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# Research and Development

## HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR ARAMITE

## Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

## Prepared by

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# PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include: Reference doses (RfD's) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level which would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval which does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfD's is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfD's are not estimated. Instead, a carcinogenic potency factor, or $q_1^*$ (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQ's reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986a, respectively.

## EXECUTIVE SUMMARY

Aramite is the common name for the chemical known as sulfurous acid, 2-chloroethyl 2-[4-(dimethylethyl)phenoxy]-1-methylethyl ester by the 9th Collective Indices of the CAS. Aramite is a pesticide (miticide) and has been known by the trade names Acaricide, Aratron, Niagaramite and Ortho-Mite (SANSS, 1989). It is a colorless liquid when pure, although the technical material is a dark amber liquid. It is practically insoluble in water but is miscible in most organic solvents. Being an ester, Aramite is hydrolyzed by alkalies and is incompatible with alkaline materials, such as lime (Spencer, 1968). The United States International Trade Commission (formerly United States Tariff Commission) has not reported the production of aramite in the United States since 1970. Aramite is currently listed as a pesticide with little interest (Worthing and Walker, 1987). It is not listed in the 1977 U.S. EPA TSCA production file. No data are available to indicate that aramite is currently imported into the United States. Aramite was used as a miticide on various fruits, nuts and trees, but its use on trees bearing fruits and nuts has been restricted since 1970 (Spencer, 1968; IARC, 1974).

Environmental fate data pertaining to aramite are limited. Insufficient data are available to predict the relative importance or occurrence of chemical or biological degradation of aramite in soil or water. Although aramite is hydrolyzed by alkalies (Spencer, 1968), rate constant data are not available to determine hydrolysis rates in alkaline soil or water. Experimental studies indicate that aramite is not susceptible to direct photolysis (Gore et al., 1971; Mitchell, 1961). Based upon a reported water solubility of 0.1 mg/ℓ (Naishtein, 1964), the $K_{oc}$ for aramite is an estimated 15,500 from a regression-derived prediction equation

(Lyman, 1982), which indicates that aramite is immobile in soil (Swann et al., 1983). The estimated $K_{oc}$ value suggests that aramite may partition significantly from the water column to sediment and suspended material; therefore, the bulk of aramite released to the aquatic environment may become associated with sediment material. Aramite is nonvolatile (Mitchell, 1961) and is not expected to volatilize significantly from water or soil. Aramite aerosol released to the atmosphere during spraying of the miticide is expected to be removed from air by dry and wet deposition.

Pertinent monitoring data regarding water, food, inhalation, and dermal exposure of aramite were not located in the available literature cited in Appendix A; therefore, it is impossible to estimate inhalation, ingestion and dermal exposure to this chemical. Workers involved in spraying or other applications of aramite as a miticide are probably subject to inhalation and dermal exposure. Consumption of fruits and nuts sprayed with this pesticide is also a likely source of exposure for the general population.

Static acute toxicity data on aramite have been reported for four species of freshwater fish and one saltwater fish (Applegate et al., 1957; Clemens and Sneed, 1959; LeBlanc, 1984). Lethality was noted at concentrations $\geq$0.35 mg/ℓ in bluegill sunfish, Lepomis macrochirus (LeBlanc, 1984). This concentration is the only 96-hour $LC_{50}$ for fishes in the available literature; data for other species were collected from shorter-duration tests.

Frear and Boyd (1967) reported a 26-hour $LD_{50}$ of 0.069 for the water flea, D. magna, which is a lower concentration than the 48-hour $EC_{50}$ of 0.16 mg/ℓ reported by LeBlanc (1984) and Sanders and Cope (1966). The 48-hour $EC_{50}$ of 0.18 mg/ℓ reported by Sanders and Cope (1966) for the cladoceran, S. serrulatus, indicates similar sensitivity for these two

crustaceans. The scud, G. lacustris, was slightly more sensitive than either of the other crustaceans, with a 96-hour $LC_{50}$ of 0.06 mg/ℓ.

Data regarding the toxic effects of aramite to saltwater species were not located in the available literature.

Acute toxic effects of aramite in terrestrial fauna have been assessed in birds (Hill and Camardese, 1986; Hill et al., 1975; Heath et al., 1972) and in mites (Streu, 1972; Jeppson et al., 1969; Eldefrawi et al., 1965). These data indicate that acute toxic effects can occur at concentrations ≥0.90 ppm in mites, but that young birds (bobwhites, C. virginianus; Japanese quail, C. c. japonica; and ring-necked pheasant, P. colchicus) can consume dietary concentrations of 5000 ppm for 5 days without mortality.

The toxicity of aramite to terrestrial flora was assessed by Gentile and Gallagher (1972). Germination and growth of petunia pollen tubes were inhibited by concentrations of 1000 ppm of active ingredient of the pesticide, Aramite 15% wp, 2-(p-tert-butylphenoxy)-1-methylethyl 2-chloroethyl sulfite, added to agar medium.

The lack of adequate data regarding the toxicity of aramite precluded the development of freshwater or saltwater criteria by the method of U.S.EPA/OWRS (1986).

Data regarding the pharmacokinetics of aramite are limited to a single study of urinary metabolites of orally-treated rats (Truhaut et al., 1978). The identification of 1-(p-tert-butylphenoxy) 2-propanol in the urine of aramite-dosed rats suggests that one of the sulfite ester bonds of aramite undergoes metabolic hydrolysis.

Data regarding the carcinogenicity of aramite in humans were not located in the available literature cited in Appendix A. However, chronic dietary exposure to aramite caused neoplastic nodules or tumors in the

livers and biliary tracts of several rat strains (FDRL, CFN and Wistar) (Oser and Oser, 1960; Truhaut et al. 1975; Popper et al., 1960), in the livers of males of one mouse strain [(C57BL/6xC3H/Anf)$F_1$] (Innes et al., 1969) and in the extrahepatic biliary tract of dogs (Sternberg et al., 1960; Oser and Oser, 1962). In addition, data from the three studies of FDRL rats (Oser and Oser, 1960, 1962; Popper et al.,1960) suggests a dose-duration response for the carcinogenicity of aramite, as well as a dose-related increase in the proportion of malignant tumors.

Long-term dietary exposure to aramite also causes nonneoplastic liver effects. Degenerative liver changes (liver cord swelling, vacuolated cytoplasm, occlusion bodies and portal fibrosis) were observed in dogs fed 1580 ppm aramite for 1 year (Oser and Oser, 1960). Rats fed 200 ppm dietary aramite for 2 years displayed liver hypertrophy (in males) and degenerative alterations that included hydropic swelling, small focal areas of centrolobular necrosis and passive congestion (Deichmann et al., 1967). Aramite-induced liver weight increases were noted in dietary studies in which FDRL and CFN rats were administered $\geq$100 ppm for $\leq$2 years (Popper et al., 1960, Oser and Oser, 1960).

Aramite also affects reproduction in rats. In a study of the chronic toxicity of dietary aramite (Oser and Oser, 1960), pups of $F_0$ rats fed 1580 and 5000 ppm displayed decreased body weights at weaning. Survivability of pups during lactation significantly decreased in $F_0$ and $F_1$ rats fed 5000 ppm and in $F_2$ rats fed all three concentrations (500, 1580 and 5000 ppm). Pregnancies failed to develop after five matings in $F_0$ rats fed 5000 ppm, but indices of fertility and reproduction were otherwise unaffected in all three generations (Oser and Oser, 1960).

Pertinent data regarding the toxicity of inhalation exposure or the teratogenicity of aramite were not located in the available literature cited in Appendix A. Pertinent data regarding the mutagenicity of aramite were restricted to one negative dominant lethal assay with mice (Epstein et al., 1972).

An oral $LD_{50}$ of 3.9 g/kg aramite was determined for rats, and this dose was lethal to guinea pigs (Oser and Oser, 1960).

Aramite was assigned to U.S. EPA Group B2, probable human carcinogen, on the basis of positive results in cancer studies using rats (Oser and Oser, 1960, 1962; Popper et al., 1960; Truhaut et al., 1975), mice (Innes et al., 1969) and dogs (Sternberg et al., 1960). A slope factor ($q_1^*$) of $2.45 \times 10^{-2}$ $(mg/kg/day)^{-1}$ was derived for both oral and inhalation exposure from the increased incidence of benign and malignant liver neoplasms in rats in the dietary study by Popper et al. (1960). A cancer-based RQ of 100 was also assigned based on these data.

An RfD for chronic oral exposure to aramite of 0.05 mg/kg/day was derived by applying an uncertainty factor of 100 to the NOAEL of 5 mg/kg/day for noncancer liver effects in rats in the dietary study by Popper et al. (1960) and Oser and Oser (1962). The chronic oral RfD was also adopted as the subchronic oral RfD. An RQ of 1000 for chronic (noncancer) toxicity was based on decreased survival in suckling pups in the reproduction study in rats by Oser and Oser (1960).

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

TABLE OF CONTENTS (cont.)

LIST OF TABLES

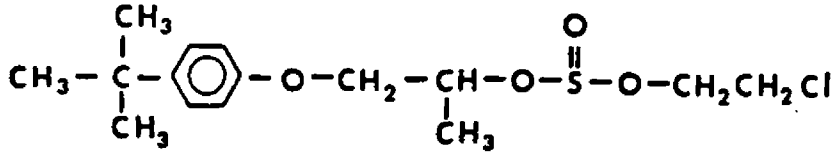
# LIST OF ABBREVIATIONS

| | |
|---|---|
| AEL | Adverse effect level |
| BCF | Bioconcentration factor |
| BOD | Biological oxygen demand |
| CAS | Chemical Abstract Service |
| CBI | Confidential Business Information |
| CS | Composite score |
| $ED_{10}$ | Effective dose to 10% of recipients |
| FEL | Frank effect level |
| GMAV | Genus mean acute value |
| GMCV | Genus mean chronic value |
| $K_{oc}$ | Octanol/water partition coefficient |
| $K_{ow}$ | Soil sorption coefficient |
| $LC_{50}$ | Concentration lethal to 50% of recipients (and all other subscripted concentration levels) |
| $LD_{50}$ | Dose lethal to 50% of recipients (and all other subscripted dose levels) |
| LOAEL | Lowest-observed-adverse-effect level |
| MTD | Maximum tolerated dose |
| NOAEL | No-observed-adverse-effect level |
| NOEL | No-observed-effect level |
| ppm | Parts per million |
| RfD | Reference dose |
| RQ | Reportable quantity |
| $RV_d$ | Dose-rating value |
| $RV_e$ | Effect-rating value |
| UV | Ultraviolet |
| wp | Wettable powder |

# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS NUMBER

Aramite is the common name for the chemical known as sulfurous acid, 2-chloroethyl 2-[4-(dimethylethyl)phenoxy]-1-methylethyl ester by the 9th Collective Indices of the Chemical Abstract Service and as sulfurous acid, 2-(p-tert-butylphenoxy)-1-methylethyl 2-chloroethyl ester by the 8th Collective Indices of the CAS. Aramite is also known as Acaracide, Aracide, Aratron, butylphenoxyisopropyl chloroethyl sulfite, cyanoethyl sucrose, CES, Niagaramite, Ortho-Mite, 2-(p-t-butylphenoxy)-1-methylethyl 2-chloroethyl sulfite and 2-(p-t-butylphenoxy)-1-isopropyl 2-chloroethyl sulfite (SANSS, 1989). The structure, molecular weight, empirical formula and CAS number for aramite are as follows:



Molecular weight: 334.87

Empirical formula: $C_{15}$ $H_{23}$ CL 04 S

CAS Registry number: 140-57-8

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

Aramite is a colorless liquid when pure, although the technical material is a dark amber liquid (Spencer, 1968). It is practically insoluble in water but miscible in most organic solvents. Solubility in petroleum oils decreases rapidly with decreasing temperature (Spencer, 1968; IARC, 1974). Selected physical properties of aramite are as follows:

| | | |
|---|---|---|
| Melting point: | -31.7°C | Windholz, 1983 |
| Boiling point: | 200-210°C (at 7 mm Hg) | Windholz, 1983 |
| Specific gravity: | 1.145-1.62 (technical grade 20/20°C) | Spencer, 1968 |
| Water solubility: | 0.1 mg/ℓ | Naishtein, 1964 |
| Vapor pressure: at 175°C | 0.1 mm Hg | Spencer, 1968 |
| Log $K_{ow}$: | no data | |

Being an ester, aramite is hydrolyzed by alkalies (Spencer, 1968). Technical aramite, which may contain 5-10% bis-2(4-tert-butylphenoxy)-1-methylethyl sulfite, decomposes in sunlight and develops an ordor of sulfur dioxide. Photodecomposition can be stabilized by adding polypropylene glycol (Spencer, 1968; IARC, 1974). Aramite is incompatible with alkaline materials such as lime or Bordeaux mixture (mixture made by adding slaked dim to a copper sulfate solution) (Spencer, 1968).

## 1.3. PRODUCTION DATA

The U.S. International Trade Commission (formerly U.S. Tariff Commission) has not reported the production of aramite in the United States since 1970, when the only producer listed was Uniroyal (USTC, 1972). Worthing and Walker (1987) list aramite as a pesticide with little current commercial interest. Aramite is not listed in the 1977 U.S. EPA TSCA production file. It was made by the reaction of 2-chlorethyl chlorosulfinate with 1-(p-tert-butylphenoxy) propanol-2 (IARC, 1974). No available data indicate that aramite is currently imported into the United States.

## 1.4. USE DATA

Aramite is a miticide used to control certain phytophagous mites (Spencer, 1968). In 1970, aramite was registered for use on only 20 crops, which were fruits and nuts. Usage was restricted by U.S. EPA to postharvest applications or nonbearing trees (IARC, 1974). Aramite was used extensively on citrus until Federal restrictions were imposed after extended animal feeding studies indicated potential carcinogenic properties (Jeppson and Gunther, 1970).

## 1.5. SUMMARY

Aramite is the common name for the chemical known as sulfurous acid, 2-chloroethyl 2-[4-(dimethylethyl)phenoxy]-1-methylethyl ester by the 9th Collective Indices of the CAS. Aramite is a pesticide (miticide) and has been known by the trade names Acaricide, Aratron, Niagaramite and Ortho-Mite (SANSS, 1989). It is a colorless liquid when pure, although the technical material is a dark amber liquid. It is practically insoluble in water but is miscible in most organic solvents. Being an ester, aramite is hydrolyzed by alkalies and is incompatible with alkaline materials, such as lime (Spencer, 1968). The United States International Trade Commission (formerly United States Tariff Commission) has not reported the production of aramite in the United States since 1970. Aramite is currently listed as a pesticide with little interest (Worthing and Walker, 1987). It is not listed in the 1977 U.S. EPA TSCA production file. No available data indicate that aramite is currently imported into the United States. Aramite was used as a miticide on various fruits, nuts and trees, but its use on trees bearing fruits and nuts has been restricted since 1970 (Spencer, 1968; IARC, 1974).

## 2. ENVIRONMENTAL FATE AND TRANSPORT

### 2.1. AIR

Aramite has been described as nonvolatile (Mitchell, 1961). Its vapor pressure of 0.1 mm Hg at 175°C (Spencer, 1968) also suggests low volatility; therefore, aramite emitted to the atmosphere probably exists in the aerosol/particulate phase rather than the vapor phase. A typical example of emission to the atmosphere is spraying of trees to control mites. In the absence of any known chemical or photolytic reaction, aramite aerosol released by spraying is expected to be removed from air primarily by dry and wet deposition.

### 2.2. WATER

2.2.1. Hydrolysis. Aramite is hydrolyzed by alkalies (Spencer, 1968). A rate constant for the aqueous hydrolysis of aramite was not located; therefore, the importance of hydrolysis in environmental media is not known. Aramite residues were observed in subcuticular areas of citrus fruits >30 days after no residue was detected in extracuticular parts (Jeppson and Gunther, 1970), suggesting that aramite is relatively stable in acidic media.

2.2.2. Photolysis. Aramite in hexane solution does not absorb UV light >290 nm (Gore et al., 1971), indicating that aramite will not directly photolyze in sunlight. Mitchell (1961) found little or no degradation of aramite by spotting it on a chromatographic paper and exposing it to a germicidal lamp of 253.7 nm maximum wavelength for 30 minutes and developing the spot in aqueous and nonaqueous solvents. Although germicidal lamps produce wavelengths shorter than sunlight, the paper chromatography tests demonstrate aramite's stability to direct photolysis.

Technical aramite reportedly decomposes in sunlight, developing a sulfur dioxide odor (Spencer, 1968). Technical aramite is only ≈90% pure and may contain 5-10% bis-2(4-tert-butylphenoxy)-1-methylethyl sulfite (Spencer, 1968; IARC, 1974) and other impurities. Based upon the photolysis data discussed previously, the reported photodecomposition of technical aramite is probably due to photodecomposition of the impurities rather than of aramite itself.

2.2.3. Microbial Degradation. Pertinent data regarding the microbial degradation of aramite were not located in the available literature cited in Appendix A; therefore, the importance of biodegradation in the environment is not known. Naishtein (1964) reported that aramite, at concentrations of 0.01 mg/ℓ to several mg/ℓ, does not affect the BOD of water. This indicates that low concentrations of aramite are not toxic to aquatic microbes.

2.2.4. Volatilization. Aramite is a relatively nonvolatile compound (see Section 2.1) and significant volatilization from water is not expected.

2.2.5. Adsorption. Based upon an estimated $K_{oc}$ of 15,500 (Section 2.3), aramite may partition significantly from the water column to sediment and suspended material. The bulk of aramite released to the aquatic environment may become associated with sediment material.

2.3. SOIL

The following regression-derived equation can be used to estimate the $K_{oc}$ of organic compounds (Lyman, 1982): log $K_{oc}$ = -0.55 log water solubility (in ppm) + 3.64. Using the water solubility of 0.1 mg/ℓ (section 1.2), the $K_{oc}$ for aramite is an estimated 15,500. Since this has not been verified by experimental data, it may not be accurate. A $K_{oc}$

value of this range of magnitude, however, suggests that a compound is generally immobile in soil systems (Swann et al., 1983) and is not expected to leach into groundwater.

Pertinent data regarding the degradation of aramite in soil were not located in the available literature cited in Appendix A. Aramite is hydrolyzed by alkalies (Spencer, 1968); therefore, aramite may be susceptible to hydrolysis in alkaline soils. The rate at which alkaline hydrolysis may occur in soil is not known.

## 2.4. SUMMARY

Environmental fate data pertaining to aramite are limited. Insufficient data are available to predict the relative importance or occurrence of chemical or biological degradation of aramite in soil or water. Although aramite is hydrolyzed by alkalies (Spencer, 1968), rate constant data are not available to determine hydrolysis rates in alkaline soil or water. Experimental studies indicate that aramite is not susceptible to direct photolysis (Gore et al., 1971; Mitchell, 1961). Based upon a reported water solubility of 0.1 mg/ℓ (Naishtein, 1964), the $K_{oc}$ for aramite is an estimated 15,500 from a regression-derived prediction equation (Lyman, 1982) which indicates that aramite is immobile in soil (Swann et al., 1983). The estimated $K_{oc}$ value suggests that aramite may partition significantly from the water column to sediment and suspended material; therefore, the bulk of aramite released to the aquatic environment may become associated with sediment material. Aramite is nonvolatile (Mitchell, 1961) and is not expected to volatilize significantly from water or soil. Aramite aerosol released to the atmosphere during spraying of the miticide is expected to be removed from air by dry and wet deposition.

## 3. EXPOSURE

### 3.1. WATER

Pertinent monitoring data regarding the levels of aramite in surface water, groundwater or drinking water were not located in the available literature cited in Appendix A. No water monitoring data pertaining to aramite were available from the U.S. EPA STORET data base.

### 3.2. FOOD

Pertinent monitoring data regarding food exposure of aramite were not located in the available literature cited in Appendix A. Citrus residue studies using aramite found that ≈3/4 of initial applications become cuticular or subcuticular residue within 3 days, with all residues becoming subcuticular within 25 days (Jeppson and Gunther, 1970).

### 3.3. INHALATION

Pertinent monitoring data regarding inhalation exposure of aramite were not located in the available literature cited in Appendix A. It is possible that workers involved in spraying or other applications of aramite as a miticide are subject to inhalation and dermal exposure.

### 3.4. DERMAL

Pertinent monitoring data regarding levels of aramite in water, food and air were not located in the available literature cited in Appendix A.

### 3.5. SUMMARY

Pertinent monitoring data regarding water, food, inhalation, and dermal exposure of aramite were not located in the available literature cited in Appendix A; therefore, it is impossible to estimate inhalation, ingestion and dermal exposure to this chemical. Workers involved in spraying or other

applications of aramite as a miticide are probably subject to inhalation and dermal exposure. Consumption of fruits and nuts sprayed with this pesticide is also a likely source of exposure for the general population.

# 4. ENVIRONMENTAL TOXICOLOGY

## 4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects On Fauna. Clemens and Sneed (1959) tested the static acute toxicity of aramite (15%) to channel catfish, Ictalurus punctatus. Ten fingerlings, 2-3 inches long, were placed in 4-gallon aquaria and tested at each of 10 concentrations at 20°C. The $LD_0$, $LD_{50}$ and $LD_{100}$ for periods ≤24 hours were >100 ppm.

A concentration of 5.0 mg/ℓ of aramite was lethal within 10 hours to larval sea lampreys, Petromyzon marinus, rainbow trout, Salmo gairdneri, and bluegill sunfish, Lepomis macrochirus, in static acute tests performed by Applegate et al. (1957). LeBlanc (1984) reported a 96-hour $LC_{50}$ of 0.35 mg/ℓ from static acute toxicity tests with bluegill sunfish, L. macrochirus.

Static acute toxicity tests conducted with aramite and the water flea, Daphnia magna, yielded a 48-hour $LC_{50}$ of 0.16 mg/ℓ (LeBlanc, 1984; Sanders and Cope, 1966). A 26-hour $LD_{50}$ of 0.069 mg/ℓ was calculated by Frear and Boyd (1967) from 10 definitive, well controlled assays with D. magna. Ten daphnids, <24 hours in age, were added to 100 mℓ solutions of aramite in 4-ounce bottles to which 1 mℓ of acetone was added to enhance the solubility. Controls were subjected to acetone/water solutions.

Sanders and Cope (1966) assessed the static acute toxicity of aramite at 16°C to the cladoceran, Simocephalus serrulatus. The 48-hour $EC_{50}$ was 0.18 mg/ℓ.

The acute toxicity of aramite to the scud, Gammarus lacustris, was tested by Sanders (1969). Ten 2-month-old scuds were placed in 1.5-gallon glass aquaria containing 4 ℓ of test water and submerged in temperature-

controlled water baths. The 24-, 48- and 96-hour $LC_{50}$ values reported at 70±1°C were 0.35, 0.10 and 0.06 mg/ℓ, respectively.

Data regarding the static acute toxicity of aramite to saltwater species were not located in the available literature cited in Appendix A.

4.1.2. Chronic Effects On Fauna.

4.1.2.1. TOXICITY -- Pertinent data regarding the effects of chronic exposure of aquatic fauna to aramite were not located in the available literature cited in Appendix A.

4.1.2.2. BIOACCUMULATION/BIOCONCENTRATION -- Pertinent data regarding the bioaccumulation/bioconcentration potential of aramite in aquatic fauna were not located in the available literature cited in Appendix A.

4.1.3. Effects On Flora.

4.1.3.1. TOXICITY -- Pertinent data regarding the toxic effects of exposure of aquatic flora to aramite were not located in the available literature cited in Appendix A.

4.1.3.2. BIOCONCENTRATION -- Pertinent data regarding the bioconcentration potential of aramite in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects On Bacteria. Pertinent data regarding the effects of exposure of aquatic bacteria to aramite were not located in the available literature cited in Appendix A.

4.2. TERRESTRIAL TOXICOLOGY

4.2.1. Effects On Fauna. Hill and Camardese (1986), Hill et al. (1975) and Heath et al. (1972) investigated the toxicity of aramite to young birds during 8-day tests that included 5 days of treated diet followed by 3 days of untreated diet. Ten incubator-hatched offspring from breeding colonies

were tested at each exposure, along with equal numbers of controls fed untreated diets. Ten-day-old bobwhites, Colinus virginianus, were tested with concentrations ≤5000 ppm of aramite. Twenty percent mortality was noted at this level, and 10% mortality was reported at 2500 ppm aramite. Fourteen-day-old Japanese quail, Coturnix c. japonica, and ring-necked pheasant, Phasianus colchicus, fed concentrations ≤5000 ppm suffered no mortality. The researchers reported $LC_{50}$s of >5000 ppm for these species.

Streu (1972) assessed the toxicity of aramite to young female twospotted spider mites, Tetranychus urficae, and reported an $LC_{50}$ of 0.90 ppm.

Citrus red mites, Panonychus citri, reared in captivity were exposed to the commercial product, Aramite (2-p-tert-butylphenoxy) isopropyl 2-chlorethyl sulfite, an acaricide, in the laboratory (Jeppson et al., 1969). Mites held ventral-side up on sticky tape were sprayed with concentrations ranging from 0.01-0.07%, resulting in mortality levels ranging from 20-98%. An $LC_{50}$ of 0.017% may be estimated from the dose-response curve provided by this study. The comparative lethality of direct contact with spray and with residue of this acaricide was also evaluated by these researchers. Lemon fruit and rootings were sprayed with varied concentrations and infested with mites. The $LC_{50}$ for nymphs of this species from contact exposure was ≈0.01% of the acaricide and, from exposure to residue only, 0.02%. Adults were slightly less sensitive. The percent aramite content of the test substance was not reported.

Eldefrawi et al. (1965) evaluated the toxicity of several acaricides to the mite, Tetranychus cinnabarinus. Laboratory tests of Aramite (2-p-tert-butylphenoxy) isopropyl 2-chloroethyl sulfite identified $LC_{50}$ concentrations (calculated on the basis of active ingredient) of 33.5 ppm by

the slide dip method and 164 ppm by the leaf spray method for adult mites. The $LC_{50}$ for the egg stage of T. cinnabarinus was 224 ppm.

4.2.2. Effects On Flora. Gentile and Gallagher (1972) assessed the toxicity of the commercial product, Aramite 15% wp, 2-(p-tert-butylphenoxy)-1-methyl-ethyl 2-chloroethyl sulfite, to petunia pollens, "Blue Lagoon" and "White Cascade" varieties, grown under greenhouse conditions. Pollen was obtained from dehiscing anthers of young flowers and germinated on discs of agar medium treated either with 1000 ppm active ingredient of the pesticide or with distilled water (controls). The percent germination was derived from random counts of 100 pollen grains from each of five test discs. Average length of the pollen tube was derived from measurement of 10 tubes/disc at 150x with an ocular micrometer. Treated pollen showed 12.25% germination as compared with 82.3% among controls. Average length of treated pollen tubes was 0.18 mm, compared with 0.33 mm among controls.

4.3. FIELD STUDIES

Pertinent data regarding the effects of aramite on flora and fauna in the field were not located in the available literature cited in Appendix A.

4.4. AQUATIC RISK ASSESSMENT

The lack of adequate data regarding exposure of aquatic fauna and flora to aramite precluded the development of a freshwater criterion (U.S.EPA/OWRS, 1986) (Figure 4-1). Available data indicate that acute toxic effects can occur at concentrations $\geq$0.35 mg/ℓ in fish and $\geq$0.06 mg/ℓ in aquatic invertebrates. Additional data required for the development of a freshwater criterion include the results of acute assays with a salmonid fish species, another fish species or an amphibian, an insect, a nonarthropod and nonchordate species, and an insect or species from a phylum not previously

| Family | TEST TYPE | | |
|---|---|---|---|
| | GMAV[a] (mg/L) | GMCV[a] (mg/L) | BCF[a] |
| #1 Chordate (Salmonid-fish) | NA | NA | NA |
| #2 Chordate (warmwater fish) | 0.35[b] | NA | NA |
| #3 Chordate (fish or amphibian) | NA | NA | NA |
| #4 Crustacean (planktonic) | 0.16[c] | NA | NA |
| #5 Crustacean (benthic) | 0.06[d] | NA | NA |
| #6 Insectan | NA | NA | NA |
| #7 non-Arthropod/-Chordate | NA | NA | NA |
| #8 New Insectan or phylum representative | NA | NA | NA |
| #9 algae | XXXXXXXXXXX XXXXXXXXXXX | NA | NA |
| #10 Vascular plant | XXXXXXXXXXX XXXXXXXXXXX | NA | NA |

[a]NA=Not Available; [b]96-h $LC_{50}$ for bluegill sungish, Lepomis macrochirus; [c]48-h $EC_{50}$ for the water flea, Daphnia magna; [d]96-h $LC_{50}$ the scud, Gammarus lacustris.

FIGURE 4-1

GMAVs, GMCVs and BCFs Required to Derive Numerical Water Quality Criteria (U.S. EPA/OWRS, 1986) to Protect Freshwater Aquatic Life from Aramite Exposure.

represented. The development of a freshwater criterion would also require data from chronic toxicity tests with two species of fauna, one species of algae or vascular plant and at least one bioconcentration study.

The lack of adequate data regarding exposure of aquatic fauna and flora to aramite precluded the development of a saltwater criterion (U.S.EPA/OWRS, 1986). Available data indicate that acute toxic effects can occur at concentrations $\geq$10 ppm. Additional data required for the development of a saltwater criterion include the results of acute assays with two chordate species, a nonarthropod and nonchordate species, a mysid or panaeid crustacean, two additional nonchordate species and one other species of marine fauna. The development of a saltwater criterion would also require data from chronic toxicity tests with two species of fauna, one species of algae or vascular plant and at least one bioconcentration study.

4.5. SUMMARY

Static acute toxicity data on aramite have been reported for four species of freshwater fish and one saltwater fish (Applegate, 1957; Clemens and Sneed, 1959; LeBlanc, 1984). Lethality was noted at concentrations $\geq$0.35 mg/ℓ in bluegill sunfish, L. macrochirus (LeBlanc, 1984). This concentration is the only 96-hour $LC_{50}$ for fishes in the available literature; data for other species were collected from shorter-duration tests.

Frear and Boyd (1967) reported a 26-hour $LD_{50}$ of 0.069 for the water flea, D. magna, which is a lower concentration than the 48-hour $EC_{50}$ of 0.16 mg/ℓ reported by LeBlanc (1984) and Sanders and Cope (1966). The 48-hour $EC_{50}$ of 0.18 mg/ℓ reported by Sanders and Cope (1966) for the cladoceran, S. serrulatus, indicates similar sensitivity for these two

crustaceans. The scud, G. lacustris, was slightly more sensitive than either of the other crustaceans, with a 96-hour $LC_{50}$ of 0.06 mg/ℓ.

Data regarding the toxic effects of aramite to saltwater species were not located in the available literature cited in Appendix A.

Acute toxic effects of aramite in terrestrial fauna have been assessed in birds (Hill and Camardese, 1986; Hill et al., 1975; Heath et al., 1972) and in mites (Streu, 1972; Jeppson et al., 1969; Eldefrawi et al., 1965). These data indicate that acute toxic effects can occur at concentrations ≥0.90 ppm in mites, but that young birds (bobwhites, C. virginianus; Japanese quail, C. c. japonica; and ring-necked pheasant, P. colchicus) can consume dietary concentrations of 5000 ppm for 5 days without mortality.

The toxicity of aramite to terrestrial flora was assessed by Gentile and Gallagher (1972). Germination and growth of petunia pollen tubes were inhibited by concentrations of 1000 ppm of active ingredient of the pesticide, Aramite 15% wp, 2-(p-tert-butylphenoxy)-1-methylethyl 2-chloroethyl sulfite, added to agar medium.

The lack of adequate data regarding the toxicity of aramite precluded the development of freshwater or saltwater criteria by the method of U.S.EPA/OWRS (1986).

# 5. PHARMACOKINETICS

## 5.1. ABSORPTION

Pertinent data regarding the extent and rate of absorption of aramite were not located in the available literature cited in Appendix A. A number of studies have provided indirect evidence for the gastric absorption of aramite, however, by demonstrating that chronic feeding of aramite-dosed food to rodents (Oser and Oser, 1960; Popper et al., 1960; Innes et al., 1969; Truhaut et al., 1975) and to dogs (Sternberg et al., 1960) causes toxic and cancerous effects of the liver and biliary tract.

## 5.2. DISTRIBUTION

Pertinent data regarding the distribution of aramite were not located in the available literature cited in Appendix A.

## 5.3. METABOLISM

Truhaut et al. (1977) examined urinary metabolites of rats given acute (2 g/kg in olive oil by gavage) and chronic (400 mg/kg/day in diet) oral doses of aramite. Although aramite was not detected in the urine of treated animals, two compounds were identified that were absent in the urine of control rats. One of these metabolites was identified as 1-(p-tert-butyl-phenoxy) 2-propanol. Thus, aramite was apparently metabolized by hydrolysis of one of its sulfite ester bonds. Neither the extent nor the site of metabolism was examined. Other data regarding the metabolism of aramite were not located in the available literature cited in Appendix A.

## 5.4. EXCRETION

Pertinent data regarding the rate or extent of excretion of aramite were not located in the available literature cited in Appendix A.

## 5.5. SUMMARY

Data regarding the pharmacokinetics of aramite are limited to a single study of urinary metabolites of orally-treated rats (Truhaut et al., 1978). The identification of 1-(p-tert-butylphenoxy) 2-propanol in the urine of aramite-dosed rats suggests that one of the sulfite ester bonds of aramite undergoes metabolic hydrolysis.

# 6. EFFECTS

## 6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure. Pertinent data regarding the subchronic and chronic toxicity of aramite from inhalation exposure were not located in the available literature cited in Appendix A.

6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC ORAL -- Oser and Oser (1960) fed groups of young male and female mongrel dogs sex diets supplemented with 0, 500 and 1580 ppm aramite for 1 year. All treated dogs survived. Body weights were unaffected at 500 ppm, but at 1580 ppm, reduced terminal body weights were associated with reduced food intake. After 1 year, no treatment-related changes were noted in blood indices (total and differential white cell counts, blood sugar and hemoglobin), although slightly diminished red cell counts were measured in most dogs. Histological examination of the major organs and tissues revealed no treatment-related changes except in the liver. Degenerative liver changes were noted at the 1580 ppm level. Changes included liver cord swelling, vacuolated cytoplasm and occasional occlusion bodies in two dogs and a slight degree of portal fibrosis in one dog at the 1580 ppm level. At 500 ppm, the authors observed cloudy swelling and rarefactions of the liver cells with some focal cell necrosis, but stated that these changes were comparable in degree with those seen in the control dogs.

6.1.2.2. CHRONIC ORAL -- Oser and Oser (1960) also examined the chronic toxicity of dietary aramite in FDRL rats. Groups of 10 weanling rats of both sexes were fed diets containing 0, 500, 1580 or 5000 ppm aramite for 2 years. Animals were mated and, after weaning, $F_1$ and $F_2$

offspring were fed diets identical to those of their parents. Blood and urine from $F_0$ rats were collected and examined periodically, but the nature of the urinalysis was unspecified. Body weights were evaluated periodically in $F_0$, $F_1$ and $F_2$ rats. Post-mortem histological examinations were made of the livers and kidneys of all rats and of the other major organs in $\geq$ two rats/sex/concentration. Reproductive indices of all three generations were evaluated and are discussed in Section 6.5.

In the $F_0$ rats (as well as in the $F_1$ and $F_2$ rats), growth through the first 12 weeks of treatment was affected only at the 5000 ppm level. The difference in growth, however, could be attributed to reduced food intake. Survival significantly decreased in the $F_0$ groups fed the highest concentration in the first year of feeding (10 and 20% survival for females and males vs. 75 and 90% for the respective control groups). In the second year, however, all aramite-treated groups displayed significantly decreased, concentration-related survival relative to the control group. No rats survived 96 weeks of treatment at the highest concentration. After 104 weeks of treatment, survival for females and males of the remaining groups were 0 and 18% for 1580 ppm, 10 and 60% for 500 ppm and 50 and 70% for controls, respectively.

Examination of several blood indices (sugar and hemoglobin levels, erythrocyte and leukocyte counts) indicated no significant difference between treated and control rats (Oser and Oser, 1960). Histopathological examinations of the major organs and tissues of rats that died or were sacrificed at termination of the experiment revealed no treatment-related changes except in the liver. At the 1580 and 5000 ppm levels, pathological liver changes were reported ("varying from focal hyperplasia and

inflammatory reactions to malignancy"), but details of the incidence of these changes were limited to lesions, which were diagnosed as malignant or precancerous (Section 6.2.2). The histology of the livers of the 20 rats fed 500 ppm did not differ from that of the controls, except for the occurrence of a hyperplastic nodule in the liver of one rat.

Diets containing 0, 100, 200 or 400 ppm aramite were provided for 2 years to three strains of rats (FDRL, Sprague-Dawley and CFN and two strains of mice (C3H and C57BL). Rat data were reported by Popper et al. (1960) and Oser and Oser (1962), and mouse data by Oser and Oser (1962). Groups of 100 animals of each strain (50/sex) were fed aramite-dosed diets. For each strain, control groups contained 200 animals (100/sex). Major organs and tissues of moribund animals and survivors at 2 years were examined for gross changes. All livers were examined microscopically, but other organs were examined microscopically only if macroscopic changes were apparent.

Neither growth nor survival was affected by aramite treatment in any of the strains of rats or mice (Popper et al., 1960; Oser and Oser, 1962). Survival of the Sprague-Dawley and CFN rats was significantly reduced (≃40 and 70%, respectively) relative to that of FDRL rats (≃90%) because of respiratory infections which were not treatment-related. The extremely high mortality of the Sprague-Dawley rats, which occurred predominantly in the ninth and tenth months, precluded evaluation of liver effects after 2 years of aramite treatment. Liver weights were not measured for the mice, but significantly increased absolute and relative liver weights were observed at the highest concentration (400 ppm) in both sexes of the FDRL and CFN rats. At the 100 and 200 ppm levels, significant absolute and relative liver weight increases were seen only in FDRL rats. Gross abnormalities of

various organs were observed in all strains of both species, but the authors stated that the severity and incidence were not treatment-related except for the increased incidence of liver abnormalities in rats. Rat liver abnormalities were cancerous or precancerous and are described in Section 6.2.2. Histological changes in the livers of treated mice were not remarkable (Oser and Oser, 1962).

Deichmann et al. (1967) fed groups of 60 Osborne-Mendel rats (30/sex/group) diets containing mixtures of DDT, methoxychlor, aldrin, thiourea and 200 ppm aramite, diets containing individual pesticides (aramite at 200 ppm), or a non-supplemented basal diet. Treatment periods were 24-27 months. Body weights and hematological indices (hematocrit, hemoglobin, erythrocytes and leukocytes) were measured periodically, and all tumors and major organs were examined histologically. Aramite, when fed alone at 200 ppm, did not affect weight gain, hematological indices or survival of the rats, but increased absolute and relative liver weights in male rats (but not in females). Aramite treatment was associated also with histological changes of the liver (hydropic swelling, granular cytoplasm, slight fatty metamorphosis, small focal areas of centrolobular necrosis and passive congestion). Evidence for additive or synergistic toxicological effects was not provided by the treatments with pesticide mixtures.

6.1.3. Other Relevant Information. Oser and Oser (1960) determined an oral $LD_{50}$ value for aramite of 3.9 g/kg in rats. In this study, aramite (in a 2% aqueous gum tragacanth solution) was administered by stomach tube to rats of both sexes (five animals/sex/dose). A single dose of aramite (3.9 g/kg) was administered by gavage to 10 guinea pigs, and within 2 weeks, five of the animals died, thus indicating that aramite's acute toxicity in

guinea pigs is similar to that in rats. Attempts to determine oral $LD_{50}$ values for dogs were unsuccessful because dogs regurgitated doses of aramite immediately after administration.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of inhalation exposure to aramite were not located in the available literature cited in Appendix A.

6.2.2. Oral. There is evidence of carcinogenicity of chronic oral exposure to aramite in rats (Oser and Oser, 1960; Popper et al., 1960; Oser and Oser, 1962; Truhaut et al., 1975), in dogs (Sternberg et al., 1960) and in mice (Innes et al., 1969).

In the chronic feeding study by Oser and Oser (1960) described in section 6.1.2.2, six of 20 rats (10 male and 10 female FDRL Wistar) fed 5000 ppm aramite had lesions described as hepatomas or cholangiomas. Two of 21 rats fed 1580 ppm aramite had hepatocellular lesions described as malignant, and one of 20 rats fed 500 ppm had a hyperplastic nodule in the liver. The authors did not report the incidence of hyperplastic nodules at the two highest doses (Table 6-1).

Studies of the chronic toxicity of food dosed with aramite at lower concentrations (0, 100, 200 and 400 ppm) showed that Aramite caused increased incidences of tumors in rats but not in mice (Popper et al., 1960, Oser and Oser, 1962). Experimental details for these studies were described in Section 6.1.2.2. Significantly increased incidences of hyperplastic liver nodules were noted at the 400 ppm level in both FDRL and CFN rats (Table 6-2). Significantly increased incidences of nodules also were observed in CFN rats fed 200 ppm, but incidences in FDRL rats fed 200 ppm and in both strains fed 100 ppm were virtually identical to control

TABLE 6-1

Incidence of Tumors in FDRL Wistar Rats Treated with Aramite in the Diet[a]

| Sex | Dose (ppm) | Duration of Treatment (weeks) | Target Organ | Tumor Type | Tumor Incidence (p value)[b] |
|---|---|---|---|---|---|
| M/f (10/sex) | 0 | 104 | liver | hyperplastic nodules<br>liver tumors | 0/20<br>0/20 |
| | 500 | 48-96 | liver | hyperplastic nodules<br>liver tumors | 1/20 (p>0.05)<br>0/20 |
| | 1580 | 48-96 | liver | hyperplastic nodules<br>liver tumors[c] | NR<br>2/21 (p>0.05) |
| | 5000 | 24-48 | liver | hyperplastic nodules<br>liver tumors[d] | NR<br>6/20 (p=0.01) |

QUALITY OF EVIDENCE

Strengths of Study: Compound was administered by a relevant route of exposure of three doses in both sexes; data indicate dose-dependence for tumor incidence and time-to-death-with-tumor; adequate duration of exposure and numbers of animals.

Weaknesses of Study: Survival was dose-related at highest dose; inadequate numbers survived to be at risk for late-developing tumors; reporting of histological data was only semiquantitative; incidence of hyperplastic nodules not reported for two highest doses; only one strain of one species. Sex of rats with tumors not reported.

Overall Adequacy: Adequate

[a]Source: Oser and Oser, 1960

[b]Fisher exact test performed at SRC

[c]Tumors only identified as "malignant"

[d]Tumors identified as "hepatomas/cholangiomas." Tumor type (benign or malignant) not specified.

NR = Not reported

TABLE 6-2

Incidence of Tumors in FDRL and CFN Rats Treated with Aramite in the Diet[a]

| Species/ Strain | Sex/ Number | Dose (ppm) | Duration of Treatment (weeks) | Target Organ | Tumor Type | Tumor Incidence (p value)[b] |
|---|---|---|---|---|---|---|
| Rat/FDRL | M/F, 50/50 | 0 | 104 | liver | hyperplastic nodules | 2/193 |
| | | 100 | 104 | liver | hyperplastic nodules | 2/93 (p>0.05) |
| | | 200 | 104 | liver | hyperplastic nodules | 3/100 (p>0.05) |
| | | 400 | 104 | liver | hyperplastic nodules[c] and carcinomas | 25/90 (p<0.01)[d] |
| Rat/CFN | M/F, 50/50 | 0 | 104 | liver | hyperplastic nodules | 5/180 |
| | | 100 | 104 | liver | hyperplastic nodules[e] | 3/93 (p>0.05) |
| | | 200 | 104 | liver | hyperplastic nodules[e] | 10/90 (p<0.01) |
| | | 400 | 104 | liver | hyperplastic nodules[e] | 22/96 (p<0.01) |

QUALITY OF EVIDENCE

Strengths of Study: Relevant route of exposure at three doses to both sexes of two strains; duration of exposure equal to rat's lifespan; more than adequate numbers of animals; data indicate dose relationship for tumor incidence.

Weaknesses of Study: Highest dose may be slightly below MTD (Oser and Oser, 1960; see Table 6-1); malignancy of tumors of liver parenchyma only demonstrated in one strain.

Adequacy: Adequate

[a]Source: Popper et al., 1960; Oser and Oser, 1962

[b]Fisher exact test performed at SRC

[c]Liver carcinomas were only identified in FDRL rats fed 400 ppm.

[d]Five bile duct adenomas were identified in this group, but report did not specify if animals with bile duct adenomas were distinct from those with hyperplastic nodules and carcinomas of the liver. Tumor incidence tally, therefore, does not include bile duct adenomas.

[e]No liver carcinomas identified, but low (one-two/group), nonsignificant (p<0.05) incidences of bile duct adenomas were observed

incidences (see Table 6-2). In FDRL rats fed 400 ppm, two liver carcinomas and five bile duct adenomas were identified. The authors stated that the animals with carcinomas also had hyperplastic nodules, but did not specify if animals with bile duct adenomas also had hyperplastic liver nodules or carcinomas. In CFN rats, low nonsignificant incidences of bile duct adenomas were identified in all three groups of aramite-treated rats. The authors did not specify, however, whether or not animals with adenomas also had hyperplastic nodules. No other treatment-related neoplastic alterations were observed in the livers of treated rats.

Data from the two studies of FDRL rats (see Tables 6-1 and 6-2) suggest a dose-related response for the carcinogenicity of aramite, as well as a dose-related increase in the proportion of malignant tumors.

The carcinogenicity of chronic oral exposure to aramite is further indicated by a study in which male Wistar rats were fed diets containing 0 or 5000 ppm aramite for 56 weeks (Table 6-3) (Truhaut et al., 1975). Thirty-three animals were fed aramite-dosed diets, and 20 rats served as controls. The authors estimated the daily intake of aramite as 400 mg/kg/day. Data from this study were also presented in two later reports (Blanc et al., 1978 and Truhaut et al., 1978). Aramite-treated rats displayed significantly decreased body weight gain and terminal body weights (not attributable to decreased food intake) and increased absolute and relative liver weights (Truhaut et al., 1975; Blanc et al., 1978). Nineteen of 33 treated rats survived 56 weeks of treatment. Liver tumors (neoplastic proliferation of parenchyma cells) were evident in all treated animals surviving to 56 weeks. Information regarding survival and incidences of neoplasms in the control group was not reported.

TABLE 6-3

Incidence of Tumors in Male Wistar Rats Treated with Aramite in the Diet[a]

| Dose (ppm) | Duration of Treatment (weeks) | Target Organ | Tumor Type | Tumor Incidence |
|---|---|---|---|---|
| 0 | 56 | liver | liver tumors | NR[b] |
| 5000 | 56 | liver | liver tumors | 19/19[c] |

QUALITY OF EVIDENCE

| | |
|---|---|
| Strengths of Study: | Relevant route of exposure; adequate numbers of treated animals |
| Weaknesses of Study: | Only one sex of one species; only one dose level; tumor incidence for controls not reported; dose appeared to be above MTD |
| Overall Adequacy: | Inadequate for quantitative risk assessment |

[a]Source: Truhaut et al., 1975

[b]Twenty control animals were included, but incidence of liver tumors in these animals was not specified.

[c]Nineteen of 33 rats fed aramite-dosed food survived to 56 weeks of treatment; liver tumors (neoplastic proliferation of liver parenchyma cells) were identified in all 19.

NR = Not reported

Innes et al. (1969) administered daily doses (464 mg/kg/day) of aramite in 0.5% gelatin by stomach tube to groups of (C57BL/6xC3H/Anf)$F_1$ and (C57BL/6xAkR)$F_1$ mice of both sexes (16 mice/sex/strain). Gavage treatment began 7 days after birth and continued until the mice were weaned at 4 weeks. After weaning, aramite was provided in the diet at a concentration of 1112 ppm for ≈80 weeks. Examination of necropsied animals revealed an incidence of tumors in male (C57BL/6xC3H/Anf)$F_1$ mice (6/16) significantly ($p=0.01$) larger than the incidence in control mice (Table 6-4). The tumors were predominantly liver tumors described as hepatomas and were considered potentially malignant by the authors. Incidences of tumors in female (C57BL/6xC3H/Anf)$F_1$ mice and in both sexes of (C57BL/6xAkR)$F_1$ mice did not differ significantly from those in controls.

Chronic oral exposure of dogs to aramite causes cancer; however, the primary site in dogs has been identified as the biliary tract rather than the liver (Sternberg et al., 1960) (Table 6-5). Forty mongrel dogs of both sexes (17 male and 23 female) were fed diets containing aramite for 462-1220 days (Sternberg et al., 1960) (see Table 6-5). The dogs were divided into three groups of 12, 12 or 16 animals receiving aramite concentrations of 0, 500 or 828-1420 ppm, respectively. The control dogs and five of the low-dose animals were not autopsied and examined for tumors, although all of these dogs appeared outwardly healthy throughout the experiment. The remaining 7 dogs of the low-dose group and 12 dogs of the high-dose group appeared moribund (or died) during the treatment period and were examined for histological changes in the liver and biliary tract. In 14 of the 19 autopsied dogs, ≥1 adenocarcinoma was identified in the examined areas (see Table 6-5). Five dogs died before 811 days (short duration of treatment); one had a neoplastic nodule of the liver. The other 14 autopsied dogs who

TABLE 6-4

Incidence of Tumors in Mice Treated with Aramite in the Diet[a]

| Species/ Strain | Sex | Dose (ppm) | Duration of Treatment (weeks) | Target Organ | Tumor Type (p value)[b] | Tumor Incidence |
|---|---|---|---|---|---|---|
| Mice/ (C57BL/6x $C_3H$/Anf)$F_1$ | M | 0 | 80 | liver | hepatomas | 8/73 |
| | | 1112[c] | 80 | liver | hepatomas | 6/16 (p=0.01)[d] |

QUALITY OF EVIDENCE

Strengths of Study: Relevant route of exposure; adequate duration of exposure and number of animals; dose apparently near MTD

Weaknesses of Study: Only one sex of one species with positive results; only one dose level

Adequacy: Adequate

[a]Source: Innes et al., 1969

[b]Study also tested aramite in females of same strain and both sexes of another mouse strain [(C57BL/6xAKR)$F_1$] according to the same protocol; results for carcinogenicity were negative.

[c]For first 3 weeks, aramite was administered by gavage (464 mg/kg/day in treated group).

[d]Significance tested by Mantel-Haenszel procedure

TABLE 6-5

Incidence of Tumors in Dogs Treated with Aramite in the Diet[a]

| Species/ Strain | Sex | Dose (ppm) | Duration of Treatment (days) | Target Organ | Tumor Type | Tumor Incidence |
|---|---|---|---|---|---|---|
| Dog/mongrel | M/F[b] | 0 | 1220 | extrahepatic biliary system | adenocarcinomas | NE[c] |
| | | 500 | 811-1220 | extrahepatic biliary system | adenocarcinomas | 7/12[d] |
| | | 828-1429[e] | 462-1206 | extrahepatic biliary system | adenocarcinomas | 7/12[f] |

QUALITY OF EVIDENCE

Strengths of Study: Compared administered by relevant route of exposure; adequate numbers of animals; adequate duration of exposure; MTD obtained

Weaknesses of Study: Animals healthy at termination of experiment (12 controls and 5 fed 500 ppm) were not examined for tumors; tumor incidence in controls not reported. Sites other than liver and biliary tract were not examined.

Adequacy: Inadequate for quantitative risk assessment

[a]Source: Sternberg et al., 1960

[b]Nineteen dogs examined for tumors (7 fed 500 ppm and 12 fed >500 ppm), 10 female and 9 were male.

[c]Not examined; 12 control dogs appeared healthy throughout 1220-day experimental period, but organs of these dogs were not examined for tumors.

[d]Five of 12 dogs fed 500 ppm appeared healthy throughout experiment and were not examined for tumors.

[e]Twelve dogs were provided diets containing maximum concentrations of aramite at which body weights could be maintained. From food intake data and level of aramite in food, the authors calculated average dietary concentrations ranging from 828-1429 ppm.

[f]Five of 12 dogs treated with maximum tolerated dosage levels were diagnosed microscopically as noncancerous; all five, however, died early in experiment (four of the five died before 600 days).

lived 811 days or longer had the following tumors: 7 had adenocarcinoma of the gall bladder and extrahepatic biliary duct), mainly dogs of the high-dose group); 2 had adenocarcinoma of the hepatic biliary duct only; 1 had adenocarcinoma of the gall bladder only; 1 had adenocarcinoma of the gall bladder and intrahepatic biliary duct; and 3 had adenocarcinoma of the extra- and intrahepatic biliary duct. No calculi were present in the gall bladder or biliary ducts. Neoplastic nodules in the liver parenchyma and adenocarcinomas of liver bile ducts were also observed in some of the animals that had adenocarcinomas of the extrahepatic biliary tract.

In a series of 2-year feeding experiments with Osborne-Mendel rats, Radomski et al. (1965) and Deichmann et al. (1967) administered aramite individually at two concentrations (80 and 200 ppm) and in mixtures with other pesticides at three concentrations (50, 80 and 200 ppm). Groups of sixty rats (30/sex/group) received the 80 ppm (Radomski et al., 1965) and 200 ppm (Deichmann et al., 1967) treatments, and a group of 100 (50/sex/group) received the 50 ppm treatment (Radomski et al., 1965). Tumors detected by gross examination of major organs and tissues were examined histologically. Incidences of tumors in any of the groups treated with aramite alone were not significantly different from incidences of tumors in control groups. Furthermore, the data from experiments with mixtures did not provide evidence for synergistic carcinogenic effects among the pesticides.

Single subcutaneous injections of aramite into C3H/Anf mice (10 mg/mouse; 50 mice/sex) were not carcinogenic within periods of observation ranging from 273-575 days postapplication. Weekly applications of aramite (0.1 mg or 10 mg in acetone) were applied to the skin of the same strain of mice for periods ranging from 44-74 weeks. Weekly visual observations of the skin were recorded. At the end of the exposure period, mice were

subjected to gross autopsy. Sections of the skin were prepared and examined microscopically for histologic alteration. Mice treated at either dose showed no evidence of skin tumors as revealed by macroscopic and microscopic examination (Hodge et al., 1966).

6.3. MUTAGENICITY

Pertinent data regarding the mutagenicity of Aramite were restricted to one negative dominant lethal assay in mice (Epstein et al., 1972). Single intraperitoneal doses of 200 and 500 mg/kg aramite were administered to groups of seven and nine male ICR Ha Swiss mice, respectively. The treated males were then mated during sequential weekly periods with groups of untreated virgin females. The number of early fetal deaths and preimplantation losses associated with the treated groups were not different from control values.

6.4. TERATOGENICITY

Pertinent data regarding the teratogenicity of aramite were not located in the available literature cited in Appendix A.

6.5. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of aramite were restricted to the chronic oral study by Oser and Oser (1960) described in Section 6.1.2.2. $F_0$ rats were mated >7-8 times during their lifespans, but $F_1$ and $F_2$ generations were restricted to the production of only two litters. The authors did not specify the duration of exposure before the first mating. Indices of fertility (number of pregnancies/mating) and reproduction (number of litters/pregnancies) were not affected by chronic feeding of aramite-dosed food in any of three generations, except that pregnancies failed to result after the fifth mating in the $F_0$ rats at 5000 ppm. Pups of $F_0$ rats fed 1580 and 5000 ppm displayed decreased average body weights at weaning. Survivability of pups during lactation (number of

pups weaned/number of pups born) decreased significantly in $F_0$ and $F_1$ rats fed the highest dose (5000 ppm) and in $F_2$ generations at all dose levels (500, 1580 and 5000 ppm). At 5000 ppm, none of the $F_2$ generation lived through the lactation period.

6.6. SUMMARY

Data regarding the carcinogenicity of aramite in humans were not located in the available literature cited in Appendix A. However, chronic dietary exposure to aramite caused neoplastic nodules or tumors in the livers and biliary tracts of several rat strains (FDRL, CFN and Wistar) (Oser and Oser, 1960; Truhaut et al. 1975; Popper et al., 1960), in the livers of males of one mouse strain [(C57BL/6xC3H/Anf)$F_1$] (Innes et al., 1969) and in the extrahepatic biliary tract of dogs (Sternberg et al., 1960; Oser and Oser, 1962). In addition, data from the three studies of FDRL rats (Oser and Oser, 1960, 1962; Popper et al.,1960) suggest a dose-duration response for the carcinogenicity of aramite, as well as a dose-related increase in the proportion of malignant tumors.

Long-term dietary exposure to aramite also causes nonneoplastic liver effects. Degenerative liver changes (liver cord swelling, vacuolated cytoplasm, occlusion bodies and portal fibrosis) were observed in dogs fed 1580 ppm aramite for 1 year (Oser and Oser, 1960). Rats fed 200 ppm dietary aramite for 2 years displayed liver hypertrophy (in males) and degenerative alterations that included hydropic swelling, small focal areas of centrolobular necrosis and passive congestion (Deichmann et al., 1967). Aramite-induced liver weight increases were noted in dietary studies in which FDRL and CFN rats were administered $\geq$100 ppm for $\leq$2 years (Popper et al., 1960, Oser and Oser, 1960).

Aramite also affects reproduction in rats. In a study of the chronic toxicity of dietary aramite (Oser and Oser, 1960), pups of $F_0$ rats fed 1580 and 5000 ppm displayed decreased body weights at weaning. Survivability of pups during lactation significantly decreased in $F_0$ and $F_1$ rats fed 5000 ppm and in $F_2$ rats fed all three concentrations (500, 1580 and 5000 ppm). Pregnancies failed to develop after five matings in $F_0$ rats fed 5000 ppm, but indices of fertility and reproduction were otherwise unaffected in all three generations (Oser and Oser, 1960).

Pertinent data regarding the toxicity of inhalation exposure or the teratogenicity of aramite were not located in the available literature cited in Appendix A. Pertinent data regarding the mutagenicity of aramite were restricted to one negative dominant lethal assay in mice (Epstein et al., 1972).

An oral $LD_{50}$ of 3.9 g/kg aramite was determined for rats, and this dose was lethal to guinea pigs (Oser and Oser, 1960).

# 7. EXISTING GUIDELINES AND STANDARDS

Current guidelines and standards regarding Aramite were not located in the available literature cited in Appendix A.

## 7.2. AQUATIC

Aramite has been identified and listed as a hazardous constituent (U.S. EPA, 1981).

# 8. RISK ASSESSMENT

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that CBI, which this document could not address, do not exist. From examination of the bibliographies of the CBI data, however, it was determined that CBI data would not alter the approach to risk assessment or the risk assessment values presented herein.

## 8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of inhalation exposure to aramite were not located in the available literature cited in Appendix A.

8.1.2. Oral. As discussed in Section 6.2.2., positive results were available for the carcinogenicity of chronic oral exposure to aramite in rats (Oser and Oser, 1960; Popper et al., 1960; Truhaut et al., 1975), in dogs (Sternberg et al., 1960) and in mice (Innes et al., 1969).

Two of 21 rats fed 1580 ppm aramite and 6 of 20 rats fed 5000 ppm aramite had liver tumors in the 2-year study by Oser and Oser (1960) (see Table 6-1). In another 2-year feeding study (Popper et al., 1960), significantly increased incidences of hyperplastic nodules were observed in rats fed diets containing 200 or 400 ppm aramite (see Table 6-2). Nineteen of 33 male Wistar rats fed 5000 ppm aramite survived 56 weeks of treatment (Truhaut et al., 1975); liver tumors were identified in all surviving rats (see Table 6-3). In a group of 24 dogs provided diets containing $\geq$500 ppm aramite for 462-1220 days (Sternberg et al., 1960), 14 had adenocarcinomas in their bile ducts or gall bladder (see Table 6-5). A significantly increased incidence of liver tumors (see Table 6-4) was observed also in

male (C57BL/6xC3H/Anf)$F_1$ mice given aramite by gavage at 464 mg/kg/day for 3 weeks during suckling, followed by 1112 ppm in the diet for 80 weeks (Innes et al., 1969).

8.1.3. Other Routes. Neither single subcutaneous injections nor weekly skin-painting applications of aramite were tumorigenic in mice (Hodge et al., 1966). Additional data regarding the carcinogenicity of Aramite by other routes of exposure were not found.

8.1.4. Weight of Evidence. There are no data regarding the carcinogenicity of aramite in humans. Information regarding aramite's mutagenicity is limited to a single report that aramite did not cause dominant lethal mutations in mice (Epstein et al., 1972).

Qualitative and quantitative evidence exists for the carcinogenicity of aramite in three species of animals. Chronic dietary exposure to aramite caused statistically significant increased incidences of liver tumors or neoplastic nodules in three strains of rats (Oser and Oser, 1960; Popper et al., 1960; Oser and Oser, 1962; Truhaut et al., 1975) and males of one strain of mice (Innes et al., 1969). Chronic dietary exposure was associated with a high incidence of tumors in the extrahepatic biliary system of dogs (Sternberg et al., 1960); however, lack of examination of control dogs precluded statistical analysis of the data (see Table 6-5). Three of the rat studies indicate that increases in the incidences of liver neoplasms and proportions of malignant liver tumors were related to dose (Oser and Oser, 1960, 1962; Popper et al., 1960)

The available data in several species provide sufficient evidence for carcinogenicity of aramite in animals and indicate a potential for aramite to cause cancer in humans. Because there is sufficient evidence for the

carcinogenicity of aramite in animals but no human data, aramite is classified in U.S. EPA Group B2 -- Probable Human Carcinogen (U.S. EPA, 1986a).

8.1.5. Quantitative.

8.1.5.1. INHALATION -- Pertinent data regarding the carcinogenicity of inhaled aramite were not located in the available literature cited in Appendix A. A tentative quantitative estimate of carcinogenic risk ($q_1^*$) that is due to inhalation exposure to aramite can be derived from oral exposure data, assuming that aramite is carcinogenic following any route of exposure and that there are no route-specific differences in pharmacokinetics such as differences between routes in absorption efficiencies. Support for the first assumption is provided by demonstrations that orally administered aramite induces tumors at sites distant from the gastrointestinal tract (in the liver and extrahepatic biliary system). The lack of pharmacokinetic data for aramite underscores the tentative nature of this estimate.

From the oral $q_1^*$ of $2.45 \times 10^{-2}$ $(mg/kg/day)^{-1}$ (calculated in Section 8.1.5.2.), the concentrations of aramite in air associated with increased lifetime risk of cancer at risk levels of $10^{-5}$, $10^{-6}$ and $10^{-7}$ are calculated to be $1.43 \times 10^{-3}$, $1.43 \times 10^{-4}$ and $1.43 \times 10^{-5}$ $mg/m^3$, respectively. These concentrations were calculated by dividing a given risk level by the $q_1^*$, multiplying by the reference human body weight (70 kg) and dividing by 20 $m^3$/day, the reference inhalation rate for humans (U.S. EPA, 1986b).

8.1.5.2. ORAL -- Three dietary studies with rats and mice (Oser and Oser, 1960; Popper et al., 1960; Innes et al., 1969) provided data suitable for calculation of quantitative estimates of cancer risk ($q_1^*$s). From

these data, four $q_1^*$s were derived using the multistage model of Howe and Crump (1982). Data used in the derivations are presented in Appendix B.

The incidences of liver hyperplastic nodules and tumors in FDRL rats from the Popper et al. (1960) and Oser and Oser (1962) studies (see Table 6-2) provide the highest quality data upon which to base an oral $q_1^*$ for aramite. The experiment was well designed, with more than adequate numbers of animals, a duration of exposure equal to the rat's lifespan and a high dose level that appeared to be only slightly below the MTD. Furthermore, the occurrence of liver carcinomas at the highest dose indicates that there was a progression from benign hyperplastic liver nodules to malignancy. The data for CFN rats from the same study (see Table 6-2) is of similar quality, but there is no evidence of progression from hyperplastic nodules to malignancy.

The study of FDRL Wistar rats by Oser and Oser (1960) demonstrated a statistically significant increased incidence of liver tumors at high dietary doses (1580 and 5000 ppm) (see Table 6-1). The data of the highest dose group was dropped from consideration in the Howe and Crump (1982) model (Appendix B), since this group was exposed to aramite for a shorter duration of time than the other two dose groups in the study. Also, a limitation of this study is that incidences of hyperplastic liver nodules were incompletely reported.

Although the data for male (CB57BL/6xC3H/Anf)$F_1$ mice from Innes et al. (1969) indicate that dietary aramite can cause liver tumors in mice (see Table 6-4), there was only one treatment level and no indication of progression from benign to malignant tumors.

The available rat and mouse data support a $q_1^*$ based upon rat data rather than one based upon mouse data. The available data for tumorigenicity in mice are largely negative. In the study by Innes et al.

(1960), negative responses were obtained for female mice of the (CB57BL/6xC3H/Anf)F1 strain and both sexes of the (CB57/6xAkr)$F_1$ strain. As indicated above, treatment-related tumors occurred only in male (CB57BL/6xC3H/Anf)F1 mice in this study. Oser and Oser (1962) provided dietary aramite at concentrations $\leq$400 ppm and found no increased incidence of tumors in treated mice of two other strains (C3H and CB57BL). Additionally, carcinomas were induced in rats (Popper et al., 1960), but not in mice (Innes et al., 1969). Aramite-induced tumors have been observed more consistently in rats; positive results exist for all three rat strains examined in two independent studies (Popper et al., 1960; Truhaut et al., 1975).

The $q_1^*$ of $2.45 \times 10^{-2}$ $(mg/kg/day)^{-1}$ from the FDRL rat data from Popper et al. (1960) (Appendix B), therefore, is the most appropriate quantitative estimate of cancer risk for aramite. The concentrations of aramite in drinking water associated with increased lifetime risks of cancer are $1.43 \times 10^{-2}$, $1.43 \times 10^{-3}$ and $1.43 \times 10^{-4}$ mg/ℓ at risk levels of $10^{-5}$, $10^{-6}$ and $10^{-7}$, respectively. These concentrations were calculated by dividing a given risk level by the $q_1^*$, multiplying by the body weight for humans (70 kg) and dividing by the reference daily water consumption for humans (2 ℓ) (U.S. EPA, 1986b).

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure -- Pertinent data regarding the subchronic or chronic toxicity of inhaled aramite were not located in the available literature cited in Appendix A.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURE (SUBCHRONIC ORAL) -- Data for the subchronic systemic toxicity of aramite are limited to the 1-year feeding study by Oser and Oser (1960) in which dogs were fed aramite at concentrations of 0, 500 and 1580 ppm. A LOAEL of 1580 ppm was identified for degenerative liver changes including liver cord swelling, vacuolated cytoplasm and portal fibrosis (rec #8). In dogs fed 500 ppm, liver changes were observed and described as cloudy swellings and rarefactions of liver cells with some focal cell necrosis and occasional occlusion bodies (rec #9). These changes were comparable with those seen in control dogs; therefore, 500 ppm has been designated a NOAEL. Because limited numbers of animals (three/concentration) were used and additional subchronic data are not available, confidence in this study and the data base is low. Nevertheless, a subchronic RfD (of low confidence) can be derived from the NOAEL in this study. Assuming that dogs consume 0.025 kg food/kg body weight/day (U.S. EPA, 1986b), the treatment concentrations for the LOAEL and NOAEL correspond to 39.5 and 12.5 mg/kg/day, respectively. An oral subchronic RfD of 0.125 mg/kg/day is derived by dividing the NOAEL by an uncertainty factor of 100 (10 to extrapolate from animals to humans and 10 to provide additional protection for unusually sensitive individuals).

Given the limitations of the subchronic data base and those of the key study from which the subchronic oral RfD was derived, it may be preferable to adopt the value of the chronic oral RfD (0.05 mg/kg/day) for the subchronic RfD. As explained in the next section, confidence is medium in the chronic value because of an adequate data base and a suitably designed key study.

8.2.2.2. CHRONIC EXPOSURES (ORAL) -- Three rat studies provide information suitable for derivation of a chronic oral RfD for aramite. The rat study by Oser and Oser (1960) demonstrated reduced survival of the suckling offspring of $F_0$, $F_1$ and $F_2$ generations fed dietary aramite. In this study, $F_0$ rats were mated >7-8 times throughout a 2-year exposure period. $F_1$ and $F_2$ rats were provided the same dietary concentrations as their parents but were allowed to produce only two litters. Reduced survival of pups of the $F_2$ generation was significant at all three of the provided concentrations (500, 1580 and 5000 ppm) (rec #5, 6 and 7, respectively). Thus, 500 ppm represents the lowest FEL for this effect in rats, and a NOAEL was not identified.

Liver weight increases were measured in FDRL rats provided dietary aramite at 100 (rec #1), 200 and 400 ppm (rec #2) for 2 years (Popper et al., 1960; Oser and Oser, 1962). Because other nonneoplastic, histological effects of the liver were not observed in this rat strain, all three of these levels are NOAELs. In the same study, CFN rats fed 400 ppm had increased liver weights (rec #3), but those fed 100 and 200 ppm did not. Other noncancerous liver effects in the CFN rats were not revealed by histopathological examination. Thus, 400 ppm is the highest NOAEL for liver effects in this study (rec #3).

In the study by Deichmann et al. (1967), Osborne-Mendel rats fed diets containing 200 ppm aramite displayed degenerative liver changes (hydropic swelling, small focal areas of centrolobular necrosis and passive congestion). The 200 ppm concentration, therefore, represents a LOAEL for degenerative liver changes in Osborne-Mendel rats (rec #4). A NOAEL cannot be identified because additional levels were not tested.

The lowest LOAEL among these dietary studies, 200 ppm [10 mg/kg/day, assuming rats consume 0.05 kg food/kg body weight/day (U.S. EPA, 1980)], is for degenerative liver effects in Osborne-Mendel rats (Deichmann et al., 1967) (rec #4). Although this study did not identify a NOAEL or NOEL for liver effects in Osborne-Mendel rats, nonadverse liver effects (increased liver weights without nonneoplastic alterations) (rec #1) were observed in FDRL rats at a lower dietary concentration, 100 ppm (5 mg/kg/day) (Popper et al., 1960; Oser and Oser, 1962). The NOAEL of 5 mg/kg/day is, therefore, selected as the basis for the chronic oral RfD. A chronic oral RfD of 0.05 mg/kg/day is derived by dividing the NOAEL by an uncertainty factor of 100 (10 to extrapolate from animals to humans and 10 to provide additional protection for the most sensitive individuals). Confidence in the key study is medium because, although more than adequate numbers of animals were provided with three treatment levels and all livers were examined microscopically, tissues other than the liver were examined microscopically only if macroscopic abnormalities were apparent. Confidence is medium also in the data base and the RfD. Two adequately designed, independent studies of rats provided data regarding liver effects that were due to chronic feeding of aramite in three different strains. In addition, information was available concerning the reproductive effects of dietary aramite. The data base could be improved with information regarding teratogenicity, effects at sites other than the liver and systemic toxicity in other species.

# 9. REPORTABLE QUANTITIES

## 9.1. BASED ON SYSTEMIC TOXICITY

Data regarding the systemic toxicity of aramite were discussed in Section 6.1. Dose-response data appropriate for derivation of CSs are summarized in Table 9-1. Inhalation studies for aramite were not available. Degenerative liver changes were noted by Oser and Oser (1960) where dogs were provided dietary aramite at concentrations of 1580 ppm (39.5 mg/kg/day) for 1 year. In chronic feeding studies with rats, increased liver weights were observed at dietary concentrations ≥100 ppm (5 mg/kg/day) (Popper et al., 1960; Oser and Oser, 1962), and degenerative liver changes occurred at dietary concentrations of 200 ppm (10 mg/kg/day) (Deichmann et al., 1967). Oser and Oser (1960) also reported decreased survival in the suckling offspring of $F_2$ rats fed dietary concentrations ≥500 ppm (25 mg/kg/day).

Table 9-2 derives candidate CSs for the human equivalent doses associated with the effects presented in Table 9-1. Since Oser and Oser (1960, 1962), Popper et al. (1960) and Deichmann (1967) reported effects on the liver that may have been related to carcinogenesis, these studies are not further considered for the derivation of an RQ based on systemic toxicity; however, CSs of these studies are provided in Table 9-2 for comparision. Decreased survival of suckling pups, noted by Oser and Oser (1960), had a CS of 20, which corresponds to an RQ of 1000. This is selected as the RQ for Aramite based on systemic toxicity (Table 9-3).

## 9.2. BASED ON CARCINOGENICITY

As discussed in Chapter 6, aramite caused hyperplastic nodules or tumors in rat livers (see Tables 6-1, 6-2 and 6-3), in the extrahepatic biliary system of dogs (see Table 6-4) and in mouse livers (see Table 6-5). Aramite

TABLE 9-1

Toxicity Summary for Aramite

| Route | Species/ Strain | Sex | Number at Start | Average Weight (kg) | Vehicle/ Physical State | Purity | Exposure | Transformed Animal Dose[c] (mg/kg/day) | Equivalent Human Dose[a] (mg/kg/day) | Response | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Oral | dogs/ mongrel | M/F | 3 | 5.8 | food | commercial | 1580 ppm in diet for 52 weeks | 39.5[d] | 1.7[f] | degenerative liver changes liver cord swelling, vacuolated cytoplasm, occlusion bodies, slight degree of portal fibrosis | Oser and Oser, 1960 |
| Oral | rats/ FDRL | M/F | 10 $F_0$/ sex | 0.350[b] | food | commercial | 500 ppm provided in diet for two matings (preceded by treatment of two preceding generations) | 25[e] | 4.3 | decreased survival of suckling pups of F2 generation | Oser and Oser, 1960 |
| Oral | rats/ FDRL | M/F | 50/ sex | 0.285 | food | commercial | 100 ppm provided in diet for 104 weeks | 5[e] | 0.8 | increased liver weights | Popper et al., 1960; Oser and Oser, 1962 |
| Oral | rats/ Osborne-Mendel | M/F | 30/sex | 0.350[b] | food | commercial | 200 ppm provided in diet for 104 weeks | 10[e] | 1.7 | degeneration liver changes hydropic swelling, granular cytoplasm, slight fatty metamorphosis, small focal areas of centrolobular necrosis, and passive congestion | Deichmann et al., 1967 |

[a]Calculated by multiplying the animal transformed dose by the cube root of the ratio of the animal body weight to the human body weight (70 kg)

[b]Reference rat body weight (U.S. EPA, 1986b)

[c]Calculated by multiplying the dietary aramite concentration (in ppm) by the reference animal food factor (in kg food/kg body weight/day) (U.S. EPA, 1986b)

[d]Assuming that dogs consume 0.025 kg food/kg body weight/day (U.S. EPA, 1986b)

[e]Assuming that rats consume 0.05 kg food/kg body weight/day (U.S. EPA, 1980)

[f] An uncertainty factor of 10 was applied to expand from subchronic to chronic exposure.

TABLE 9-2

Composite Scores for Aramite

| Route | Species | Animal Dose (mg/kg/day) | Chronic Human MED (mg/day) | $RV_d$ | Effect | $RV_e$ | CS | RQ | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Oral | dogs | 39.5 | 119 | 2 | degenerative liver changes | 6 | 12 | 1000 | Oser and Oser, 1960 |
| Oral | rats | 25 | 301 | 2 | decreased survial of suck-ling pups | 10 | 20 | 1000 | Oser and Oser, 1960 |
| Oral | rats | 5 | 56 | 3 | increased liver weights | 4 | 12 | 1000 | Popper et al., 1960; Oser and Oser, 1962; |
| Oral | rats | 10 | 119 | 2 | degenerative liver changes | 6 | 12 | 1000 | Oelchmann et al., 1967 |

TABLE 9-3

Aramite

(CAS NO. 140-57-8)

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

| | |
|---|---|
| Route: | oral |
| Species/sex: | rat/male and female |
| Dose*: | 301 mg/day |
| Duration: | two matings (preceded by treatment of two preceding generations) |
| Effect: | decreased survival of suckling pups of $F_2$ generation |
| $RV_d$: | 2 |
| $RV_e$: | 10 |
| CS: | 20 |
| RQ: | 1000 |
| Reference: | Oser and Oser, 1960 |

*Human equivalent dose

is classified as a U.S. EPA Group B2 chemical, because sufficient evidence of carcinogenicity in animals and lack of human data were presented. The data for aramite-induced liver tumors in FDRL rats (Popper et al., 1960; Oser and Oser, 1962) provided the most appropriate oral $q_1^*$ with a value of $2.5 \times 10^{-2}$ $(mg/kg/day)^{-1}$, as discussed in Chapter 8. According to the model of Howe and Crump (1982), the $ED_{10}$ is 14.13 mg/kg/day. Inversion of this value, followed by an adjustment to extrapolate from animals to humans, leads to an F factor of $4.512 \times 10^{-1}$ $(mg/kg/day)^{-1}$ for aramite (Table 9-4). Aramite is, therefore, assigned to Potency Group 3, and, because of its assignment to Group B2, is given a low hazard ranking, which corresponds to a cancer-based RQ of 100.

TABLE 9-4

Derivation of Potency Factor (F) for Aramite

| | | | | |
|---|---|---|---|---|
| Reference: | Popper et al., 1960; Oser and Oser, 1962 | | | |
| Exposure route: | oral, diet | | | |
| Species: | rat | | | |
| Strain: | FDRL | | | |
| Sex: | male and female | | | |
| Vehicle or physical State: | food | | | |
| Body weight: | 0.270 kg | | | |
| Duration of treatment: | 104 weeks | | | |
| Duration of study: | 104 weeks | | | |
| Lifespan of animal: | 104 weeks | | | |
| Target organ: | liver | | | |
| Tumor type: | hyperplastic nodules and carcinomas | | | |
| Experimental dose/ exposure (ppm): | 0 | 100 | 200 | 400 |
| Transformed dose (mg/kg/day): | 0 | 5 | 10 | 20 |
| Tumor incidence: | 2/193 | 2/93 | 3/100 | 25/90 |
| Unadjusted $1/ED_{10}$: | $7.077 \times 10^{-2}$ $(mg/kg/day)^{-1}$ | | | |
| Adjusted $1/ED_{10}$*: | $4.512 \times 10^{-1}$ $(mg/kg/day)^{-1}$ | | | |
| RQ: | 100 | | | |

*Calculated by multiplying the unadjusted $1/ED_{10}$ by the cube root of the ratio of the reference human body weight by the average experimental animal body weight (U.S. EPA, 1980)

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Sanders, H.O. 1969. Toxicity of pesticides to the crustacean Gammarus lacustris. Bur. Sport Fish. Wildl. Fish Wildl. Serv. Tech. Paper No. 25. 18 p.

Sanders, H.O. and O.B. Cope. 1966. Toxicities of several pesticides to two species of cladocerans. Trans. Am. Fish. Soc. 95: 165-169.

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Spencer, E.Y. 1968. Guide to the chemicals used in crop protection. Publication 1093, 5th ed. Canada Department of Agriculture, Research Branch. p. 49.

Sternberg, S.S., H. Popper, B.L. Oser and M. Oser. 1960. Gallbladder and bile duct adenocarcinomas in dogs after long term feeding of aramite. Cancer. 13: 780-789.

Streu, H.T. 1972. Two spotted spider mite. Its biology and control (acerina: tetranychidae). Proc. Ohio State Hor. Soc. 125: 83-85.

Swann, R.L., D.A. Laskowski, P.J. McCall, K. VanderKuy and H.J. Dishburger. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Residue Reviews. 85: 17-28.

Truhaut, R., J.R. Claude, V.N. Huyen, J.M. Warnet and F. Blanc. 1975. Primary liver carcinogenesis in rats after feeding of a pesticide 2,4-tert butylphenoxy-1-methylethyl-2-chloroethyl sulfite aramite. C.R. Hebd Seances Acad. Sci. Ser. Sci. Nat. 281(9): 599-604.

Truhaut, R., J.R. Claude and F. Blanc. 1977. The metabolism of aramite, a pesticide inducing liver tumors. In: Proc. European Soc. Toxicol. 18: 326-328.

Truhaut, R., J.R. Claude, J.M. Warnet, Vu Ngoc Huyen and P. Blanc-Habets. 1978. Aramite: Experimental cancerogenicity and metabolism. Meded. Fac. Landbouwwet. Rijksuniv. Gent. 43(2): 1225-1231.

U.S. EPA. 1980. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 79347-79357.

U.S. EPA. 1981. Identification and Listing of Hazardous Waste. 40 CFR 261. App. VIII.

U.S. EPA. 1984. Methodology and Guidelines for Ranking Chemicals Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1986a. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

U.S. EPA. 1986b. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA/OWRS (U.S. Environmental Protection Agency/Office of Water Regulations and Standards). 1986. Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses. U.S. EPA, Washington, DC. 106 p.

USTC (United States Tariff Commission). 1972. Synthetic Organic Chemicals. Unites States Production and Sales, 1970. TC Publication 479. U.S. Tariff Commission, Washington, DC. p. 203.

Windholz, M., Ed. 1983. Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ. p. 112.

Worthing, C.R. and S.B. Walker. 1987. The Pesticide Manual. 8th ed. British Crop Protection Council, Croydon, England. p. 862.

# APPENDIX A

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB
SCISEARCH
Federal Research in Progress

These searches were conducted in April, 1989, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices. 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2C. John Wiley and Sons, NY. 3817-5112 p.

Grayson, M. and D. Eckroth, Ed. 1978-84. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology. 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. IARC, Lyons, France: WHO.

Jaber, H.M., W.R. Mabey, A.T. Lieu, T.W. Chou and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening for compounds of interest to the Office of Solid Waste. EPA-600/6-84-010. (NTIS PB84-243906) Menlo Park, CA: SRI International.

NTP (National Toxicology Program). 1988. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1984. Dangerous Properties of Industrial Materials. 6th edition. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. Stanford, CA.

U.S. EPA. 1986. Report on Status Report in the Special Review Program, Registration Standards Program and the Data Call in Programs. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

USITC (United States International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publication 1892. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals. 2nd edition. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M. Ed. 1983. The Merck Index. 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. United States Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria. 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

APPENDIX B1

CANCER DATA SHEET FOR DERIVATION OF $q_1^*$

Compound: aramite

Reference: Oser and Oser, 1960

Species, strain, sex: rat, FDRL, male and female

Tumor site and type: liver tumors

Route, vehicle: oral, diet

| | | | |
|---|---|---|---|
| Dietary concentration (ppm): | 0 | 500 | 1580 |
| Transformed animal dose[a] (mg/kg/day): | 0 | 25 | 79 |
| Duration of exposure (weeks): | 104 | 48 | 48 |
| Measured body weights (kg): | 0.300 | 0.285 | 0.280 |
| Human equivalent dosage[b]: | 0 | 0.392 | 1.230 |
| Incidence (Number Responding/ Number tested or examined): | 0/20 | 0/20 | 2/21 |

---

Human $q_1^*$ : 0.6861 (mg/kg/day$^{-1}$)[c]

---

[a]Estimated using rat food factor of 0.05 (U.S. EPA, 1980).

[b]Transformed animal dose multiplied by: (1) cube root of the ratio of animal body weight: reference human body weight and 2) cube of the ratio of the duration of the experiment (i.e., duration of treatment) to the lifespan of the rat (U.S. EPA, 1980)

[c]Data from the high-dose group (5000 ppm) were dropped from analysis in order to fit the data to the model.

APPENDIX B2

CANCER DATA SHEET FOR DERIVATION OF A $q_1^*$

Compound: aramite

Reference: Popper et al., 1960; Oser and Oser, 1962

Species, strain, sex: rats, FDRL, male and female

Body weight: 0.270 (measured)

Length of exposure (le) = 104 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: hyperplastic liver nodules and carcinomas

Route, vehicle: oral, diet

| Dietary Concentrations (ppm) | Transformed Animal Dose[a] (mg/kg/day) | Incidence (number responding/number tested or examined) |
|---|---|---|
| 0 | 0 | 2/193 (0 carcinomas) |
| 100 | 5 | 2/93 (0 carcinomas) |
| 200 | 10 | 3/100 (0 carcinomas) |
| 400 | 20 | 25/90 (2 carcinomas) |

Unadjusted $q_1^*$ = $3.8485 \times 10^{-3}$ $mg/kg/day^{-1}$

Human $q_1^*$ = $2.454 \times 10^{-2}$ $(mg/kg/day^{-1})$[b]

[a]Assumed: rats consume 0.05 kg food/kg body weight/day (U.S. EPA, 1980)

[b]Human $q_1^*$ was calculated by dividing the unadjusted $q_1^*$ by the cube root of the ratio of the reference human body weight (70 kg, U.S. EPA, 1986b) to the experimental time-weighted average animal body weight (0.270 kg).

APPENDIX B3

CANCER DATA SHEET FOR DERIVATION OF A $q_1^*$

Compound: aramite

Reference: Popper et al., 1960; Oser and Oser, 1962

Species, strain, sex: rats, CFN, male and female

Body weight = 0.278 (measured)

Length of exposure (le) = 104 days

Length of experiment (Le) = 104 days

Lifespan of animal (L) = 104 days

Tumor site and type: hyperplastic liver nodules and carcinomas

Route, vehicle: oral, diet

| Experimental Doses or Exposures | Transformed Animal Dose[a] (mg/kg/day) | Incidence (number responding/number tested or examined) |
|---|---|---|
| 0 | 0 | 5/180 (0 carcinomas) |
| 100 | 5 | 3/93 (0 carcinomas) |
| 200 | 10 | 10/90 (0 carcinomas) |
| 400 | 20 | 22/96 (0 carcinomas) |

Unadjusted $q_1^*$ = $0.121 \times 10^{-2}$ mg/kg/day$^{-1}$

Human $q_1^*$ = $7.64 \times 10^{-3}$ (mg/kg/day$^{-1}$)[b]

[a]Assuming that rats consume 0.05 kg food/kg body weight/day (U.S. EPA, 1980)

[b]Calculated by the following equation: human $q_1^*$ = (unadjusted $q_1^*$) (cube root of HBW divided by ABW) (L/le) where HBW is the reference human body weight, 70 kg (U.S. EPA, 1986b), ABW is the experimental animal body weight (0.278 kg), L is the lifespan of rats (104 weeks) and le is the duration of exposure of the rats (104 weeks).

APPENDIX B4

CANCER DATA SHEET FOR DERIVATION OF A $q_1^*$

Compound: aramite

Reference: Innes et al., 1969

Species, strain, sex: mice, (C57BL/6xC3H/Anf)$F_1$, male

Body weight = 0.03 kg (reference value: U.S. EPA, 1980)

Length of exposure (le) = 80 weeks

Length of experiment (Le) = 80 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver hepatoma

Route, vehicle: oral, gavage for first 3.5 weeks followed by diet for remainder of study

| Dietary Concentration (ppm) | Transformed Animal Dose[a] (mg/kg/day) | Incidence (number responding/number tested or examined) |
|---|---|---|
| 0 | 0 | 8/73 |
| 112 | 14.6 | 6/16 |

---

Unadjusted $q_1^*$ = $5.20648 \times 10^{-2}$ $mg/kg/day^{-1}$

Human $q_1^*$ = 1.51717 $(mg/kg/day^{-1})$[b]

---

[a]Assuming that mice consume 0.13 kg food/kg body weight/day (U.S. EPA, 1986b)

[b]To calculate the human $q_1^*$, the unadjusted $q_1^*$ was multiplied by the cube root of the ratio of the reference body weight for humans (70 kg) to the reference body weight for the mice (0.03 kg) and ratio of the animal lifespan (104 weeks) to the length of the experiment (80 weeks) (U.S. EPA, 1980).

APPENDIX C

SUMMARY TABLE FOR ARAMITE

| | Species | Exposure | Effect | RfD or q$_1^*$ | Reference |
|---|---|---|---|---|---|
| Inhalation Exposure | | | | | |
| Subchronic | ID | ID | ID | ID | ID |
| Chronic | ID | ID | ID | ID | ID |
| Carcinogenicity | ID | ID | ID | $2.45 \times 10^{-2}$ (mg/kg/day)$^{-1}$, from oral exposure | Popper et al., 1960; Oser and Oser, 1962 |
| Oral Exposure | | | | | |
| Subchronic | dog | 500 ppm in diet (12.5 mg/kg/day), 52 weeks | degenerative liver effect at higher levels | 0.125 mg/kg/day | Oser and Oser, 1960 |
| Chronic | rat | 100 ppm in diet (5 mg/kg/day), 104 weeks | increased liver weight | 0.05 mg/kg/day | Popper et al., 1960; Oser and Oser, 1962 |
| Carcinogenicity | rat | 400 ppm in diet (20 mg/kg/day), 104 weeks | increased incidence of liver tumors | $2.45 \times 10^{-2}$ (mg/kg/day)$^{-1}$ | Popper et al., 1960 Oser and Oser, 1962 |

REPORTABLE QUANTITIES

Based on chronic toxicity: 1000

Based on carcinogenicity: 100

ID = Insufficient Data

APPENDIX D

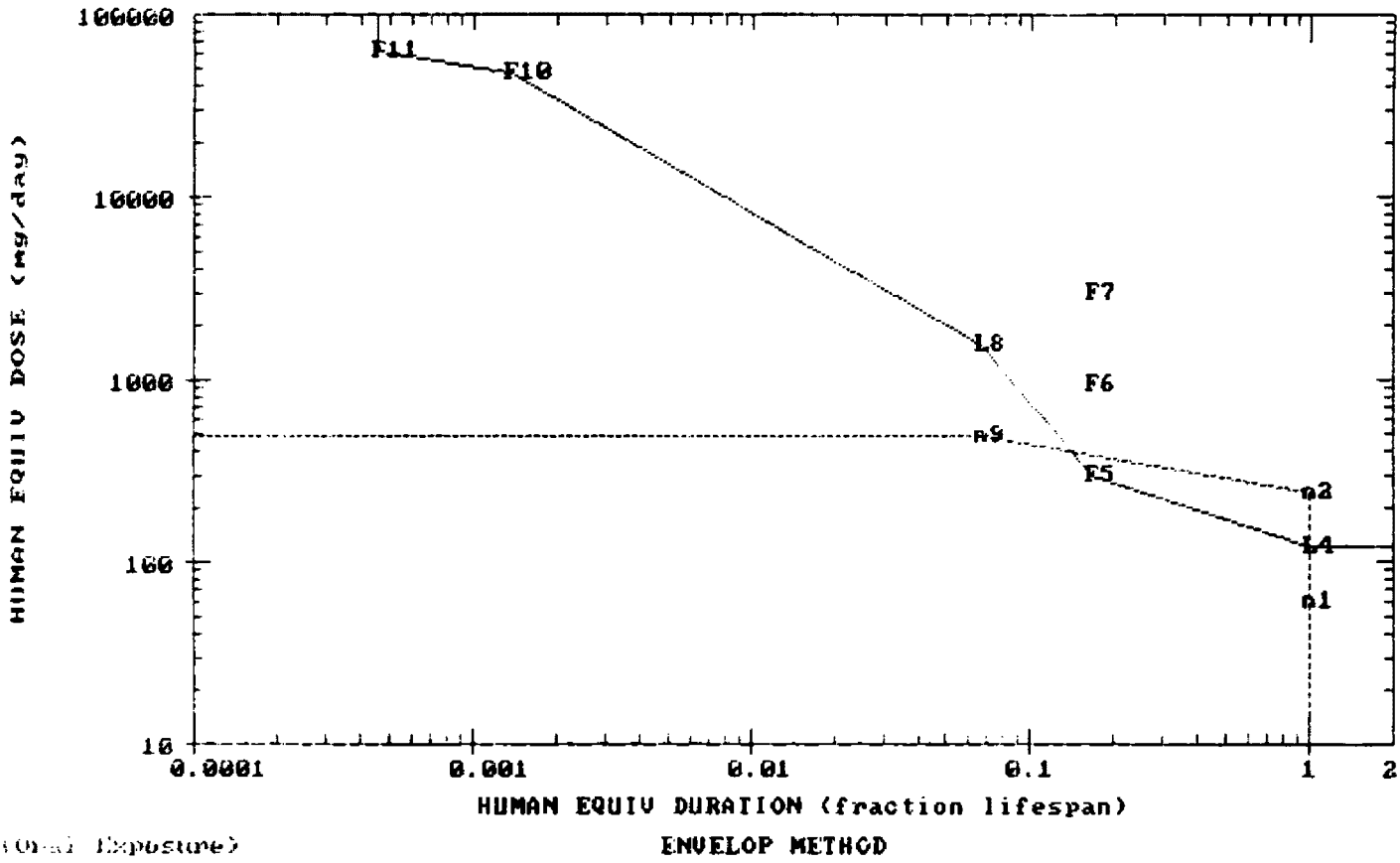
DOSE/DURATION RESPONSE GRAPHS FOR ORAL EXPOSURE TO ARAMITE

D.1. DISCUSSION

Dose/duration-response graphs for oral exposure to aramite generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1988) developed under contract to ECAO-Cincinnati are presented in Figures D-1 and D-2. Data used to generate these graphs are presented in Section D-2. In the generation of the figures all responses are classified as adverse (FEL, AEL or LOAEL) or non-adverse (NOEL or NOAEL) for plotting. For oral exposure, the ordinate expresses dosage as human equivalent dose. The animal dosage in mg/kg/day is multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1975). The result is then multiplied by 70 kg, the reference human body weight, to express the human equivalent dose as mg/day for a 70 kg human.

The Boundary for Adverse Effects (solid line) is drawn by identifying the lowest adverse effect dose or concentration at the shortest duration of exposure at which an adverse effect occurred. From this point, an infinite line is extended upward, parallel to the dose axis. The starting point is then connected to the lowest adverse effect dose or concentration at the next longer duration of exposure that has an adverse effect dose or concentration equal to or lower than the previous one. This process is continued to the lowest adverse effect dose or concentration. From this point, a line is extended to the right, parallel to the duration axis. The Region of Adverse Effects lies above the Adverse Effects Boundary.

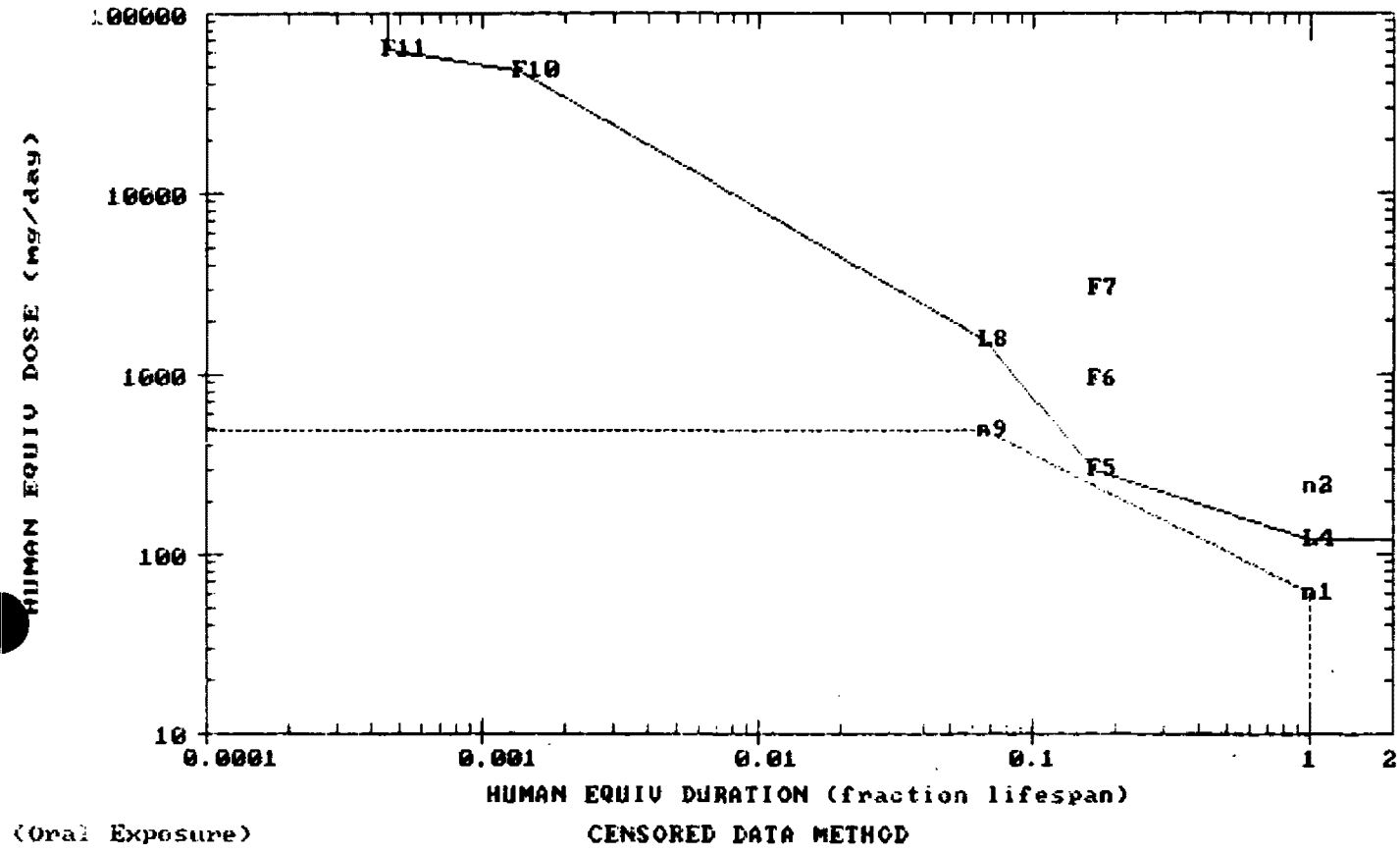
Using the envelope method, the Boundary for No Adverse Effects (dashed line) is drawn by identifying the highest no adverse effects dose or




Key: F = FEL
L = LOAEL
N = NOAEL
Solid line = Adverse Effects Boundary
Dotted line = No Adverse Effects Boundary

FIGURE D-1

Dose/Duration - Response Graph for Oral Exposure to Aramite
Envelope Method




Key: F = FEL
L = LOAEL
N = NOAEL
Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE D-2

Dose/Duration - Response Graph for Oral Exposure to Aramite
Censored Data Method

concentration. From this point, a line parallel to the duration axis is extended to the dose or concentration axis. The starting point is then connected to the next lower or equal no adverse effect dose or concentration at a longer duration of exposure. When this process can no longer be continued, a line is dropped parallel to the dose or concentration axis to the duration axis. The No Adverse Effects Region lies below the No Adverse Effects Boundary. At either ends of the graph between the Adverse Effects and No Adverse Effects Boundaries are Regions of Ambiguity. The area (if any) resulting from intersection of the Adverse Effects and No Adverse Effects Boundaries is defined as the Region of Contradiction.

In the censored data method, all no adverse effect points located in the Region of Contradiction are dropped from consideration, and the No Adverse Effects Boundary is redrawn so that it does not intersect the Adverse Effects boundary and no Region of Contradiction is generated. This method results in the most conservative definition of the No Adverse Effects Region.

The Adverse Effects Boundary for oral exposure to aramite is defined by five data points in Figures D-1 and D-2. Starting from the upper left of each figure, these points represent: the lethal dose for guinea pigs (rec #11); the $LD_{50}$ for rats (rec #10); the LOAEL for degenerative liver effects in dogs (rec #8); the lowest FEL for decreased survival of $F_1$ rat pups during lactation (rec #5); and the LOAEL for degenerative liver effects in rats (rec #4). The first four data points come from the report by Oser and Oser (1960) and the fifth from the study by Deichmann et al. (1967).

The No Adverse Effects Boundary is defined in Figure D-1 by the NOAEL for degenerative liver effects in dogs (rec #9) from the study by Oser and Oser (1960) and the highest NOAEL for liver effects (rec #2) in rats (Popper

et al., 1960; Oser and Oser, 1962). In Figure D-2, the latter of these points is censored and the Region Of Contradiction is absent. The right side of the No Adverse Effects Boundary is then defined by the lowest NOAEL (rec #1) for liver effects in rats (Popper et al., 1960; Oser and Oser, 1962), which provided the basis for the chronic oral RfD derived in Section 8.2.2.2.

D.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS FOR ORAL EXPOSURE TO ARAMITE

Chemical Name: Aramite
CAS Number: 140-57-8
Document Title: Health and Environmental Effects Document for Aramite
Document Number: pending
Document Date: pending
Document Type: HEED

RECORD #1:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 5.000 | |
| Sex: | Both | Duration Exposure: | 104.0 weeks |
| Effect: | NOAEL | Duration Observation: | 104.0 weeks |
| Route: | Food | | |

| | |
|---|---|
| Number Exposed: | 100 |
| Number Responses: | NR |
| Type of Effect: | WGTIN |
| Site of Effect: | LIVER |
| Severity Effect: | 4 |

Comment: Experimental doses: 0, 100, 200, 400 ppm in diet. Transformed doses: 0, 5, 10, 20 mg/kg/day. FDRL rats. No adverse, non-neoplastic liver histology, even at highest dose.

Citation: Popper et al., 1960; Oser and Oser, 1962.

---

RECORD #2:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 20.000 | |
| Sex: | Both | Duration Exposure: | 104.0 weeks |
| Effect: | NOAEL | Duration Observation: | 104.0 weeks |
| Route: | Food | | |

Number Exposed: 100
Number Responses: NR
Type of Effect: WGTIN
Site of Effect: LIVER
Severity Effect: 4

Comment: See previous record.

Citation: Popper et al., 1960; Oser and Oser, 1962.

---

RECORD #3:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 20.000 | |
| Sex: | Both | Duration Exposure: | 104.0 weeks |
| Effect: | NOAEL | Duration Observation: | 104.0 weeks |
| Route: | Food | | |

Number Exposed: 100
Number Responses: NR
Type of Effect: WGTIN
Site of Effect: LIVER
Severity Effect: 4

Comment: Experimental details as per rec #1, except that CFN rats were studied. No adverse, non-cancerous liver effects were observed in histological examinations.

Citation: Popper et al., 1960; Oser and Oser, 1962

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RECORD #4:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 10.000 | |
| Sex: | Both | Duration Exposure: | 104.0 weeks |
| Effect: | LOAEL | Duration Observation: | 104.0 weeks |
| Route: | Food | | |

| | | |
|---|---|---|
| Number Exposed: | 60 | 30 |
| Number Responses: | NR | NR |
| Type of Effect: | DEGEN | WGTIN |
| Site of Effect: | LIVER | LIVER |
| Severity Effect: | 6 | 4 |

Comment: Experimental concentration: 200 ppm in diet. Osborne-Mendel rats. Liver histology: hydropic swelling, granular cytoplasm, centrolobular necrosis, passive congestion. Liver weight increase only in males.

Citation: Deichmann et al., 1967

---

RECORD #5:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 25.000 | |
| Sex: | Both | Duration Exposure: | 17.0 weeks |
| Effect: | FEL | Duration Observation: | 17.0 weeks |
| Route: | Food | | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: Experimental concentrations: 0, 500, 1580, 5000 ppm. More than 7-8 matings/dose for $F_0$; 2 matings/dose for $F_1$ and $F_2$. Decreased survival during lactation of $F_3$ at 500, 1580 and 5000 ppm and of $F_1$, $F_2$ at 5000 ppm. Exposure duration roughly estimated from parents' exposure at an assumed time of first mating. Pregnancies failed after fifth mating at 5000 ppm in $F_0$.

Citation: Oser and Oser, 1960

---

RECORD #6:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 79.000 | |
| Sex: | Both | Duration Exposure: | 17.0 weeks |
| Effect: | FEL | Duration Observation: | 17.0 weeks |
| Route: | Food | | |

Number Exposed: NR
Number Responses: NR
Type of Effect: DEATH
Site of Effect: BODY
Severity Effect: 10

Comment: As per rec #5.

Citation: Oser and Oser, 1960

---

RECORD #7:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 250.000 | |
| Sex: | Both | Duration Exposure: | 17.0 weeks |
| Effect: | FEL | Duration Observation: | 17.0 weeks |
| Route: | Food | | |

Number Exposed: NR
Number Responses: NR
Type of Effect: DEATH
Site of Effect: BODY
Severity Effect: 10

Comment: As per rec #5, except that decreased survival during lactation was also noted in $F_1$ and $F_2$ generations at this dose level.

Citation: Oser and Oser, 1960

---

RECORD #8:

| | | | |
|---|---|---|---|
| Species: | Dogs | Dose: 39.500 | |
| Sex: | Both | Duration Exposure: 52.0 weeks | |
| Effect: | LOAEL | Duration Observation: 52.0 weeks | |
| Route: | Food | | |

| | |
|---|---|
| Number Exposed: | 3 |
| Number Responses: | 3 |
| Type of Effect: | DEGEN |
| Site of Effect: | LIVER |
| Severity Effect: | 6 |

Comment: Experimental concentrations: 0, 500, 1580 ppm. Liver cord swelling, vacuolated cytoplasm, occlusion bodies, slight degree of portal fibrosis.

Citation: Oser and Oser, 1960.

---

RECORD #9:

| | | | |
|---|---|---|---|
| Species: | Dogs | Dose: 12.500 | |
| Sex: | Both | Duration Exposure: | 52.0 weeks |
| Effect: | NOAEL | Duration Observation: | 52.0 weeks |
| Route: | Food | | |

| | |
|---|---|
| Number Exposed: | 3 |
| Number Responses: | 3 |
| Type of Effect: | DEGEN |
| Site of Effect: | LIVER |
| Severity Effect: | 6 |

Comment: See previous record. No adverse liver effects at this level.

Citation: Oser and Oser, 1960.

---

RECORD #10:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 3900.000 | |
| Sex: | Both | Duration Exposure: | 1.0 days |
| Effect: | FEL | Duration Observation: | 14.0 days |
| Route: | Gavage | | |

| | |
|---|---|
| Number Exposed: | 10 |
| Number Responses: | 5 |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: $LD_{50}$ value.

Citation: Oser and Oser, 1960

---

RECORD #11:

| | | | |
|---|---|---|---|
| Species: | Guinea Pigs | Dose: | 3900.000 |
| Sex: | Both | Duration Exposure: | 1.0 days |
| Effect: | FEL | Duration Observation: | 14.0 days |
| Route: | Gavage | | |

| | |
|---|---|
| Number Exposed: | 10 |
| Number Responses: | 5 |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: One dose tested.

Citation: Oser and Oser, 1960.

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