagenicity - 163.84-1 through-4.
Metabolism - 163.85-1.

Manufacturing - Use Product:

Acute oral toxicity - 163.81-1.
Acute dermal toxicity - 163.81-2.
Acute inhalation toxicity - 163.81-3.
Primary eye irritation - 163.81-4.
Primary dermal irritation - 163.81-5.
Dermal sensitization - 163.81-6.

Formulated Product:

Acute oral toxicity - 163.81-1.
Acute dermal toxicity - 163.81-2.
Acute inhalation toxicity - 163.81-3.
Primary eye irritation - 163.81-4.
Primary dermal irritation - 163.81-5.
Dermal sensitization - 163.81-6.

Acute Toxicity Testing

Acute Oral Toxicity 163.81-1

The minimum data requirement for testing acute oral toxicity is one test for the technical chemical and one test for the manufacturing use and end use formulatin, preferably using laboratory rat. Separate testing is not required on a formulated product if adequate testing has been done on a similar product where inert ingredients are expected to produce similar toxicity or if the inert ingredients are not expected to add to the toxicity of the product.

Technical Endosulfan:

The acute oral LD_{50} values were determined in groups of 10-20 Sprague Dawley rats per dose level (1964, MRID 00003762). The LD_{50} values were found to be 142 and 53 mg/kg for males and females respectively using cottonseed oil as a vehicle, and 34 and 26 mg/kg for males and females respectively when propylene glycol was the vehicle. This study was classified as Core-Minimum data.

In another study submitted by FMC Corp. (1957, MRID 00003693), the LD_{50} was found to be 110 mg/kg for male rats when cottonseed oil was the vehicle. This study was classified as Core-Supplementary.

Other LD_{50} values for rats were also reported by Gains (1969,). In this report the LD_{50} values were found to be 43 and 18 mg/kg for male and female Sherman rats respectively when peanut oil was used as a vehicle. In this study 60-70 animals were used per test group.

In another study by Boyd and coworkers (1970, MRID 05002183), endosulfan was orally administered in cottonseed oil to male Albino Wistar rats. Eight dose levels, and 10-15 animals per dose level were used. The LD_{50} was found to be 102 mg/kg. This study was classified as Core-Supplementary.

In another study (1975,) endosulfan was administered in 0.5% sodium carboxymethyl cellulose to six groups of 5 male and 8 groups of 5 female Sprague-Dawley rats. Animals were observed for a period of 14 days and survivors were sacrificed thereafter. The LD_{50} values were found to be 40 and 9 mg/kg for males and females respectively. Clinical signs included listlessness, tremors, prostration and hypernea. Necropsy showed reddened intestinal tracts. This study was classified as Core-Minimum data and the chemical was assigned Tox Category I.

The acute oral toxicity of endouslfan sulfate, a major metabolite of endosulfan, was also investigated in rats (1964, MRID 00003762). The LD_{50} values were found to be 82 and 21 mg/kg for males and females respectively when Wesson oil was the vehicle and 31 and 7.5 mg/kg for males and females respectively when the vehicle was propylene glycol This study was classified as Core-Minimum data.

Dorough and coworkers (1978, MRID 05003703) investigated the acute toxicity of each of the - and B isomers as well as the major metabolites of endosulfan in mice. The acute oral LD_{50} values were found to be 11 and 36 mg/kg for the - and B isomers respectively. The acute oral LD_{50} values for the metabolites were, 8 mg/kg for the sulfate, 120 mg/kg for both the - hydroxy ether and the lactone of endosulfan, 270 mg/kg for the ether and > 2,000 mg/kg for the diol.

The acute oral toxicity tests mentioned above can satisfy the data requirements. On the basis of the available acute oral toxicity data, the chemical can be assigned to Tox Category I. Further testing is not required.

Endosulfan Formulations:

1. Dust (2,4,5 and 25%).
2. Granules (3%).
3. Wettable Powder (35 and 50%).
4. Emulsifiable Concentrate (9, 22-24, 33-34, and 50%).
5. Pressure Fumigant (15%).
6. Pressurized Liquid (Aerosal 10%).

No reasonable oral toxicity studies were available to satisfy the data requirements. Testing is required for representatives of formulations 1,3 and 4. Testing is not required for formulation 2, 5 and 6.

Acute Dermal Toxicity 163.81-2

The minimum data requirement for testing acute dermal toxicity is one test for the technical material and one test for each manufacturing use and formulation product, preferably using the albino rabbit. Separate testing is not required on a formulated product if adequate testing has been done on a similar product whose inert ingredients are expected to produce similar toxicity or if the inert ingredients are not expected to add to the toxicity of the product.

Technical Endosulfan:

The acute dermal toxicity of endosulfan was studied in albino rabbits (1957, MRID 00003693) using 10 and 20% solution of endouslfan in cotton-seed oil. The chemical remained in contact with the clipped unabraded abdominal skin for 24 hours. Four animals were used for each dose level. Five dose levels were tested. The seven days acute dermal LD_{50} was determined to be 359 mg/kg. The test was classified as Core-Supplementary data. No Tox Category could be assigned because the toxicity of endosulfan is sex dependent and sex was not specified. This study is insufficient to fulfill the acute dermal toxicity data requirements.

In a recently reviewed study (1975,), six groups of 4 New Zealand white rabbits each received 24 hour occluded exposure to 1000, 2150 and 21,500 mg/kg test material premoistured with saline on abraided skin. The animals were observed for 14 days and the survivors were sacrificed and subjected to necropsy. The LD_{50} was found to be 5930.7 mg/kg (1,344-26,158). This study was classified as Core-Supplementary data since no body weight data were reported and confidence limits did not permit classification of this product on the basis of dermal toxicity.

In a study by Gupta and Chandra (1975, MRID 05003361), a chloroform solution of technical endosulfan was applied to a 10% clipped skin of the total body surface of female rabbits. Four animals were used per dose level, but the number of dose levels were not specified. The animals were observed for a period of 7 days and the survivors were sacrificed thereafter and subjected to necropsy. The dermal LD_{50} values were found to be 182 and 167 mg/kg for the 91 and 90% technical respectively. This study was classified as CoreSupplementary data. The chemical can be assigned to Tox Category I on the basis of acute dermal toxicity reported under the conditions of this study.

Further acute dermal toxicity testing is not required for the technical chemical.

Endosulfan Formulations:

1. Dust (2,4,5 and 25%).
2. Granules (3%).
3. Wettable Powder (35 and 50%).
4. Emulsifiable Concentrate (9, 22-24, 33-34 and 50%).
5. Pressure Fumigant (15%).
6. Pressurized Liquid (Aerosol 10%).

No reasonable acute dermal toxicity studies were available to assess the toxicity of endosulfan formulations. Testing is required for representative formulations in 1,3, and 4. However, testing is not required for formulations in 2,5 and 6.

Acute Inhalation Toxicity 163.81-3

Acute inhalation testing is required to support the registration of the manufacturing use product and formulated products if: the product is a gas, the product produces a respirable vapor or 20% or more of the aerodynamic equivalent of the product is compound of particles not larger than 10 microns. Testing in the laboratory rat is preferred.

The use pattern indicates that the formulation products of this chemical are applied by means that would permit inhalation exposure. Therefore acute inhalation testing is required.

Technical Endosulfan:

Two groups of ten male albino rats were exposed to endosulfan technical dust at a nominal concentration of 1.16 and 5.66 mg/L for one hour. The animals were observed for 14 days following the application and survivors were sacrificed. No mortality occurred in the first group, but 7/10 in the second group died at 1,2 and 3 days after exposure. This study was classified as Core- Supplementary data since the exposure period was only one hour instead of four and the LC_{50} was not determined.

In another study by Ely and coworkers (1967, MRID), the 4 hr LC_{50} vlaues for technical endosulfan were 0.35 and 0.08 mg/L for male and female rat respectively. No other experimental details were reported. If the results of this report were obtained according to an acceptable standard procedure, the chemical would then be assigned to Tox Category I on the basis of acute inhalation toxicity. This study may be classified as Core-Supplementary data.

Since the chemical is assigned to the highest Tox category and the highest precautionary measures would be taken, and since further testing will not shift the Tox category any higher, therefore, more testing is not required.

Endosulfan Formulations:

1. Dust (2,4,5 and 25%).
2. Granules (3%).
3. Wettable Powder (35 and 50%).
4. Emulsifiable Concentrate (9, 22-24, 33-34, and 50%).
5. Pressure Fumigant (15%).
6. Pressurized Liquid (Aerosol 10%).

No reasonable acute inhalation studies were available to assess the toxicity of formulations. Testing is required for representative formulations 1,3,5, and 6. Data from the dust can be used for the granules.

Primary Eye Irritation 163.81-4

The minimum data requirement for primary eye irritation is one test for the manufacturing use product and formulated products, preferably using the albino rabbit. Separate testing is not required on a formulated product if adequate testing has been done on a similar product whose inert ingredients are expected to produce similar toxicity or if the inert ingredients are not expected to add to the toxicity of the product.

In addition, a primary eye irritation data requirement may be waived if data is submitted demonstrating that the test substance has pH of 1-3 or 12-14; for regulatory purpose, a test substance with a pH of 1-3 or 12-14 will be considered corrosive to the eye.

Technical Endosulfan:

Three mg of technical endosulfan placed into the conjunctival sac of the left eye of each of 3 rabbits (1957, MRID 00003693) . The untreated eye served as a control. The treated eyes were held closed for approximately 30 seconds following application. The eyes were examined for gross signs of irritation at 30 seconds, 1, 4 and 24 hours and daily thereafter for an additonal 6 days. Immediately after treatment the eyes showed very mild irritation, characterized by slight erythema and vascularization of the sclera and nictitating membrane. The observed signs gradualy subsided and the eyes appeared normal within 24 hours. This study was classified as invalid because of the insufficient number of animals used, the very low dose of the chemical applied, and no individual scores were used to indicate the degree of irritation.

In another study (1975,) six New Zealand rabbits each received 0.1 ml (83 mg) of endosulfan in the left eye. Observations were made at 24, 48, and 72 hours following instillation. The eyes were not washed. No corneal opacity occured. All animals showed slight conjunctivae which cleared in 4/6 animals by 72 hours. The study was classified as Core-Supplementary data, since eyes were not washed, and observation lasted only for 72 hours after application instead of one week. However, based on this study the chemical can conservatively be assigned to Tox Category III. Further testing is not required.

Endosulfan Formulations:

1. Dust (2,4,5 and 25%).
2. Granules (3%).
3. Wettable Powder (35 and 50%).
4. Emulsifiable Concentrate (9, 22-24, 33-34, and 50%).
5. Prssure Fumigant (15%).
6. Pressurized Liquid (Aerosol 10%).

No reasonable eye irritation studies were available to assess the toxic effects of these formulations. Testing is required for representatives of formulation 1, 2, 3, and 4.

Primary Dermal Irritation: 163.81-5

The minimum data requirement for primary dermal irritation is one test on the manufacturing use and formulated products, preferably using the albino rabbits. Separate testing is not required on a similar product where inert ingredients are not expected to add to the toxicity of the product.

In addition, a primary dermal irritation data requirement may be waived if data is submitted demonstrating that the test substance has a pH of 1-3 or 12-14; for regulatory purposes, a test substance with a pH 1-3 or 12-14 will be considered corrosive to the skin.

Technical Endosulfan:

Six New Zealand white rabbits were dermally treated with 0.5 gm of endosulfan on abraded and non-abraded skin areas. The exposure continued for 24 hours and the treated spots were occluded. Observations were made at 24, 48 and 72 hours after instillation. Primary irritation score was 0.9 and all animals showed minor erythema (1/4 showing erythma D.S. 4) at 24 hours with clearing in 4/6 animals by 72 hours. This study was classified as Core-Guideline data and the product was assigned to Tox Category IV. Further testing is not required.

Endosulfan Formulations:

1. Dust (2, 4, 5, and 25%).
2. Granulas (3%).
3. Wettable Powder (35 and 50%).
4. Emulsifiable Concentrate (9, 22-24, 33-34 and 50%).
5. Pressure Fumigant (15%).
6. Pressurized Liquid (Aerosol 10%).

No reasonable dermal irritation studies were available to assess the toxic effects of these formulations. Testing is required, for representatives of formulations 1,3,4 and 6.

Dermal Sensitization 163.81-6

The minimum data requirement for dermal sensitization is an intradermal test on the manufacturing use and formulated products, preferably using the guinea pig. Separate testing is not required on a formulated product if adequate testing has been done on a similar product whose inert ingredients are expected to produce similar toxicity or if the inert ingredients are not expected to add to the toxicity of the product.

Technical Endosulfan:

No data were available to evaluate the dermal sensitization potential of the technical chemical. Test is required.

Endosulfan Formulations:

1. Dust (2, 4, 5, and 25%).
2. Granules (5%).
3. Wettable Powder (35 and 50%).
4. Emulsifiable Concentrate (9, 22-24, 33-34 and 50%).
5. Pressure Fumigant (15%).
6. Pressurized Liquid (Aerosol 10%).

No data were available to evaluate the dermal sensitization potential of these formulations. However, it is not expected that these formulations would react differently, therefore, testing is not required.

12

Acute Delayed Neurotoxicity 163.81-7

The minimum data requirement for acute delayed neurotoxicity is one test on the technical chemical using the adult hen.

An acute delayed neurotoxicity test is required if the active ingredient, or any of its metabolites, degradation products, or impurities cause esterase depression or are structurally similar or related to a substance that induces delayed neurotoxicity.

Although endosulfan does not relate to a known group of cholinesterase inhibitors, it was reported by Truhaut and coworkers (1974, MRID 05011227) to cause the inhibition of hamster serum and rat hepatic cholinesterase.

Gupta (1976, MRID 05007646) reported that acetylcholinesterase activity of rat brain was decreased by 23-33% after i.p. injection of 30 or 60 mg/kg.

Furthermore, the chief signs of acute intoxication were mainly manifested as tremors and clonic convulsions that could be centrally mediated (1967, MRID 05007645). The intensity of these symptoms correlated well with the concentration of endosulfan in all areas of the central nervous system (1979, MRID 05004972).

Therefore, testing is required for the technical chemical. The neurological effects may be included as an additional parameter in the subchronic and/or chronic studies.

Subchronic Testing

Subchronic Oral Toxicity 163.82-1.

The minimum data requirement for subchronic oral toxicity is one test on the technical material in two mammalian species, preferably using the rat and dog.

A subchronic toxicity test is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation or is likely to result in repeated human exposure through the oral route. Tolerances exist for endosulfan residues on a variety of raw agricultural commodities, therefore, subchronic toxicity testing is required.

In a study by Gupta and Chandra (1977, MRID 0500307), endosulfan was administered orally to rats at 0, 5 or 10 mg/kg daily for 15 days. All animals were killed at the end of this period. Three animals in the high dose group died during the study. The only significant change in the low dose group was an increase in liver weight ($p < 0.05$). At 10 mg/kg, the absolute weight of kidney, lungs, and adrenal decreased ($p < 0.05$) and the absolute weigh of the liver and the absolute and relative weights of testis decreased ($p < 0.01$). Histopathological examination of the liver in both treated groups revealed dilation of sinusoid around central veins and areas of focal necrosis and degeneration of hepatocytes, and mononuclear monoleucocytes.

Kupffer cell hyperplasia and proliteration in the bile duct, degenerative alterations in the epithelial lining of kidney tubultes, inflamatory areas in the subpleural of the lungs and dilation of the alveoli, severe degeneration of the seminiferous epithelium were also observed in the high dose. No NOEL could be established. The test was only conducted on males. The effect of endosulfan on the female reproductive system also needs to be investigated. This study is inadequate for the limited number of animals and dosage levels employed. More investigation is required.

In another report by Keller (1959, MRID 00003600), groups of two male and two female mongrel dogs received endosulfan at 0, 0.25, or 0.75 mg/kg in gelation capsules, six days a week for one year. A fourth group that received 2.5 mg/kg/day for three days was switched to a reduced level of 0.075 mg/kg/day.

Administration of endosulfan at these levels did not seem to have any treatment related adverse effects with respect to rate of growth, internal organs weight, biochemical and hematological testing, and urinalysis. Gross and histopathological examinations also did not reveal any significant difference between treated animals and controls.

However, although discounted by the authors, there were several findings that were "suggestive" in nature, i.e. the low values for cel volume, hemoglobin levels, and erythrocytes. These findings were not considered statitically significant, most probably because of the very limited number of animals used. [redacted]. This study was classified as Core-Supplementary. The NOEL was considered by the authors to be 0.75 mg/kg or 30 ppm. It is recommended that a more conservative NOEL to be established at 0.25 mg/kg or 10 ppm.

In a report by FMC (1964, IBT C-2665), endosulfan sulfate was administered orally to groups of three male and three female Beagle dogs, at the level of 0, 0.075, 0.75 or 2.5 mg/kg daily for 90 days. After 18 days, the 2.5 mg/kg level was reduced to 1.5 mg/kg because of severe toxic reactions.

No mortality occurred during the 90 days. The body weight gain was depressed in females of all dose levels, while this depression was only exhibited by the males of the highest dose level. Animals received 2.5 mg/kg/day for the first 18 days showed toxic reactions manifested as salivations, tremors and convulsions.

In an original review this study was classified as Core-Supplementary. However, in a recent audit (Canadian report, 8/22/78) the study could not be validated for the lack of raw data in addition to other major deficiencies such as replacement of a high dose female and failure to sacrifice and autopsy the control.

In another study, by Industrial Bio-Test Laboratories (FMC 1964, IBT-C2665), endosufan sulfate was administered to groups of 15 male and 15 female Sprague-Dawley rats in diets at concentrations of 3, 10, 30, 50 and 500 ppm for 12 weeks. At the end of the feeding period, five animals from each sex were then maintained on endosulfan sulfate free diet for 5 months.

Hematological and urologic values and microscopic examination did not reveal any significant difference between the controls and the highest dose level groups.

Significant increases were seen in the absolute and relative weight of the liver in males of the 50 and 500 ppm groups and in females of 30, 50, and 500 ppm groups. Significant increases in these parameters were also observed for kidneys in males of the middle and high dose group. The NOEL was considered to be 10 ppm.

This study was classified as invalid. Further testing is required

Subchronic 21-Day Dermal Toxicity 163.82-2

The minimum data requirements for subchronic 21-day dermal toxicity is one study on the technical chemical, preferably using the albino rabbit.

A subchronic 21-day dermal toxicity test is required if pesticidal use is likely to result in repeated human skin contact. The use pattern for endosulfan is likely to result in repeated human skin contact. Therefore, testing is required.

No data were available to assess the subchronic 21-day dermal toxicity of technical endosulfan. Testing is required.

Subchronic 90-day Dermal Toxicity 163.82-3

The minimum data requirement for subchronic 90-day dermal toxicity is one test for the technical chemical, preferably using the albino rabbit.

The subchronic 90-day dermal toxicity test is required if pesticidal use will involve purposeful application to the skin or will result in human exposure comparable to that, for example, from swimming pool disinfectants or additives or pesticide impregnated fabrics. Endosulfan is not used in the ways described, therefore, testing is not rquired.

Subchronic Inhalation Toxicity 163.82.4

The minimum data requirement for subchronic inhalation toxicity is one test on the technical chemical, preferably using the laboratory rat.

A subchronic inhalation toxicity test is required if pesticidal use may result in repeated inhalation exposure at a concentration that is likely to be toxic, as determined from results of an acute inhalation test.

No data were available. Testing is required.

Subchronic Neurotoxicity 163.82-5

The minimum data requirement for subchronic neurotoxicity testing is one test for the technical chemical, using adult hen or a mammalian species.

A subchronic neurotoxicity test is required if the pesticide has shown positive results in the acute delayed neurotoxicity test or induced irreversible neurological toxicity in a mammalian species.

The decision of whether testing is required can not be determined until results of the acute testing is submitted and reviewed.

Chronic Testing

Chronic Feeding 163.83-1

The minimum data requirement for chronic feeding is one test for the technical chemical, preferably using the laboratory rat.

A chronic feeding study is required if pesticidal use requires a tolerance or exemption from a tolerance, requires issuance of a food additive regulation or is likely to result in repeated human exposure over a significant portion of the life span. Tolerances exist for endosulfan on a variety of raw agricultural commodities, therefore, a chronic feeding testing is required.

In a chronic feeding study (Hazleton Laboratories, Inc., MRID 00003602), groups of 50 (25 males and 25 females) Wistar strain rats were fed 0, 10, 30 or 100 ppm of technical endosulfan incorporated in their diets for two years. Gross appearance, behavior, body weight, food consumption, and hematological values were found to be within normal ranges for all groups.

A significant decrease in the number of surviving females in the 100 ppm group was reported. Males received 100 ppm showed a slight to moderate growth suppression throughout the study. No increase in the tumor incidence was observed in the treated groups. Significant increase in the absolute and relative weights of kidney were observed in males of the 100 ppm group.

Microscopic examination revealed that liver and kidney were the organs most affected by the exposure to the high level of endosulfan. The major kidney lesion manifested as renal tubule dilation, formation of albuminus casts, focal interstitital nephritis, and degeneration of the renal tubule epithilium. Histopathologic examination of the livers of males of the 100 ppm group revealed hydrophopic hepatic cells with pale eosinophilic cytoplasmic inclusions.

These liver and kidney changes were not seen in the females that survived the 100 ppm treatment for the duration of the study. The NOEL was considered to be 30 ppm.

However, in addition to the small number of animals that were initially assigned to each test group, the number of animals survived the two year feeding were also limited. Furthermore, hematologicl and pathological examinations and the number of animals examined were also limited. In addition, no blood chemistry or urinalysis were performed. For these reasons, this study was classified as invalid and can not be used for an adequate assessment of toxic reactions resulting from the ingestion of endosulfan. Therefore, a two years feedng study in rat is required.

In another study by Industrial Bio-Test Laboratories, Inc., (1967, MRID 0000374 four groups of eight Beagle dogs (4 males and 4 females) were administered 0, 3, 10, or 30 ppm of endousulfan in the diet for two years. One male and one female of each group were sacrificed after one year. One male from the 3 ppm group died after 460 days. The rest of the animals were sacrificed at the end of the study. Gross and histopathologic examinations were performed on all animals. No abnormal behavioral reactions were noted. Hematological and clinical chemical testing and urinalysis did not reveal significant treatment-related effects. Gross and histopathological examinations also did not reveal any treatment-related effects. The NOEL was considered to be 30 ppm.

This study was originally classified in a Branch review as Core - Minimum data. Validation in a recent audit report (Canadian report 8/30/78) was inconclusive. The study obviously had major deficiencies that could render the study invalid, e.g. the lack of raw body weight data that prevents complete validation as whether the same animals were used throughout, the presence of differential leukocyte counts record at 18 and 21 months for a male that died at 15 months although these were not included in the final report, histopathological reports were not dated and contained no gross pathology or organ weights, no raw data for food consumption, in addition two females were suspected as being from a previous study. This study can not be used to satisfy the chronic feeding data requirement.

Two chronic feeding studies are required using both rat and dog.

Oncogenicity 163.83-2

The minimum data requirement for oncogenicity, is testing in two mammalian species, preferably the rat and the mouse, using the technical chemical.

An oncogenicity test is required if the active ingredient, or any of its metabolites, degradation products, or impurities, is structurally related to a recognized carcinogen or causes a mutagenic effect, or if the pesticidal use requires an issuance of a food additive regulation or is likely to result in repeated human exposure over a significant portion of the life span.

Tolerances exist for endosulfan for a variety of raw agricultural commodities, therefore oncogenicity testing is required.

In a study by Hazleton Laoratories and sponsored by the National Cancer Institute (1978, MRID 00004256), endosulfan was administered in diets to groups of 50 male and 50 female B6C3F1 mice at the time weighted average concentrations of 3.5 or 6.9 ppm and 2.0 or 3.9 ppm, respectively for 78 weeks. Twenty mice of each sex served as controls.

No treatment-related increase in neoplastic or non-neoplastic effects were noted. No definit compound related effects were noted on body weight, appearance, or general behavior. However high mortality among the males was observed but did not appear to be in a dose related manner. The mortality rate among females was not as high and again was not dose related.

This study is classified as Core-Supplementary. The high incidence of death among the males preclude the conclusion that endosulfan does not have oncogenic potential and the negative results in this sex should be regarded as inconclusive.

In another study included in the same report (1978, MRID 00004256), endosulfan was administered in the diet to groups of 50 male and 50 female Osborn Mendel rats at the time weighted average concentrations of 408 or 952 ppm and 223 or 445 ppm, respectively. Female rats were treated for a period of 78 weeks which was followed by a 23 week observation period. Because of the toxic effects associated with high doses of endosulfan, high dose and low dose males were sacrificed at the end of 73 and 81 weeks, respectively. Twenty rats of each sex served as controls.

The males in this study showed a significant dose related depression in the rates of growth and survival. The incidence of toxic nephropathy was significantly elevated in both sexes at both dose levels. A significant increase in parathyroid hyperplasia associated with these renal lesions and testicular atrophy were noted in male rats at both dose levels. Also associated with the parathyroid lesion was medial calcification of the blood vessels.

No evidence of carcinogenicity was found. However, the early death of the male rats preclude the usefulness of any analysis of late developing tumors. Again, as with the mouse study, such negative results for the males should be viewed with a great deal of caution.

For a variety of reasons these studies do not meet the current agency requirement for oncogenic evaluation for the male, but not the female rats and mice.

Furthermore, several serious non-neoplastic lesions due to endosulfan treatment were noted at both dose levels. Therefore, it was concluded that any future regulatory actions for endosulfan should await the establishment of NOEL's for these lesions.

In another study by Bionetics Research Laboratories (1968, MRID 05010016), endosulfan was tested in two strains of mice B6C3F1 and B6AKF1 by incorporation in the diet at 3 or 6 ppm for 18 months or by a single subcutaneous injection. A total of 18 males and 18 females of both strains were assigned to each of the oral treatment groups and 24 animals of each sex of each strain were used as control. In the subcutaneous experiment 18 males and 18 females were assigned to either the treatment or control group.

In the feeding study, survival was very poor for both strains at the high dose level. Only one animal of each sex survived for 18 months in the B6C3F1 strain and 6 males and 8 females of the B6AKF1 strain survived for the duration of experiment.

There were 4 pulmonary adenomas found in the 16 males of the B6AKF1 strain at the low dose level examined for tumors. Two of such tumors were also observed among the male controls. There were 3 hepatomas reported in the 14 males of the B6C3F1 strain at the low dose level examined for tumors. There were no significant difference in tumor incidence at other organ sites in either strains. The authors also reported a significant increase of pulmonary adenoma in treated mice ($p < 0.05$). However, no distinctions were made between animals of different sex or strain.

In the subcutaneous study, there were no significant treatment related differences in the number of mice surviving for the duration of the experiment. There were no increase in the tumors incidence in the treated groups.

This study may be classified as Core-Supplementary data and therefore can not provide an adequate assessment of the oncogenic potential of endosulfan.

Further oncogenic studies are required.

Teratogenicity 163.83-3

The minimum data requirement for teratogenicity is testing in two mammalian species using the technical material.

Teratogenicity testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires an issuance of a food additive regulation, or is likely to result in a significant exposure to females.

Tolerances exist for endosulfan on a variety of raw agricultural commodities, and therefore teratogenicity testing is required.

A study was conducted by Industrial Bio-Test Laboratories (1972, MRID 00003712) to assess the teratogenic potential of endosulfan. Twenty female Charles River rats were treated orally with 0.5 mg/kg/day, and another 23 females were treated with 1.5 mg/kg/day, from the sixth day through day 15 of gestation, all females were sacrificed.

No significant difference was noted between the treated and control animals with respect to mortality and body weight of dams, number of implantations, resorption sites, viable fetuses, fetal skeletal development, and fetal external and internal abnormalities.

Formation of terata was not evident in this study. The higher incidence of changed atria size in the treatment groups perhaps represent a fetotoxic effect. The significance of this finding is dubious, considering the developmental state of the fetuses and the lack of clear dose response regarding small atria. Hence, it must be concluded that further investigation is required to more clearly define the fetotoxic/teratogenic potential of endosulfan.

This study has recently undergone an audit (Cunningham, 7/19/79) which indicated that the raw data do not support the data or conclusions in the final report. In addition, the fetuses in all groups were underdeveloped possibly due to the fact that the animals were sacrificed prior to the scheduled 20th day of gestation. There was unreported increase of the small atria of 59.5% in one group and 42.9% in the other group. There was also a 10 fold increase in large atria in one group was not reported.

As a result of these discrepencies and problems, this study is considered invalid and should not be used to support the safety of endosulfan with respect to the teratogenic potential. However, the adverse effects noted in this study should be investigated in the replacement study.

Gupta et al; (1978, MRID 05003227) investigated the teratogenic and embryotoxic effects of endosulfan in rats. Endosulfan was administered orally at 0, 5, or 10 mg/kg daily from day 6 to day 14 of gestation to groups of 20, 26 and 32 pregnant female albino rats respectively. On day 21, animals were sacrificed and fetuses were delivered by cesarean section.

The authors stated that no adverse effects could be attributable to endosulfan treatment were observed on dams. However, one and 5 females died from the 5 and 10 mg/kg groups respectively.

Of the 20, 25 and 27 females that had positive sperm check and that survived to day 21 of gestation, 2, 5 and 6 females respectively carried no fetuses but had enlarged uteri.

The numbers of resorption sites were 5, 26, and 29 for the control, 5 mg/kg and 10 mg/kg groups respectively. The number of litters with resorptions was said to be significantly increased in the high dose group ($p < 0.05$).

Cerebral hyperplasia or enlargement of the renal pelvis occurred in 5.3, 6.8, and 7.4 of the fetuses of the 0, 5, and 10 mg/kg groups respectively. What are #'s on litter basis

There was a statistically significant increase in litters with skeletal abnormalities.

However, no raw data were reported therefore, this study can not be considered a reliable assessment for the teratogenic potential of endosulfan and can only be considered as Core-Supplementary data.

Another study was conducted by Raltech Scientific Service (1981, MRID) to evaluate the teratogenic potential of endosulfan. In this study, endosulfan was administered to pregnant female Sprague Dawley rats from day 6 to day 19 of gestation at the level of 0, 0.66, 2.0 or 6.0 mg/kg/day. On day 20 of gestation, animals were sacrificed and fetuses removed.

A number of skeletal, visceral and external anomalies, as well as significant reduction in size and weight were reported in fetuses of the 6 mg/kg groups. However, at this dose level maternal toxicity was evident as manifested by decreased body weight and body weight gain ($p < 0.01$) and clinical observations indicating CNS stimulation.

At lower dose levels no compound related terata were apparent although misaligned sternebrae were noted.

No positive controls were included and food consumption was not reported. The study was classified as Core-Minimum data and the NOEL for fetotoxic effects was considered to be 2 mg/kg/day. However, a more conservative NOEL should be considered at 0.66 mg/kg/day.

This study is acceptable as a reliable assessment for teratogenic potential of endosulfan. However, another study in another mammalian species is required.

Reproduction 163.83-4

The minimum data requirement for reproduction is testing in one mammalian species, preferably the laboratory rat, using the technical chemical and lasting two generations.

Reproduction testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires issuance of a food additive regulatin or is likely to result in repeated human exposure over a significant portion of the life span.

Tolerances exist for endosulfan on a variety of raw agricultural commodities and therefore reproduction testing is required.

In a three-generation reproduction study by Industrial Bio Test Laboratories (1966, MRID 00003765), endosulfan was administered in the diet to Sprague Dawely rats at 5 or 50 ppm.

The F_0 parents were mated at 100 days of age and kept on treated diets until sacrifice following the weaning of F_{1b} litters. Each of 16 females in each treatment group was mated randomly with a male from the same group. Eight males and 16 females from the F_{1b} litters of each group were selected at weaning (21 days) for use as parents for the next generation. This selection was continued through the next two generations.

The results of the first generation revealed no differences between F_0 treated and control animals with respect to their progeny (F_{1a} or F_{1b}) with respect to growth, mortality, behavioral reactions, gross pathological findings, absolute and relative organ weights, histopathological findings or in the mating indices, fertility indices, or lactation indices of the F_0 parents.

In the second generation as in the first, treatments of the parental animals (F_1) or their progeny (F_{2a} and F_{2b}) did not result in effects that were different from the controls for the same parameters.

The results of the third generation study revealed no abnormalities among the parental stock (F_2) or their progeny (F_{3a} and F_{3b}) as a result of endosulfan treatment.

This study has undergone an audit (Canadian report, 3/14/80) and considered invalid and therefor can not support the safety of endosulfan with respect to possible reproductive effects. A reproduction study is required.

Mutagenicity 163.84-1 through 4

Although the mutagenicity testing requirements are not final yet, one may refere to the Agency's Proposed Guideline (FR 43, No. 163, August 22, 1978) for information concerning the type of studies the agency is considering. The following studies represent only the minimum requirements for data on the potential heritable effects of a chemical and are likely to be required:

1. A mammalian in vitro point mutation test.
2. A sensitive sub mammalian point mutation test (bacteria, fungi, insect).
3. A primary DNA damage test (i.e. sister chromatid exchange or unscheduled DNA synthesis).
4. A mammalian in vitro cytogenetics test. If this test suggests a positive result, a dominant lethal or heritable translocation test may be required.

Choice within these categories must be accompanied with a rational. Substitutions will be considered after discussion with the agency.

Tolerances exist for endosulfan residues on a variety of raw agricultrual commondities, and therefore mutagenicity testing is required.

A dominant lethal study was conducted by Industrial Bio Test Laboratories (1972, MRID 00003711) using albino mice. Endosulfan was administered interperitoneally in corn oil at 5 or 10 mg/kg. Ethylmethanosulfate was used as a positive control.

Three untreated virgin females were caged with each treated male and were replaced on weekly basis for six weeks. The females were sacrificed one week after removal from the breeding cage.

Males treated at 10 mg/kg were slightly lethargic for several days after exposure, but no mortality occurred and the ability to mate successfully was not affected.

The number of implantations, resorptions, and embryos indicated no effect of treatment on these parameters. The results did not indicate a dominant lethal response.

This study has recently undergone an audit (L. Anderson, 1/2/79; H. Cunningham, 8/10/79) and declared valid.

In another study by Dikshith and Datta (1978, MRID 05003502), endosulfan was orally administered to rats at 0, 11.0, 22.0, 36.0 and 55 mg/kg daily for five days. Rats were injected with 4 mg/kg of colchicine, 4 hours before they were killed by decapitation.

Seminiferous tubules and bone marrows from the femurs were examined. The mitotic index was determined by counting the number of metaphases in a total of 100 cells per slide. Fifty well spread metaphases per treatment were examined for chromatid breaks, chromosome breaks, and exchange figures.

The authors stated that "there were no major chromosomal aberrations either in bone marrow cells or spermatogonial cells". An unspecified number of chromatid break with "1 to 2 exchange figures" were found in bone marrow cells but not spermatogonial cells. The authors reported that "there was no chromosomal deletion nor formation of large numbers of fragments". The authors further reported that "no significant mitotic inhibition in any of the treated groups". The authors then concluded "endosulfan produced little or no effect on somatic as well as on germinal cells".

No details or quantitative effects data were reported, therefore, no reliable conclusions can be drawn from this study.

In a recent study by Dorough and coworkers (1978, MRID 05003703), endosulfan and its major metabolites were tested in Salmonella typhimurium mutagenicitys test using tester strains TA98, TA100, TA1535 and TA1978. The chemicals were tested at concentrations of 10, 100, 500, and 1,000 ug/plate in duplicates in the presence and absence of an activating system. Acetoaminofluorine was included as a positive control. Neither α - or B endosulfan isomers, nor any of the metabolites tested showed any increase in the reversion rate beyond the controls, both in the presence or absence of the activating systems. The diol, α hydroxy ether, and lactone severly inhibited bacterial growth even at the lowest concentration tested.

In this experiment, it is obvious that only one S-9 concentration, and insufficient duplication were used. Furthermore, no raw data were provided. For these reasons this study can not provide a reliable assessment for the mutagenic potential of endosulfan.

Fahrig (1974, MRID) reported that endosulfan did not show any positive response when tested for mutagenic potential in Saccharomyces servisia (mitiotic gene conversion), Escherichia coli (forward mutation) and Serratia marcescens (reverse mutation).

No further details were provided and therefore this information does not provide a strong ground for the mutagenic potential assessment for endosulfan. Further mutagenic testing is required.

The Agency requires a battery of valid mutagenicity tests which demonstrate the potency of the chemical to induce point mutations, chromosomal mutations, either directly or indirectly. The registrant may submit a testing plan, with a rational for test selection. The rational shall address the principles outlined in the "Proposed Mutagenicity Risk Assessment Policy".

Special Studies

Metabolism 163.85-1

The minimum data requirement for metabolism is testing with a single dose of the analytically pure grade of the active ingredient in the radioactively labeled form.

In general, a metabolism study is required if a chronic study or an oncogenicity is required. Since both these studies are required for endosufan, therefore a metabolism study is a requirement in this case.

In a recent study by Dorough and coworkers (1978, MRID 05003703), female rats were treated orally with 2 mg of ^{14}C labeled of either α - or B endosulfan. Animals administered the α - isomer eliminated 74.8% and 13.2% in the feces and urine respectively, while those administered the B - isomers eliminated 68.3% and 18.5% in feces and urine respectively in a period of 120 hours.

In another experiment by the same authors (1978, MRID 05003703), rats were treated with 1.2 mg/kg of the ^{14}C - labeled α - or B - endosulfan and their bile ducts were then cannulated. Up to 47% of the administered dose was eliminated via the bile. Enterohepatic circulation was not apparent.

In a separate experiment (1978, MRID 05003703) groups of 10 female rats were fed diets containing 5 ppm of ^{14}C labeled α-or B endosulfan for 14 days. One animal from each group was sacrificed on days 1, 3, 7, 10, and 14. The rest of the animals were then kept on endosulfan free diet for another 14 days. Additional groups of four animals were fed diets containing 25 ppm of ^{14}C-labeled of either α - endosulfan or a 7:3 mixture of α-and B-isomers. All animals were sacrificed on day 14.

Endosulfan metabolites accumulated in tissues, especially of kidney and liver. Metabolites of endosulfan in rat include endosulfan sulfate, endosulfan diol, endosulfan ether, endosulfan α - hydroxy ether, and endosulfan lactone. The sulfate and α - hydroxy ether are the principal metabolites accumulated in tissues.

In a study by Deema et al (1966, MRID 00004257) a single dose of either of endosulfan isomers, endosulfan alcohol, endosulfan sulfate or endosulfan ether was administered orally to groups of 2-9 male mice. Urine and feces were collected and all animals were sacrificed at 24 hours.

In another experiment, eight male and eight female mice were maintained on diets containing 10 ppm of purified endosulfan for 49 days. Two animals of each sex were used as controls. One animal of each treated group was sacrificed on days 7, 14, 21, 28, 35, 48 and 49. A control animal was sacrificed at days 11, 28, 42 and 49.

A third experiment by the same authors was also conducted using two male and four female mice. Two mice were fed 0.3, 0.25, or 0.2 mg of ^{14}C labeled endosulfan. After 24 hours animals were sacrificed.

When mice were fed unlabled endosulfan, large amounts of endosulfan sulfate were recovered in the liver, small intestine and visceral fat with a trace in muscle and kidney after 24 hours. Endosulfan was found only in the stomach, small intestine and feces. A metabolite identical to endosulfan alcohol was detected in urine.

Mice fed the α -isomer had also the unchanged material in the stomach, small intestine, and feces. Endosulfan sulfate was detected in the liver, small intestine, visceral fat and feces. Endosulfan alcohol was found in urine. Neither the parent compound nor any metabolite were detected in the brain.

Mice fed the B-isomer had the endosulfan sulfate in the liver, kidney, small intestine, muscle, and visceral fat. The alcohol was detected only in the urine, but neither the parent compound nor any metabolite were detected in the brain.

In mice fed endosulfan in diets, endosulfan sulfate was detected in the liver and visceral fat. Neither the parent compound nor any metabolite were detected in the brain. A metabolite similar to the alcohol was detected in urine.

Both isomers of endosulfan, endosulfan sulfate, endosulfan alcohol, and endosulfan ether were detected in feces.

Endosulfan alcohol was detected in the urine of animals fed either endosulfan sulfate, endosulfan ether or endosulfan diol.

In the feces of animals fed endosulfan ether, four other unidentified metabolites were detected in addition to the ether and the alcohol.

The principal metabolic products in the mouse under the test condition were endosulfan sulfate and alcohol.

In another study by Chin and Stanovick (1964, MRID 00003761), dogs were orally administered α - and B-endosulfan isomers at 0.35 and 1.75 mg/kg/day for 28 days.

Most of the material was excreted in the feces and only traces were detected in the urine.

At 0.35 mg/kg/day, 13-25% of the administered dose was excreted in the feces and about 0.1% in the urine. Nearly twice the amount of ∝ - and B-endosulfan was detected in the excreta of males as in the excreta of females.

Only small traces of ∝ - and B-endosulfan and the sulfate metabolite were detected in blood, brain, and kidney. While no ∝ - or B-endosulfan was detected in muscles, liver, or fat, significant amounts of endosulfan sulfate were detected in these tissues (muscle 0.031 - 9.44 ppm, liver 0.042 - 0.784 ppm, fat 0.671 - 8.140 ppm). Endosulfan sulfate, however, was the only metabolite found.

In a study by Gorbach and co-workers (1968, MRID 05003222), radiolabeled endosulfan was orally administered at the level of 0.3 mg/kg to Frisian milk sheep. The administered dose was almost entirely eliminated in 22 days. About 50% of the administered dose was excreted in the feces, 41% in the urine, and only 1% recovered in the milk. The feces contained the unchanged endosulfan but did not contain any of the lactone, diol, or hydroxy ether derivatives. In the urine, two metabolites characteristic of the hydroxy ether and alcohol derivatives of endosulfan were found. The liver was the organ of the highest concentration of radioactivity after 40 days (0.03 ppm).

In another study (1965, MRID 00003743), 15 mg endosulfan was administered daily to each of three female Merino sheep. Three animals were used as controls. One of the treated animals was sacrificed after 20 days the other two were sacrificed after 26 days.

About 10-30% of the administered dose was eliminated in the feces as unchanged material. No endosulfan was detected in the tissues at necropsy. Most of the administered dose was metabolized and excreted in urine as either endosulfan alcohol (10%) or another unidentified metabolite (30%). Endosulfan sulfate was the only metabolite detected in milk (0.02-0.3 ppm) and cream (0.1-1.3 ppm). However, no endosulfan was detected in milk and cream.

Schuphan and co-workers (1968, MRID 05007464) studied the metabolism of ^{14}C- labeled ∝ and B isomers of endosulfan qualitatively in Sprague-Dawley rats and albino mice orally, intraperitoneally and duodinally.

Administration of either ∝ or B isomers of endosulfan resulted in the same type of metabolites in the feces of both animals. The metabolites detected in the feces after the oral and intraperitoneal administration were identified as lacton, ∝-hydroxy ether, and sulfate derivatives of endosulfan in addition to the parent compounds. Substances identified in the urine were the lactone, and sulfate derivatives in addition to an unknown metabolite and the parent compounds. Substances detected in

the bile after duodenal administration of either isomers, were the lactone and the unknown metabolite in addition to traces of the parent compounds. In general both isomers produces the same type of metabolites in different proportion.

When both ∝ and B isomers were administered in equal amounts under unspecified conditions, the ratio of ∝ and B excreted in urine after 24 hours was 5:1. However, the diol derivative that was previously reported as a metabolite of endosulfan in rodents was not reported as a major metabolite in this study.

Gupta and Ehrnebo (1979, MRID 05003503) found after iv administration of endosulfan (2 mg/kg) to rabbits that, plasma clearance was 2.70+ 1.33 ml/hour/kg for the ∝ -isomer and 70.1+ 18.6 ml/hour/kg for the B isomer. The fraction of unchanged ∝ -endosulfan in 5 days urine was 37% of the dose while unchanged B-endosulfan amounted to only 11% of the dose. These fractions in feces were only 2.7% and 0.4% respectively.

The metabolism of endosulfan in mammals is considered adequately delineated. Further investigation is not required, but data on the clearance of endosulfan is required.

Special Requirements

Domestic Animals Safety 163.86.1

In a report by Schmidlin and Romann (1971, MRID 05013366), eight cows were accidently fed hay contaminated with 750 to 900 ppm of endosulfan. Three of the animals became severely ill. These same cows became ill with similar symptoms 10 months earlier. The symptoms in both cases manifested as tonic-clonic cramps, wobbly gait, dyspnea, muscle twitching and salivation. One of the three animals had to be sacrificed, the other two recovered after the contaminated feed was removed.

Another case of domestic animal poisoning with Endosulfan was reported by Utklev and Westbye (1971, MRID 05012611) when a group of female sheep grazed in a strawberry field that had been sprayed 4 days earlier with Thiodan 35 (35% endosulfan). Two of the lambs became ill with initial symptoms of unsteady walk and uncontrollable leg movements, followed by an inability to stand. One animal recovered after 24 hours, while it took one month until the second animal was "on its feet again." The authors reported that 5 mg/kg could be the maximum dose ingested.

Nicholson and Cooper (1977, MRID 05003772) reported accidental poisoning in five calves, when they were dusted with Endosulfan (4% dust) for lice control. About 12 hours later one calf was dead and the remaining four manifested poisoning symptoms. The chief symptoms exhibited by these animals were muscle tremors, twitching of the ears, snapping of the eyelid and violent body jerks and inability to stand with accasional convulsions. Frenzied activity and aimless jumping were also observed.

In a study conducted by Hazleton Laboratories, Inc. (1959, MRID 00003603) to evaluate the safety of endosulfan to domestic animals, mature lactating Holstein dairy cows were fed Thiodan ^{14}C at levels of 0.0, 0.3, 3.0, and 30 ppm for a period of 30 days. During this period and a subsequent 14 day recovery period, all of the animals exhibited normal appearance and behavior. Food consumption and milk production were within normal limits. At the 3.0 and 30.0 ppm dietary levels, concentration of ^{14}C Thiodan in the blood gradually increased for the first 21 days, and the level remained essentially the same for the remainder of the period. During the 14 day recovery period there was a 60% and 52% reduction in blood Thiodan levels for the 3.0 and 30.0 ppm doses respectively. A sharp increase in the amount of ^{14}C- endosulfan in milk was observed in the first week. The level remained essentially the same after that and the residue entirely disappeared at the end of the 14 day recovery period.

It is concluded that Endosulfan is very toxic to domestic animals orally, dermally and by inhalation. Animals should not be allowed to graze in a recently sprayed area and should not be allowed in any area during spraying.

Human Toxicity and Epidemiology:

Ely et al., (1967 MRID 05007645) reported nine cases of human exposure to Endosulfan dust in workers. All of these cases showed clonic convulsive episodes as the chief symptom of acute intoxication with Endosulfan in all cases the route of exposure was thought to be dermal or inhalation. A question of proper protection is present in this report.

Six cases of human exposure to Endosulfan were reported by Terziev et. al in 1974 (MRID 05007039). In all cases, ingestion was the major route of exposure. Five out of the six cases were fatal. The signs of acute poisoning were manifested as gagging, vomiting, agitation, tonal writhings, dyspnea, and cyanosis. The death occurred within 1.5 to 3 hours. Autopsy in three cases revealed circulatory abnormalities, including edema of the brain and lungs, acute emphysema, protein dystrophia in the "parenchymal organs." Staining showed almost complete chromatolysis at the neurons with karyolysis and vascuolization in some of these cases.

Wolf et al., in 1972 (MRID 05003239) found that the dermal and respiratory exposure of spraymen to a 0.06% spray of Endosulfan was 24.7 mg/hr. and 0.02 mg/hr. respectively. The stated exposure equaled 0.27% of a toxic dose per hour.

Oudbier et al., (1974, MRID 05001387) measured the exposure to Endosulfan using respirator pad analysis and found that exposure was greater during mixing operation than in spraying. With a 5 minute exposure time, 182,800 ng were detected on the respirator pad during the mixing while only 4, 664 ng were detected during a 30 minute spraying operation. No further studies are necessary and these cases appear to arise from improper use.

Pharmacology

The potential vulnerability of the central nervous system of humans to Endosulfan was demonstrated in epileptic convulsions and altered EEG patterns in three subjects exposed to the pesticide. In one of the patients, occasional EEG alterations were observed a year after the exposure (Tiberia et al., 1970, MRID 00003077).

Endosulfan was shown to exert a slight contraction action in the rectus muscle of frog at concentrations of 5×10^{-6} M or greater. Acetylcholinesterase effects were observedd only at 6.5×10^{-5}M.

A lowering of blood pressure occurred in cats at a dose level of 0.1 mg/kg or higher.

At a molar concentration of 3×10^{-4} or higher, Endosulfan apparently dampened heart frequency and strength of the cat heart beat (FMC, 1956, MRID).

After repeated oral administration of 5 or 10 mg/kg, endosulfan was detectable in plasma and different parts of rat brain. The amount of -isomer in the brain was in proportion to the blood level of - isomer, however, this was not the case for the B isomer whose concentration in the brain was much less than expected from its plasma levels (1978, MRID 05003361), indicating the difference in the blood-brain barrier permeability to each of these isomers that may partially explain the difference in their acute toxicities. Other factors that may contribute to the differnce in toxicity is the difference in the rate of metabolism and elimination of these two isomers.

The concentration of endosulfan in the lipids of the cat brain 15 minutes and up to six hours after the i.v. administration of 23 mg/kg of endosulfan in propylene glycol, was three fold greater in the cerebral cortex and cerebellum than in the brain stem and spinal cord. The intensity of the convulsions and tremors correlated well with the concentration of endosulfan in all areas of the central nervous system (1979, MRID 05004972).

Administration of endosulfan to male and female rats orally at 7 or 15 days before an injection of pentobarbital, increased liver weights, shortened sleep time, increased induction time and rapidly decreased pentobarbital levels in blood and brain after 30 minutes (1977, MRID 05003362, 05003363).

Agarwal and coworkers (1978, MRID 05005443) found that oral administration of endosulfan at 2.5 or 5.0 mg/kg daily for 14 days, induced hepatic lipid peroxidase, aminopyrine-N-demethylase, aniline hydroxylase, and tyrosine aminotransferase.

Endosulfan at 30 and 300 Ug/ml did not inhibit liver microsomal-O-demethylase, and at 50-500 Ug/ml did not inhibit rat or mouse liver UDP-glucuronyl transferase in vitro (1974, MRID 05007036).

Emergency Treatment:

Supplementary information are available (IBT No. A-661, MRID 00003886, 00003684) indicating that atropine sulfate was a more effective antidote than pentobarbital which had only a slight therapeutic effect. This study has undergone an audit and had been declared valid (Clement Associate Report, December 8, 1980).

Further studies are deemed necessary to elucidate the mode of action of the convulsions and tremors which may be centrally mediated, and to develop a more efficacious antidote for emergency treatment of the acute poisoning cases.

APPENDIX

Hazard Indicators	Toxicity Categories I	II	III	IV
Oral	Up to and including 50 mg/kg	From 50-500 mg/kg	From 500-500 mg/kg	Greater than 5000/mg/kg
Inhalation LC_{50}	Up to and including 0.2 mg/liter	From 0.2-2 mg/liter	From 2-20 mg/liter	Greater than 20 mg/liter
Dermal LD_{50}	Up to and including 200 mg/kg	From 200-2000 mg/kg	From 2,200-20,000 mg/kg	Greater than 20,000 mg/kg
Eye Effects	Corrosive; corneal opacity not reversible	Corneal opacity revers-ible within	No corneal opacity; irritation reversible within 7 days	No irritation
Skin Effects	Corrosive	Severe irrita-tion at 72 hours	Moderate irritation at 72 hours	Mild or slight irritation at 72 hours or no effect

BIBLIOGRAPHY

MRID	CITATION
05003703	Dorough, H.W., Huhtanen, K., Marshall, T. C., Bryant, B. E. (1978) Fate of endosulfan in rats and toxicological considerations of apolar metabolites. Pesticide Biochemistry and Physiology 8(3):241-252.
00004257	Deema, P., Thompson, E., Ware, G.W. (1966) Metabolism, storage, and excretion of ^{14}C-endosulfan in the mouse. Journal of Economic Entomology 59 (3):546-550. (Also in unpublished submission received July 14, 1967 under 8F0632; submitted by FMC Corp., Philadelphia, Pa., CDI:091099-A).
00003761	Chin, W.T., Stanovick, R.P. (1964) Metabolism of thiodan isomers I and II by dogs: M-1307. (Unpublished study received June 21, 1966 under 7F0526: submitted by FMC Corp., Philadelphia, Pa., DCI: 090631-A).
00003712	Haley, S. (1972) Report to Niagara Chemical Division, FMC Corporation: Teratogenic study with thiodan technical in Albino rats: NCT No. 460-42: IBT No. B1056. (Unpublished study received Nov. 17, 1972 under 3F1314: prepared by Industerial Bio-Test laboratories, Inc., submitted by FMC Corp., Philadelphia, Pa., CDI: 092246-E).
05003222	Gorbach, S.G., Christ, O.E., Kellner, H,M., Kloss, G., and Boerner, E. 91068) Metabolism of endosulfan in milk sheep. J. Agr. Food Chem. 16 (6): 950-953.
00003743	Gorbach, S. (1965) Investigations on thiodan in the metabolism of milk sheep. Includes undated method. (Unpublished study including report, received Dec. 7, 1967 under 7F0632; prepared by Farbwerke Hoechst AG, Germany, submitted by FMC Corp., Philadelphia, Pa., CDI: 091100-C).
00003711	Arnold, D. (1972) Report to Niagara Chemical Division, FMC Corporation: Mutagenic study with thiodan in Albino mice: Request No. NCT 459-99: IBT No. E1057B. (Unpublished study received Nov. 17, 1972 under 3F1314; prepared by Industrial Bio-Test Laboratories Inc., submitted by FMC Corp., Philadelphia, Pa., CDI: 09226-A).
05003502	Dikshith, T.S.S., Datta, K.K. (1978) Endosulfan; lack of cytogenetic effects in male rats. Bulletin of Environmental contamination and Toxicology 20 (6):826-833.
00003712	Haley, S. (1972) Report to Niagara Chemical Division, FMC Corporation: Teratogenic study with thiodan technical in Albino rats: NCT No. 460-42: IBT No. B1056. (Unpublished study received Nov. 17, 1972, under 3F1314; prepared by Industerial Bio-Test Laboratories, Inc., submitted by FMC Corp., Philadelphia, Pa., CDL: 092246-E).

05003227 Gupta, P. K., Chandra, S.V., Saxena, D.K. (1978) Teratogenic and embryotoxic effects of endosulfan in rats. Acta Pharmacologica et Toxicologica 42(2):150-152.

00003765 Kennedy, G., (1966) Three generation reproduction study on thiodan in Albino rats. (Unpublished study prepared by Industrial Bio-Test Laboratories, Inc. Jan. 3, 1966, submitted by FMC Corp., Middleport, N.Y. Acc. No. 090631.

00004256 National Cancer Institute (NCI). 1978. Bioassay of endosulfan for possible carcinogenicity. By Division of Cancer Cause and Prevention, Carcinogenesis Testing Program. Bethesda, Md., U.S. Dept. of Health, Education, and Welfare. DHEW (NIH) Publication No. 78-1312 (Also in unpublished submission received July 26, 1978, under 4B1430. Submitted by American Hocchst Corp., Somerville, N.J. CDI: 097264-A).

0003602 Keller, J.G. (1959). Final Report: Two-year chronic feedig study-rats, Thiodan Technical. (Unpublishe study received February 9, 1960, under PP. 0237. Prepared by Hazleton Laboratories, Inc. Submitted by FMC Corp., Philadelphia, Pa. CDL: 090265-F).

0003741 Baran, J. (1967). Two-year chronic oral toxicity of thiodan technical- Beagle dogs, for Niagra Chem. Div., FMC Corp., by Industrial Bio-Test Laboratories Inc., IBT No. C3758, Dec. 5, 1967. Received Dec. 7, 1967.

05011227 Truhat, R., Gak, J. C., and Greillot, C. (1974) [Research on the modalities and mechanisms of the toxic action of organochlrine insecticides: I-Comparative study of the acute toxic effects in hamster and the rat.] Eur. J. Toxicol. Environ. Hyg. 7:159-166.

5010016 Bionetics Research Laboratories (1968). Evaluation of carcinognic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals. Vol I: Carcinogenic Study. Bethesda, Md., National Cancer Institute, Division of Cancer Cause and Prevention. (National Cancer Institute Report No. NCI- DCCP-CG- 1973-1-; available from: NTIS, Springfield, Va., PB-223-159).

05007645 Ely, T. S. , MacFarlane, J.W., Galen, W. P., and Hine, C.H. (1967). Convulsions in Thiodan workers: A prelimenary report. J. Occup. Med. 9:35-37.

05007039 Terziev, G., Dimitrova, N., and Rusev, P. (1974). Forensic medical and Forensic chemical study of acute lethal poisonings with Thiodan. Folia Med. (Plovdiv) 16: 325-329.

05003239 Wolf,H. R., Armstrong, J. F., Staiff, D. C., Comer, S. W. (1972). Exposure of spraymen to pesticides. Archives of Environmental Health 25(1): 29-31.

05001387 Oudbier, A. J., Bloomer, A. W., Price, H. A., Welch, R. L. (1974). Respiratory route of pesticide exposure as a potential health hazard. Bulletin of Environmental Contamination and Toxicology 12 (1): 1-9.

00003077 Tiberin, P., Kristal, N., Israeli, R. (1970). EEG findings in poisoning by endosulfan (C.9-H.6-O.3-Cl-6-S). Electroencephalography and clinical neurophysiology 28 (6): 642.

00003886 Kretchman, E. (1971). Study of the efficacy of atropine sulfate
00003684 and sodium pentabarbitol as antidotes for parathion 2 thiodan 2EC and methyl parathion 2 thiodan 3EC intoxication in male albino rats.

05003222 Gorbach, S. G., Christ, O.E., Kellner, H.R., Kloss, G., Boerner, E. (1968) Metabolism of endosulfan in milk sheep. Journal of Agricultural and Food Chemistry 16(6): 950-953.

05003078 Gupta, P. K., and chandra, S.V. (1977). Toxicity of endosulfan after repeated oral administration to rats. Bull. Environ. Contam. Toxicol. 18:378-384.

00003604 Keller, J. G., (1959). Final Report: Repeatd oral administration-dogs. (Unpublished study received Feb. 9, 1960 under PP 0237, prepared by Hazleton Laboratories, Inc., submitted by FMC Corp., Philadelphia, Pa., CDL: 090265-H).

05013366 Schmidlin- Meszaros, J., and Romann, E., (1971). [Accidental poisoning of cows with endosulfan (Thiodan).] Mitteilungen aus dem Gebiete der Lebensmitteluntrsuchung and Hygiene 62:110-122.

05012611 Utklev, H. E., and Wstbye, O. (1971). [Poisoning with endosulfan.] Nor Vet. Tidsskr 83:31

05003772 Nicholson, S. S., and Coopper, G. W. (1977). Apparent endosulfan toxicosis inn Calves. J. Am. Vet. Med. Assoc. 130:319.

00003603 Keller, J. G. (1959). Final Report: Subacute Feeding Study - Dairy Cows (Supplement to report dated March 20, 1959). (Unpublished study received Feburary 9, 1960 under PP 0237; prepared by Hazleton Laboratories, Inc., submitted by FMC Corp., Philadelphia, Pa.; CDL: 090265-G).

05007464 Schuphan, I., Ballschmiter, K., and Toelg, G. (1968) [On the metabolism of endosulfan in rats and mice.] 2. Naturforsch. 23: 701-706.

05003361 Gupta, P.K. (1978). Distribution of endosulfan in plasma and brain after repeated oral administration to rats. Toxicology 9 (4): 371-377.

05004972 Khanna, R. N., Misra, D., Anand, M., Sharma, H. K. (1979). Distribution of endosulfan in cat brain. Bulletin of Environmental Contamination and Toxicology 22(1/2); 72-79.

05003362 Gupta, P. K., Gupta, R. C. (1977). Influence of endosulfan on pentobarbitone sleeping time and blood and brain concentrations in male rats. Journal of Pharmacy and Pharmacology 29 (4): 245-246.

00003363 Gupta, P. K., Gupta, R. C. (1977). Effect of endosulfan pretreatment on organ weights and on pentobarbital hypnosis in rats. Toxicology 7(3): 283-288.

05005443 Agarwal, D. K., Seth, P. K., and Gupta, P. K. (1978). Effect of endosulfan on drug-metabolising enzymes and lipid peroxidation in the rat. J. Environ. Sci. Health [C] 13: 49-62.

05007036 Fonberg-Broczek, M. (1974) [Efect of selected pesticide on activity of cytochrome P-450 and UDP glucuvonyltransferase in vitro.] Rocz. Panst. Zakl. Hig. 25:655-662.

05003503 Gupta, P. K., and Ehrwebo, M. (1979). Pharmacokinetics of - and B-isomers of racemic endosulfan following intranvenous administration in rabbits. Drug Metabolism. Dispos. 7: 7-10.

05003361 Gupta, P. K., and Chandra, S. V. (1975). The toxicity of endosulfan in rabbits. Bull. Environ. Contam. Toxicol. 14:513-519.

05002183 Boyd, E. M., Dobos, I., and Krijnen, C. J. (1970). Endosulfan toxicity and dietary protein. Archives of Environmental Health 21(1): 15-19.

05007646 Gupta, P. K. (1976). Endosulfan-induced neurotoxicity in rats and mice. Bull. Environ. Contam. Toxicol. 15:708-713.

0003762 Palazzolo, R. J. (1964). Acute oral toxicity studies on thiodan and thiodan sulfate. Agricultural Chemical Division, FMC Corp., Middleport, N.Y. (Unpublished). (Palazzolo, R. G. Report of Industrial Bio-Test laboratories, Inc., April 8, 1964. EPA Pesticide Petition File Accession No. 090631).

0003693 Elsea J. R. (1957). Progress report: Acute oral administration; acute dermal applications; acute eye application. (Unpublished study received Jan. 24, 1957, under 279-1182; prepared by hazleton laboratories, submitted by FMC Corp., Philadelphia, Pa. CDL: 100912-A).

Ely, T. S., J. W. MacFarlane, Galen, W. P., and Hine, W. H., (1967). Convulsion in thiodan workers: A prelimenary report. J. Occup. Med. 9 (2): 35-37.

FMC (1964). Ninety-day subacute oral toxicity of thiodan sulfate-beagle dogs. Agricultural Chemical Division, FMC Corp., Middleport, N.Y. (unpublished). (Cervenka, H., Report of Industrial Bio-Test Laboratories, Inc., August 20, 1964. EPA Pesticide Petition File Accession No. 090631.

FMC (1956). A report on investigations of HOE 2671. Agricultural Chemical Division, FMC Corp., Middleport, N.Y. (unpublished). (Report of Pharmacology Institute, Goettigen, Germany, August 3, 1956 EPA Pesticide Petition File Accession No. 090226).

Gains, T. B. (1969). Acute toxicity of pesticides. Toxicol. Appl. Pharmacol. 14 (3):515-534.

ENDOSULFAN

Disciplinary Review

Toxicology Profile, Hazard Assessment and Data Gaps

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TOXICOLOGY PROFILE

Sufficient data were available to show that technical endosulfan has relatively high acute oral toxicity to mammals. The oral LD_{50} values ranged from 7.5 mg/kg to 142 mg/kg. The chemical is more toxic to females than to males. Acute intoxication signs are manifestd as depression, salivation, lacrimation, labored respiration, tremors and tonic-clonic convulsions. Further acute oral toxicity testing for the technical chemical is not required.

No data were available to assess the acute oral toxicity of endosulfan formulations. Testing is required for representative formulations.

A combination of several supplementary studies indicated that technical endosulfan is highly toxic to mammals dermally. The seven days dermal LD_{50} for female rabbits were found to be 167-182 mg/kg depending on the purity of the technical material. Further acute dermal toxicity testing on the technical chemical is not required.

No data were available to assess the acute dermal toxicity of endosulfan formulations. Testing is required for representative formulations.

A combination of two supplementary studies indicatd that technical endosulfan is highly toxic to mammals by inhalation. The acute inhalation 4 hours LC_{50}'s were found to be 0.35 and 0.08 mg/L for male and female rats respectively. Further testing of the acute inhalation toxicity is not required.

No data were available to assess the acute inhalation toxicity of endosulfan formulations. Testing is required on selected fdormulations.

Some supplementary data were available to define the primary eye irritation potential of the technical chemical. These studies indicated no corneal opacity, but rather very mild irritation and slight conjunctivae that are reversible. Further investigation is not required.

No data were available to assess the primary eye irritation potential of endosulfan formulations. Testing is required for selected formulations.

An adequate study was available to assess the primary dermal irritation potential of the technical chemical. Twenty-four hours exposure caused minor erythema cleared in most animals by 72 hours. Further investigation is not required.

No data were available to assess the primary dermal irritation potential of endosulfan formulations. Testing is required for selected formulations.

No data were available to assess the dermal sensitization potential of either the technical or formulations of endosulfan. Testing is required for the technical chemical, but not required for the formulations.

Although endosulfan does not relate to any of the known cholinestrase inhibitor pesticides, some authors reported decreases in serum, brain, and hepatic cholinesterase activity. The chief signs of acute intoxication were tremors and convulsions which correlated well with the level of endosulfan in all areas of the nervous system. There were no data available to asess the delayed neurotoxic potential of endosulfan. Testing is required for the technical chemical.

In a rat subchronic oral feeding study, liver and kidney appeared to be the organs most affected. Histopathological examination of the liver and kidney revealed dilation of sinusoid around central veins and areas of focal necrosis and degeneration of hepatocytes and mononuclear monolucocytes, proliferation in the bile duct, and degenerative alterations in the apithelial lining of kidney tubules. Other effects were inflamatory areas in the subpleural of the lungs and dilation of the alveoli, and severe degeneration of the seminiferous epithelium. No NOEL could be established. In another study on dogs the NOEL was considered to be (10 ppm. another oral subchronic study in rat is required.

No data were available to asses the subchronic 21-day dermal toxicity of technical endosulfan. Investigation is required.

No data were available to assess the subchronic 90-day dermal toxicity. However, the pesticidal use pattern of endosulfan does not involve purposeful application to the skin, therefore testing is not required.

No data were available to assess the subchronic inhalation toxicity of endosulfan. Testing is required.

There were no data available to assess the subchronic neurotoxicity of endosulfan. However, a decision of whether this testing will be required can not be determined until data from the acute neurotoxicity study are available.

In a two-year feeding study in rats it was found that liver and kidney were the organs most affected in males. Females fed 100 ppm, (the highest dose tested) exhibited very poor surviving rate. However, this study was classified as invalid and therefore can not fulfill the data requirement for chronic feeding. Another study is required.

In another two-year feeding study in Beagle dogs, no significant differences were observed between control and treated animals in any of the parameters examined. The NOEL was considered to be 30 ppm which was the highest dose tested. Although this study was originally classified as Core-minimum data, a recent data audit for this study was inconclusive as of the validity of this study. However, good grounds exist on which this study could have been invalidated. Therefore, a replacement study is required.

In an oncogenic study in mice, no treatment-related increase in tumors or compound related effects were observed. However, the high incidence of death among the males preclude the conclusion that endosulfan does not have oncogenic potentical and the negative results in this sex should be regarded as inconclusive.

In another oncogenic study in rat, the high and low dose males were terminated after 73 and 81 weeks respectively because of toxic effects associated with the administration of endosulfan. The males in this study showed a significant dose-related depression in the rates of growth and survival. The incidence of toxic nephropathy was significantly elevated in both sexes and at both dose levels. A significant increase in parathyroid hyperplasia associated with these renal lesions and testicular atrophy were noted in male rats at both dose levels. Furthermore, medial calcification of the blood vessels, associated with the parathyroid lesion was evident. The early death of the males preclude the conclusion that endosulfan does not have oncogenic potential.

In a third oncogenic study in two different strains of mice, the survival was very poor for both strains at the high dose level. In the low dose level 4/16 exhibited pulmonary adenoma against 2 observed in the controls, and 3/14 animals showed hepatomas. A significant increase of pulmonary adenoma in treated mice were also reported with no distinctions between animals of different sex or strain.

For a variety of reasons all oncogenic studies do not meet the current Agency requirement for oncogenic evaluation especially for males. Oncogenic studies in both mouse and rat are required.

In a teratogenic study in rat, a number of skeletal, visceral and external anomalies as well as significant reductions in size and weight were reported in fetuses of the 6 mg/kg group (HDT). However, at this dose level, maternal toxicity was evident as manifestd by decreased body weight and body weight gain and clinical observations indicating central nervous system stimulation. The NOEL for fetotoxicity was considered to be 2 mg/kg. Howver, a more conservative NOEL should be considered at 0.66 mg/kg/day.

No other valid or reliable studies were available to further define the fetotoxic and teratogenic potential of endosulfan. Another study in another mammalian species is required.

There were no valid data to support the safety of endosulfan with respect to possible reproductive efffects. A reproduction study is required.

A dominant lethal study in mouse was available and the results indicated that the number of implantations, resorptions, and embryos were not affected by endosulfan treatment. The results also did not indicate any dominant lethal response at 5 and 10 mg/kg.

According to some supplementary literature data, endosulfan did not exhibit any mutagenic effects in microbial forward and reverse mutation tests.

The Agency requires a battery of valid mutagenicity tests which detrmine the potency of the chemical to induce point mutations, chromosomal mutations either directly or indirectly. The registrants may submit a testing plan, with rationals for test selection. The rationals should address the principles outlined in the Proposed Mutagenicity Risk Assessment Policy.

The metabolism of endosulfan is adequately delineated in different mammalian species. Metabolites of endosulfan include endosulfan sulfate, α - hydroxy ether, endosulfan lactone, endosulfan ether, endosulfan diol and in some cases endosulfan alcohol. Administration of either α - or B isomers by any route resulted in the same metabolites in feces and urine but in different proportions. Further investigation is not required, but the clearance aspects should be further delineated.

Supplementary data were available indicating that atropine sulfate was more effective as antidote than pentobarbital. However, further studies are deemed necessary to elucidate the mode of action and develope a more effective antidote.

GENERIC DATA GAPS

TYPE OF TEST	GUIDELINE CITATION	IS TESTING REQUIRED?
Acute Oral Toxicity	163.81-1	No
Acute Dermal Toxicity	163.81-2	No
Acute Inhalation Toxicity	163.81-3	No
Primary Eye Irritation	163.81-4	No
Primary Dermal Irritation	163.81.5	No
Dermal Sensitization	163.81-6	Yes
Acute Delayed Neurotoxicity	163.81-7	Yes
Subchronic Oral Toxicity	163.82-1	Yes
Subchronic 21-Day Dermal Toxicity	163.82-2	Yes
Subchronic 90-Day Dermal Toxicity	163.82-3	No
Subchronic Inhalation Toxicity	163.82-4	Yes
Subchronic Neurotoxicity	163.82-5	Can not be determine
Chronic Feeding	163.83-1	Yes (Rat & Dog)
Oncogenicity	163.83-2	Yes (Rat & Mouse)
Teratogenicity	163.83-3	Yes (Not in rat)
Reproduction	163.83-4	Yes
Mutagenicity	163.84-1 thru 4	Yes (battery of test
Metabolism	163.85-1	No (but clearance data are requir
Domestic Animals Safety	163.86-1	No
Human Toxicity and Epidomiology		No
Pharmacology and Emergency Treatment		Yes

TOXICITY HAZARD ASSESSMENT

Endosulfan has a very high acute toxicity to mammals via oral, dermal and inhalation routes. The major symptoms of acute intoxication are manifested as tremors and convulsions indicating the involvement of the central nervous system as a possible target site.

Although endosulfan does not relate structurally to the classes of carbamate or organophosphate insecticides, it exhibits some degree of cholinesterase inhibition.

Atropine sulfate was suggested as an antidote for emergency treatment in cases of acute poisoning. However, a more efficacious antidote is deemed necessary considering the possible central nervous system effects of this chemical.

A complete assessment of hazards associated with the long term exposure to this chemical can not be made for the lack of reliable chronic studies. However, there is an indication that the organs most affected by long term exposure are liver and kidney. Further more, the chemical causes parathyroid hyperphasia, testicular atrophy, seminiferous tubular epithelial degeneration, and calcium deposition in blood vessels as a result of chronic exposure. Some of these adverse effects may be attributable to calcium metabolism alteration. These aspects should be carefully examined in any future investigation.

Endosulfan did not appear to alter the tumor profiles of female mice and rats. However, no conclusion can be made with respect to the tumorigenesis in males of either species.

The ADI for this chemical was derived from a NOEL of 30 ppm with a one hundred fold safety factor based on a 2-year chronic feeding study in the dog. However, this study has been subsequently determined to have major deficiencies and is considered invalid. As a consequance, it is reocmmended that a tentative ADI derived from NOEL of 30 ppm determined in the one-year feeding study in the dog to be instituted using a more conservative safety factor. This newly derived ADI would be 0.00075 mg/kg/day.