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# Research and Development

## HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR 2-CHLOROPHENOL

## Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

## Prepared by

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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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 (RfDs) 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 that would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval that 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 RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs 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 RQs 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.

2-Chlorophenol is a colorless to yellow-brown liquid with an unpleasant, penetrating odor. It is soluble in alcohol, ether and water (Sax and Lewis, 1987; Weast et al., 1988). A weak acid, it is freely soluble in basic solutions (Freiter, 1981). Current production volume data were not located; however, between 10,000 and 100,000 pounds was manufactured or imported in the United States in 1977 (TSCAPP, 1989). Most of the 2-chlorophenol produced is either used directly in the synthesis of other chlorinated phenols or as an intermediate in the production of larger synthetic molecules. Approximately 1% of production is isolated for use in disinfectants, resins and other specialty products (Freiter, 1981; Scow et al., 1982).

In the atmosphere, 2-chlorophenol is expected to exist almost entirely in the vapor phase (Suntio et al., 1988). The gas-phase reaction with photochemically produced hydroxyl radicals is expected to be rapid, with an estimated half-life of 1.6 days (Atkinson, 1985). Nighttime degradation by the gas-phase reaction with nitrate radicals is expected to be significant in urban areas (Kanno and Nojima, 1979). Physical removal of 2-chlorophenol by wet precipitation may also occur. In water, photolysis and microbial degradation are expected to be significant. In basic waters, the ionic form of 2-chlorophenol undergoes rapid photolysis. The neutral form photolizes more slowly (Boule et al., 1982, 1984, 1987).

Microbial degradation under aerobic (Tabak et al., 1981; Baird et al., 1974; Lund and Rodriguez, 1984; Suflita and Miller, 1985) and anaerobic (Krumme and Boyd, 1988; Battersby and Wilson, 1989; Suflita and Miller, 1985) conditions has been demonstrated. Bioconcentration in aquatic organisms is not expected to be significant. Volatilization from water to

the atmosphere is expected; however, this process may be attenuated by adsorption to sediment and suspended matter. In soil, biodegradation is expected to be the dominant fate process. Microbial degradation using a soil inoculum has been demonstrated under aerobic (Alexander and Aleem, 1961; Ingols et al., 1966; Haller, 1978; Kincannon and Lin, 1985) and anaerobic (Boyd et al., 1983; Horowitz et al., 1982) conditions. Volatilization from the soil surface to the atmosphere is expected; however, it may be attenuated by the process of adsorption.

2-Chlorophenol can enter the environment as a result of its commercial synthesis or use. 2-Chlorophenol may be released to the environment by its formation by chemical transformations on other anthropogenic compounds (Kanno and Nojima, 1979; Carlson and Caples, 1975; Joshipura and Kellher, 1980; Boule et al., 1985; Yasuhara and Morita, 1988).

Data on the occurrence of 2-chlorophenol in the environment are lacking. The compound has been qualitatively identified in drinking water in the United States (Kool et al., 1982; Lucas, 1984) and quantified in effluents from publicly owned treatment plants (Ellis et al., 1982; Young, 1978; Callahan et al., 1979; Bourquin and Gibson, 1978).

The acute toxicity of 2-chlorophenol was similar in all species of freshwater fish examined, with $LC_{50}$ values ranging from 6.6-10.0 mg/ℓ in the bluegill, Lepomis macrochirus (Buccafusco et al., 1981; Lammering and Burbank, 1961; Pickering and Henderson, 1966), 9.7-14.48 mg/ℓ in the fathead minnow, Pimephales promelas (Phipps et al., 1981; Pickering and Henderson, 1966), 12.37-16 mg/ℓ in the goldfish, Carassius auratus (Kobayashi et al., 1979; Pickering and Henderson, 1966), and 7.06-20.17 mg/ℓ in the guppy, Poecilia reticulata (Konemann and Musch, 1981; Pickering and Henderson, 1966). In a screening-type study, 5 mg/ℓ had no

effect on bluegill or sea lamprey, Petromyzon marinus, but produced death in trout, Salmo gairdneri, within 13 hours (Applegate et al., 1957). Exposure to concentrations ≤4 mg/ℓ for 30 days had no effect on eggs and larvae of fathead minnows in an early life stage toxicity test (LeBlanc, 1983). The BCF determined in bluegill was 214; the elimination half-life was <1 day (Barrows et al., 1980). Studies using freshwater invertebrates revealed that toxic effects occurred at concentrations similar to those found for fish. $LC_{50}$ and immobilization $EC_{50}$ values in Daphnia ranged from 2.6-23 mg/ℓ (Bazin et al., 1987; Devillers and Chambon, 1986; Keen and Baillod, 1985; Knie et al., 1983; Kopperman et al., 1974; LeBlanc, 1980; Randall and Knopp, 1980; Tissot et al., 1985; Trabalka and Burch, 1978). The lethal threshold was 5.3 mg/ℓ in the shrimp, Crangon septemspinosa, the only saltwater animal studied. Among freshwater algae, $EC_{50}$ values for growth inhibition were 70 mg/ℓ in Selenastrum capricornutum, and 170 mg/ℓ in Chlorella vulgaris (Shigeoka et al., 1988). Effects in bacteria included 50% reduction in light emitted by Photobacterium phosphoreum at 14.7-40 mg/ℓ (Bazin et al., 1987; Cunningham et al., 1986; Curtis et al., 1982; Ribo and Kaiser, 1983), 25-27% reduction in nitrite utilization by Nitrobacter at 50 mg/ℓ (Wang and Reed, 1984), decreased ATP content in Escherichia coli and Nitrosomonas europaea at 100-1000 mg/ℓ (Parker and Pribyl, 1984) and 50% reduction in bacterial dehydrogenase activity in a mixed bacterial culture at 700 mg/ℓ. Among terrestrial organisms, the oral $LD_{50}$ in red-winged blackbirds was >113 mg/kg (Schafer et al., 1983).

Chlorophenols as a class are reportedly absorbed readily from the gastrointestinal tract and from parenteral sites of injection (Deichmann and Keplinger, 1981). Orally administered 2-chlorophenol appears to be rapidly and almost completely absorbed from the gastrointestinal tracts of rats

(Carpenter et al., 1985; Houser, 1983) and chinchilla rabbits (Spencer and Williams, 1950). In in vitro studies using human autopsy skin, 2-chlorophenol was absorbed by the epidermal membrane with a permeability coefficient of $5.51 \times 10^{-4}$/cm/min (Roberts et al., 1977).

Following oral administration of 2-chlorophenol to rats, the compound was found in the liver and kidney (Exon and Koller, 1982), but metabolism and excretion occurred so rapidly that there was little distribution to body tissues (Carpenter et al., 1985). Urinary excretion accounted for 91% of an oral dose in rats within 24 hours of treatment (Carpenter et al., 1985). Over 90% of the urinary excretion consisted of glucuronide and sulfate conjugates of the parent compound, and <2% consisted of unchanged parent compound (Carpenter et al., 1985). Other metabolites identified in the urine of treated rats include glucuronide and sulfate conjugates of 2-chlorohydroquinone (Houser, 1983), an oxidation product of 2-chlorophenol. Glucuronide and ethereal suflate conjugates of 2-chlorophenol in the urine of orally treated chinchilla rabbits accounted for virtually 100% of an oral dose (Spencer and Williams, 1950).

No information was located concerning the subchronic or chronic inhalation toxicity of 2-chlorophenol.

In rats dosed by gavage with 2-chlorophenol at 65 or 130 mg/kg for 3 weeks, there were reductions in weight gains and increases in liver weights when compared with controls (Chung, 1978). Hematological effects and hepatic degeneration were also noted at both treatment levels.

In reports of a subchronic drinking water study (Exon and Koller, 1983a, 1985) in which rats were exposed to 2-chlorophenol pre-, post-, and pre- and postnatally by the dams and then in the drinking water at levels of 0, 5, 50 and 500 ppm for $\leq$15 weeks, no immunological effects were observed at any level.

In a chronic drinking water study (Exon and Koller, 1985) in which rats were exposed to 2-chlorophenol prenatally by their dams and then in the drinking water at levels of 0, 5, 50 and 500 ppm for ≤2 years, hemoglobin levels, RBC counts and PCV were all significantly higher in the groups exposed to 500 ppm than in controls.

Chlorophenols reportedly irritate the skin and eyes, and the dusts irritate the respiratory tract (Freiter, 1979). In humans, 2-chlorophenol causes severe burns, liver and kidney damage, narcosis and respiratory depression (Davis et al., 1959).

Oral $LD_{50}$s of 670, 346-670 and 440 mg/kg have been reported for the rat (Deichmann, 1943), the mouse (Borzelleca et al., 1985; Bubnov et al., 1969) and the blue fox (Bubnov et al., 1969), respectively. A single oral dose of 300 mg/kg caused kidney and liver damage in Gunn rats, which appeared to be more sensitive to the compound than Sprague-Dawley rats (Houser, 1983). An oral dose of 63 mg/kg caused motor impairment in CD-1 mice within 5 minutes, and a dose of 1 mg/kg produced behavioral change after 2 days (Borzelleca, 1983). A gavaged dose of 175 mg/kg resulted in 80% mortality in mice, with a statistically significant weight loss before death; hyperactivity was seen at lower doses (Kallman et al., 1982). In rats, a median lethal intraperitoneal dose of 230 mg/kg caused excited behavior and convulsions, with a decrease in body temperature (Farquharson et al., 1958).

No information on carcinogenicity of 2-chlorophenol from inhalation exposures could be located. A carcinogenicity-cocarcinogenicity drinking water study (Exon and Koller, 1985) in which rats were exposed to 2-chlorophenol *in utero* and then in drinking water at concentrations ≤500 ppm was negative for carcinogenicity after 2 years of exposure. In the same study, 2-chlorophenol appeared to promote the carcinogenicity of ENU, increasing

the tumor incidence and decreasing the time-to-tumor in male rats. Dermal application of 2-chlorophenol following initiation by DMBA promoted the formation of skin tumors in mice (Boutwell and Bosch, 1959).

Up to 1000 µg/plate 2-chlorophenol was negative for mutagenicity in four strains of Salmonella typhimurium, with and without metabolic activation (Haworth et al., 1983). It did not induce SCEs or affect DNA synthesis in mice dosed with 75-300 mg/kg (Borzelleca, 1983). Chromatid deletions were reported in rat bone marrow cells from treatment with 130 mg/kg every other day for 1 week (Chung, 1978).

No information on the teratogenicity of 2-chlorophenol could be located. Reproductive effects were reported in rats exposed to 2-chlorophenol in drinking water from weaning through breeding and lactation (Exon and Koller, 1982, 1985). Reduced litter sizes and increased number of stillbirths were seen in rats exposed to 500 ppm 2-chlorophenol; these effects were not seen at $\leq$50 ppm.

Although drinking water (Exon and Koller, 1985) and dermal (Boutwell and Bosch, 1959) exposure studies suggested that 2-chlorophenol may be a tumor promoting agent, data were inadequate to implicate the chemical as a primary carcinogen. The chemical was assigned to U.S. EPA Group D: not classifiable as to carcinogenicity in humans. Neither cancer potencies nor a cancer-based RQ were derived.

U.S. EPA (1986b) derived an RfD for chronic oral exposure of 0.005 mg/kg/day from the 24-month drinking water study using rats by Exon and Koller (1985). This value is verified and available on IRIS (U.S. EPA, 1988). A chronic (noncancer) toxicity-based RQ of 1000 was calculated based on reproductive effects observed in rats exposed to drinking water containing 500 ppm 2-chlorophenol (Exon and Koller, 1982).

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## LIST OF ABBREVIATIONS

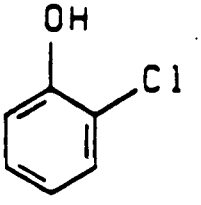
| | |
|---|---|
| ATP | Adenosine triphosphate |
| BCF | Bioconcentration factor |
| CAS | Chemical Abstract Service |
| CS | Composite score |
| DMBA | 9,10-dimethyl-1,2-benzathiacene |
| DNA | Deoxyribonucleic acid |
| DWEL | Drinking water exposure level |
| $EC_{50}$ | Concentration effective to 50% of recpients (and all other subscripted dose levels) |
| $ED_{50}$ | Effective dose to 50% of recipients |
| ENU | Ethylnitrosourea |
| GMAV | Genus mean acute value |
| GMCV | Genus mean chronic value |
| $K_{oc}$ | Soil sorption coefficient |
| $K_{ow}$ | Octanol/water partition coefficient |
| $LC_{50}$ | Concentration lethal to 50% of recipients (and all other subscripted dose levels) |
| $LD_{50}$ | Dose lethal to 50% of recipients |
| MATC | Maximum acceptable toxicant concentration |
| MED | Minimum effective dose |
| LOAEL | Lowest-observed-adverse-effect level |
| NOAEL | No-observed-adverse-effect level |
| NOEL | No-observed-effect level |
| PCV | Packed cell volume |
| pKa | The negative logarithm (to the base 10) of the equilibrium constant, K, for the reaction of chlorophenol with acid |

| | |
|---|---|
| ppb | Parts per billion |
| ppm | Parts per million |
| RBC | Red blood cells |
| RfD | Reference dose |
| RQ | Reportable quantity |
| $RV_d$ | Dose-rating value |
| $RV_e$ | Effect-rating value |
| SCE | Sister-chromatid exchange |
| $TL_m$ | Median tolerance limit |
| w/v | Weight per volume |

# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS NUMBER

2-Chlorophenol is also known as ortho-chlorophenol, 2-chloro-1-hydroxybenzene and 2-hydroxychlorobenzene (Chemline, 1989; SANSS, 1989). The structure, Chemical Abstracts Service Registry number, empirical formula and molecular weight are as follows:




CAS number: 95-57-8

Empirical formula: $C_6H_5ClO$

Molecular weight: 128.56

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

2-Chlorophenol is a colorless to yellow-brown liquid with an unpleasant, penetrating odor (Sax and Lewis, 1987). It is soluble in alcohol, ether, benzene and water (Sax and Lewis, 1987; Weast et al., 1988). A weak acid (pKa = 8.5 at 25°C), it is freely soluble in alkaline solutions (Freiter, 1981). Selected chemical and physical properties for 2-chlorophenol are as follows:

| | | |
|---|---|---|
| Melting point: | 8.7°C | Freiter, 1981 |
| Boiling point: | 175-176°C | Freiter, 1981 |
| Density at 25°C: | 1.2573 g/mℓ | Windholz et al., 1983 |
| Vapor pressure at 25°C: | 2.35 mm Hg | Suntio et al., 1988 |
| Water solubility at 25°C: | 11,350 mg/ℓ | Banerjee et al., 1980 |
| $K_{ow}$: | 2.15 | Hansch and Leo, 1985 |
| Conversion factors at 25°C: | 1 mg/m³ = 0.19 ppm<br>1 ppm = 5.25 mg/m³ | |

## 1.3. PRODUCTION DATA

During 1977, one company manufactured and two companies imported 2-chlorophenol in the United States. A plant operated by Monsanto Co. in Sauget, IL, produced between 10,000 and 100,000 pounds (TSCAPP, 1989). Current production data were not located in the available literature cited in Appendix A.

2-Chlorophenol can be synthesized by several methods, some of which produce either the 2-chloro or the 4-chloro isomer selectively. The reaction of phenol with tert-butylhypochlorite is more likely to form 2-chlorophenol than 4-chlorophenol. Sodium p-phenol sulfonate, prepared from phenol, can be chlorinated and desulfonated to give 2-chlorophenol. Hydrolysis of 1,2-dichlorobenzene with strong bases in the presence of a catalyst produces 2-chlorophenol. Ortho-chlorocumene can be oxidized to the corresponding peroxide and converted to 2-chlorophenol. 2-Chlorophenol is produced, along with numerous other chlorinated phenol isomers, by the direct chlorination of phenol at elevated temperatures. Purification of this complex mixture is one method of obtaining 2-chlorophenol (Freiter, 1981).

## 1.4. USE DATA

Most commercially produced 2-chlorophenol is used directly in the synthesis of higher chlorinated phenols or as a chemical intermediate in the production of larger synthetic molecules. Approximately 1% of total production is isolated for use as a preservative, in specialized phenolic resins, as a specialty solvent in the rubber industry, as a polymer intermediate in the manufacture of fire-retardant varnishes and as an aminizing agent for cotton fabric (Freiter, 1981; Scow et al., 1982).

## 1.5. SUMMARY

2-Chlorophenol is a colorless to yellow-brown liquid with an unpleasant, penetrating odor. It is soluble in alcohol, ether and water (Sax and Lewis, 1987; Weast et al., 1988). A weak acid, it is freely soluble in basic solutions (Freiter, 1981). Current production volume data were not located; however, between 10,000 and 100,000 pounds was manufactured or imported in the United States in 1977 (TSCAPP, 1989). Most of the 2-chlorophenol produced is either used directly in the synthesis of other chlorinated phenols or as an intermediate in the production of larger synthetic molecules. Approximately 1% of production is isolated for use in disinfectants, resins and other specialty products (Freiter, 1981; Scow et al., 1982).

## 2. ENVIRONMENTAL FATE AND TRANSPORT

### 2.1. AIR

With a vapor pressure at 25°C of 2.35 mm Hg (Suntio et al., 1988), 2-chlorophenol probably exists almost entirely in the vapor phase in the atmosphere (Eisenrich et al., 1981).

2.1.1. Reaction with Hydroxyl Radicals. An estimated rate constant for the gas-phase reaction of 2-chlorophenol with photochemically produced hydroxyl radicals is $1.03 \times 10^{-11}$ cm³/mol-sec (Atkinson, 1985). Assuming an average atmospheric hydroxyl radical concentration of $5 \times 10^5$ molecule/cm³ (Atkinson, 1985), then the half-life for this reaction is 1.6 days. 2-Chlorophenol reacts in the dark with nitrogen oxides (Kanno and Nojima, 1979). The yields of 2-chloro-6-nitrophenol and 2-chloro-4-nitrophenol after 5 hours in a $NO_x$ reactor were 30 and 36%, respectively, of the original material. Thus, the nighttime gas-phase reaction of 2-chlorophenol with nitrate radicals may be an important fate process in urban atmospheres.

2.1.2. Reaction with Ozone. The atmospheric reaction of 2-chlorophenol with ozone is not expected to be an important fate process (Atkinson, 1985).

2.1.3. Photolysis. Sufficient data are not available to predict the importance of the photolysis of 2-chlorophenol in the atmosphere. The un-ionized form undergoes photolytic breakdown in water; however, this is believed to result from stabilization of the polar zwitterionic transition state by water (Boule et al., 1982, 1984, 1987). This type of stabilization is not possible in the gas phase.

2.1.4. Physical Removal Processes. Based on the water solubility of 2-chlorophenol, 11,350 mg/ℓ at 25°C (Banerjee et al., 1980), wet deposition may be a significant fate process.

## 2.2. WATER

2.2.1. Hydrolysis. 2-Chlorophenol is not expected to undergo hydrolysis in water, as it contains no readily hydrolyzable functional groups (Harris, 1982).

2.2.2. Oxidation. Pertinent data regarding the oxidation of 2-chlorophenol in water were not located in the available literature cited in Appendix A.

2.2.3. Photolysis. The laboratory photolysis of 2-chlorophenol at a pH of 9 (ionized form) at 296 nm rapidly produced chloride ion and cyclopentadiene carboxylates, the latter dimerizing under the reaction conditions. In the relatively dilute concentration expected in the environment, dimerization of the reaction products is not expected. Photolysis of the neutral species (acidic pH) produced both cyclopentadienic acids and catechol, with a rate of disappearance 1 order of magnitude less than that for the ionized form (Boule et al., 1982, 1984, 1987).

2.2.4. Microbial Degradation. In a screening study, 2-chlorophenol at concentrations of 5 and 10 mg/mℓ underwent 86 and 83% aerobic degradation in 7 days using a settled domestic wastewater inoculum. The second subculture allowed complete degradation of both samples in the same time period (Tabak et al., 1981). 2-Chlorophenol at a concentration of 1, 10 and 100 mg/ℓ underwent 100, 100 and 17% degradation after 3, 3 and 6 hours, respectively, using a sewage sludge seed under aerobic conditions. The decrease in degradation at 100 mg/ℓ is believed to be due to the toxicity of the microbes to elevated concentrations of this substrate (Baird et al., 1974).

Domestic sewage treatment plant sludge was successfully acclimated to 2-chlorophenol within 24 days (Lund and Rodriguez, 1984). 2-Chlorophenol underwent aerobic biodegradation using water from a pristine aquifer and

when combined with acclimated organisms in groundwater obtained near a municipal waste site; degradation was complete in 9 and 6 days, respectively. Using these same sources of microorganisms under anaerobic conditions, degradation occurred only in aquifers that were actively methanogenic (Suflita and Miller, 1985).

That the anaerobic mineralization of 2-chlorophenol requires methanogenic microorganisms was also demonstrated using an upflow bioreactor and an acclimated sludge inoculum (Krumme and Boyd, 1988). However, 2-chlorophenol at a concentration of 50 mg C/ℓ did not undergo anaerobic degradation under methanogenic conditions in a screening test using an aerobic digester sludge (Battersby and Wilson, 1989). The failure for 2-chlorophenol to undergo degradation may be due to a high concentration of substrate used in this study.

2.2.5. Bioconcentration. A BCF of 214 was determined for 2-chlorophenol using bluegill sunfish, Lepomis macrochirus, in a continual-flow system for 28 days of exposure (Barrows et al., 1980). This value suggests that bioconcentration in fish and aquatic organisms is not an important fate process.

2.2.6. Adsorption. 2-Chlorophenol was found in 8% of water samples taken from Lake Ketekmeer in the Netherlands but not in sediment samples from the lake (detection limit, 10 µg/kg) (Wegman and van den Broek, 1983). Adsorption of phenols to sediment and suspended organic matter appears to be a complicated process, and its importance can vary widely with local conditions (Section 2.3.2.).

2.2.7. Volatilization. Based on a Henry's Law constant of $8.14 \times 10^{-6}$ atm·m³/mol at 25°C (Smith et al., 1983), an estimated volatilization half-life for a model river 1 m deep, flowing 1 m/sec with a wind velocity of 3 m/sec is 5.2 days (Thomas, 1982). Volatilization from water to the

atmosphere may, therefore, be significant. Adsorption to sediment and suspended organic matter, however, may attenuate this process.

2.3. SOIL

2.3.1. Microbial Degradation. The aerobic degradation of 2-chlorophenol at an initial concentration of 100 mg/ℓ was complete in 3 days using an activated soil sludge inoculum (Ingols et al., 1966). Aerobic degradation of 2-chlorophenol (16 mg/ℓ) by unadapted supernatant from domestic wastewater sludge was complete in 14-25 days. Using a soil inoculum, aerobic degradation did not occur in >25 days (Haller, 1978).

2-Chlorophenol, added as a component of a complex mixture to three undisturbed soils (ranging from clay to sandy) in a glass biological soil reactor, underwent aerobic degradation, with half-lives ranging from 28-228 days (Kincannon and Lin, 1985). 2-Chlorophenol underwent complete aerobic degradation, using two different soils, in 14 and 47 days (Alexander and Aleem, 1961).

2-Chlorophenol was completely degraded in 3 weeks using a sewage sludge seed under anaerobic conditions. Phenol was identified as an early product in this transformation; thus, the first step is believed to be loss of the chlorine substituent (Boyd et al., 1983). Anaerobic degradation of 2-chlorophenol using freshwater sediment and a digester sludge inoculum occurred in >29 and >8 weeks, respectively (Horowitz et al., 1982). Aerobic degradation of 100 µg/g (wet weight) 2-chlorophenol in a clay soil loam was very rapid; complete degradation was seen in 1.5 days. Under anaerobic conditions with the same soil, 78% degradation occurred after 80 days (Baker and Mayfield, 1980). 2-Chlorophenol at an initial concentration of 100 ppm in a clay loam underwent 91 and 94% degradation under anaerobic conditions at 4°C (6.5 days) and 0°C (8 days), respectively. In sediment from a small

stream, it underwent 100% degradation in 10-15 days at 20°C, and 78% degradation in 30 days at 0°C (Baker et al., 1980).

2.3.2. Adsorption. Experimental $K_{oc}$ values obtained in sediment from Lake Zoar, CT, were 4890 for fine samples and 3990 for coarse samples (Isaacson and Fink, 1984). For phenols, subtle factors such as pH and the organic, mineral or metal ion content can drastically influence the adsorption characteristics of 2-chlorophenol. The formation of hydrogen bonds with the organic matter or the formation of complexes with metallic ions are probably more important than hydrophobic forces. 2-Chlorophenol vapors also strongly adsorb to sediment (Isaacson, 1985). An experimental $K_{oc}$ of 51.15 was obtained on a Brookston clay loam (Boyd, 1982). Apparently, the process of adsorption involves several subtle factors that can vary widely with the local conditions.

2.3.3. Volatilization. Based on the vapor pressure of 2-chlorophenol, 2.35 mm Hg at 25°C (Suntio et al., 1988), volatilization from the soil surface to the atmosphere may occur. However, the rate of volatilization may be attenuated due to adsorption.

2.4. SUMMARY

In the atmosphere, 2-chlorophenol is expected to exist almost entirely in the vapor phase (Suntio et al., 1988). The gas-phase reaction with photochemically produced hydroxyl radicals is expected to be rapid, with an estimated half-life of 1.6 days (Atkinson, 1985). Nighttime degradation by the gas-phase reaction with nitrate radicals is expected to be significant in urban areas (Kanno and Nojima, 1979). Physical removal of 2-chlorophenol by wet precipitation may also occur. In water, photolysis and microbial degradation are expected to be significant. In basic waters, the ionic form of 2-chlorophenol undergoes rapid photolysis. The neutral form photolizes

more slowly (Boule et al., 1982, 1984, 1987). Microbial degradation under aerobic (Tabak et al., 1981; Baird et al., 1974; Lund and Rodriguez, 1984; Suflita and Miller, 1985) and anaerobic (Krumme and Boyd, 1988; Battersby and Wilson, 1989; Suflita and Miller, 1985) conditions has been demonstrated. Bioconcentration in aquatic organisms is not expected to be significant. Volatilization from water to the atmosphere is expected; however, this process may be attenuated by adsorption to sediment and suspended matter. In soil, biodegradation is expected to be the dominant fate process. Microbial degradation using a soil inoculum has been demonstrated under aerobic (Alexander and Aleem, 1961; Ingols et al., 1966; Haller, 1978; Kincannon and Lin, 1985) and anaerobic (Boyd et al., 1983; Horowitz et al., 1982) conditions. Volatilization from the soil surface to the atmosphere is expected; however, it may be attenuated by the process of adsorption.

## 3. EXPOSURE

2-Chlorophenol can enter the environment as a fugitive emission from commercial plants that synthesize or use this compound. It can also enter the environment as a product of the chemical or biological degradation of other anthropogenic compounds.

An estimated 934 workers are potentially exposed to 2-chlorophenol (NIOSH, 1984). Occupational exposure may occur by inhalation or dermal contact during the production, purification and formulation of 2-chlorophenol. Sufficient data are not available to predict exposure to the general population.

### 3.1. WATER

2-Chlorophenol has been qualitatively identified in drinking water in the United States (Kool et al., 1982; Lucas, 1984) and in 1/10 effluent samples from industrial and publicly owned treatment plants in Illinois (Ellis et al., 1982). 2-Chlorophenol was found at a concentration of <10 µg/ℓ in primary effluent from publicly owned treatment plants in Los Angeles, San Diego and Orange County, CA (Young, 1978). 2-Chlorophenol was found in 2% of 48 source samples, taken to determine possible routes of contamination to the influent of two sewage treatment plants, at an average concentration of 15 ppb (Callahan et al., 1979). It was identified as a constituent of chlorinated municipal sewage effluent at a concentration of 2 ppb (Bourquin and Gibson, 1978). 2-Chlorophenol was not detected in raw water samples obtained at drinking water treatment plants in six Canadian cities and was found in one of six samples of treated water at a concentration of 39 ng/ℓ (Sithole et al., 1986). It was also found in 1% of 86 samples taken from 19 cities during the Nationwide Urban Runoff

Program at a concentration of 2 µg/ℓ (Cole et al., 1984). In the Netherlands, it was found at concentrations ≤21 µg/ℓ in the effluent of the following industries, none of which produced 2-chlorophenol: herbicides, organic dyes and agrochemicals (Berbee, 1986). It is a known component of pulp mill effluent (Suntio et al., 1988).

2-Chlorophenol was found in groundwater samples obtained near a chemical manufacturing plant in Australia (Stepan et al., 1981). It was found in 2% of 1976 samples taken in 1976 from the Rhine River in the Netherlands at a maximum concentration of 2.3 µg/ℓ; it was not found in any samples taken from the same river in 1987 (Wegman and Hoestee, 1979).

3.2. FOOD

Pertinent data regarding exposure to 2-chlorophenol through food were not located in the available literature cited in Appendix A.

3.3. INHALATION

Data on the atmospheric concentration of 2-chlorophenol are lacking. It was identified in effluent from waste incinerators in three of five samples at concentrations ranging from 6.9-13 µg/mℓ (James et al., 1984).

3.4. DERMAL

Pertinent data regarding dermal exposure to 2-chlorophenol were not located in the available literature cited in Appendix A.

3.5. OTHER

2-Chlorophenol may be formed in the atmosphere by the sequential, photo-initiated degradation of chlorobenzene or 2-nitrochlorobenzene (Kanno and Nojima, 1979). It can also be formed by the chlorination of phenol in the disinfection of drinking water (Carlson and Caples, 1975; Joshipura and Kelliher, 1980). It is formed in water by the photoinitiated hydrolysis of 1,4-dichlorobenzene (Boule et al., 1985). Thermolysis of two different

vinylidene chloride polymers at 200-600°C produced an average of 13.5 and 11.3 µg of 2-chlorophenol/g of polymer (Yasuhara and Morita, 1988).

## 3.6. SUMMARY

2-Chlorophenol can enter the environment as a result of its commercial synthesis or use. 2-Chlorophenol may be released to the environment through its formation by chemical transformations on other anthropogenic compounds (Kanno and Nojima, 1979; Carlson and Caples, 1975; Joshipura and Kelliher, 1980; Boule et al., 1985; Yasuhara and Morita, 1988).

Data on the occurrence of 2-chlorophenol in the environment are lacking. The compound has been qualitatively identified in drinking water in the United States (Kool et al., 1982; Lucas, 1984) and quantified in effluents from publicly owned treatment plants (Ellis et al., 1982; Young, 1978; Callahan et al., 1979; Bourquin and Gibson, 1978).

# 4. ENVIRONMENTAL TOXICOLOGY

## 4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. Many studies regarding the acute toxicity of 2-chlorophenol to cladoceran invertebrates have been done. Studies on daphnids included mostly static 48-hour tests conducted in 18-22°C water with Daphnia magna that were <24 hours old. The 48-hour $EC_{50}$ values reported for immobilization of Daphnia varied from 2.6-7.43 mg/ℓ in these tests. Details of the individual studies are presented in Table 4-1.

The toxicity of 2-chlorophenol has been examined in two species of salt-water invertebrates: the shrimp, Crangon septemspinosa, and the soft-shelled clam, Mya arenaria (McLeese et al., 1979). Three members of each species were exposed simultaneously to each concentration for 96 hours at 10°C. A lethal threshold was determined based on the time to 50% mortality at each chemical concentration. The 96-hour lethal threshold (geometric mean of highest concentration with no mortality and next highest concentration with 100% mortality) in shrimp was 5.3 mg/ℓ. The data were insufficient to generate a lethal threshold for clams.

Pickering and Henderson (1966) performed acute toxicity tests on a series of freshwater fish, including bluegills, Lepomis macrochirus, fathead minnows, Pimephales promelas, goldfish, Carassius auratus, and guppies, Poecilia reticulata. Ten of each species (two groups of five) were exposed to nominal concentrations of 2-chlorophenol under static conditions in soft water (pH=7.5; alkalinity=18 mg/ℓ; hardness=20 mg/ℓ) at 25°C. Toxicity was similar in three of these species, with 96-hour $LC_{50}$ values of 10.00 mg/ℓ in bluegills, 11.63 mg/ℓ in fathead minnows, and 12.37 mg/ℓ in goldfish. Guppies, which were slightly less susceptible to 2-chlorophenol,

TABLE 4-1

Acute Toxicity Studies in *Daphnia* Using 2-Chlorophenol

| Species | Age | Test Type | Experimental Design | Temperature (°C) | Duration/Endpoint | Concentration | Reference |
|---|---|---|---|---|---|---|---|
| *Daphnia magna* | ≤24 hours | static | ≥5 nominal concentrations<br>3 replicates/concentration<br>n = 5/replicate | 22 | 24-hour $LC_{50}$<br>48-hour $LC_{50}$<br>48-hour $LC_0$ | >22 mg/ℓ<br>2.6 (2.1-3.2)mg/ℓ<br>1.0 mg/ℓ | LeBlanc, 1980 |
| *D. magna* | ≤24 hours | static | 2 replicates/concentration | 18 | 48-hour $EC_{50}$ (immobilization) | 3.91(3.31-4.91) mg/ℓ | Keen and Baillod, 1985 |
| *D. magna* | ≤24 hours | static | 2 tests | 22 | 48-hour $EC_{50}$ (immobilization) | 6.20 mg/ℓ | Randall and Knopp, 1980 |
| *D. magna* | ≥24 hours | static | ≥3 tests<br>4 concentrations/test<br>4 replicates/concentration<br>n = 5/replicate | 18 | 48-hour $LC_{50}$ | 7.43 mg/ℓ | Kopperman et al., 1974 |
| *D. magna* | NR | NR | 3 tests | NR | 24-hour $EC_{50}$ (immobilization) | 8 mg/ℓ | Bazin et al., 1987 |
| *D. magna* | NR | NR | NR | 20 | 24-hour $EC_{50}$ (immobilization) | 11.7 mg/ℓ | Tissot et al., 1985 |
| *D. magna* | <72 hours | static | 3 tests<br>4 replicates/concentration<br>n = 5/replicate | 20 | 24-hour $EC_{50}$ (immobilization) | 17.95 (16.6-19.3) mg/ℓ | Devillers and Chambon, 1986 |
| *D. magna* | NR | NR | NR | NR | $EC_{50}$<br>$EC_0$<br>$EC_{100}$ | 23 mg/ℓ<br>10 mg/ℓ<br>64 mg/ℓ | Knie et al., 1983 |
| *Daphnia pulex* | ≤24 hours | static | 10 replicates/concentration<br>n = 2/replicate | 20 | 96-hour $LC_{50}$ | 6.9 mg/ℓ | Trabalka and Burch, 1978 |

NR = Not reported

had a 96-hour $LC_{50}$ of 20.17 mg/ℓ. In a second assay, performed only with fathead minnows, a hard dilution water was used with higher pH (8.2), alkalinity (300 mg/ℓ) and hardness (360 mg/ℓ) than the soft water; the 96-hour $LC_{50}$ in hard water (14.48 mg/ℓ) was not significantly different from that obtained using soft water (11.63 mg/ℓ). This indicates that these water quality variables did not affect the toxicity of 2-chlorophenol in this study. The 24-hour $LC_{50}$ values for bluegill, goldfish and guppies were slightly higher than the 96-hour values for these species, indicating that most deaths occurred early in the study. Only in fathead minnows was the 96-hour $LC_{50}$ (11.63 mg/ℓ) significantly lower than the 24-hour value (21.96 mg/ℓ), suggesting the occurrence of significant mortality during the second and third days of the study.

Acute toxicity studies by other authors have generally reported similar results. Buccafusco et al. (1981) examined the acute toxicity of 2-chlorophenol in bluegill, L. macrochirus. One group of 10 fish was exposed to each nominal concentration under static conditions at 22°C. The 24- and 96-hour $LC_{50}$ values were 7.2 and 6.6 mg/ℓ, respectively. Lammering and Burbank (1961), also working on bluegill, L. macrochirus, reported 24- and 48-hour $LC_{50}$ values of 8.2 and 8.1 mg/ℓ, respectively, based on static tests (water renewed after 24 hours) conducted on groups of 10 fish per concentration at 20°C. Phipps et al. (1981) performed both static and flowthrough tests of the toxicity of 2-chlorophenol to fathead minnows, P. promelas. In the static test, fish were exposed in groups of 20 to different concentrations of the chemical at 21.6-25.4°C. The 48-hour $LC_{50}$ was 9.7 mg/ℓ. In the flowthrough tests, 100 fish (two groups of 50) were exposed to each measured concentration at 25°C. The 96- and 192-hour $LC_{50}$ values were 12 and 6.3 mg/ℓ, respectively. Kobayashi et al. (1979)

reported a 24-hour $LC_{50}$ of 16 ppm (mg/ℓ) in goldfish, Carassius auratus, in a static renewal test conducted at 20°C using 10 fish at each exposure concentration. Konemann and Musch (1981) conducted static acute toxicity tests on guppies, Poecilia reticulata. Eight fish were tested at each concentration; the tests were conducted at 22°C for 7-14 days. The $LC_{50}$ decreased from 13.46 mg/ℓ at pH 7.8-11.2 mg/ℓ at pH 7.3 and 7.06 mg/ℓ at pH 6.1, suggesting that the toxicity of 2-chlorophenol was influenced by pH in this study. In a screening-type study conducted on two members of three different fish species, Applegate et al. (1957) found that 24-hour static exposure to a nominal concentration of 5 ppm (mg/ℓ) of 2-chlorophenol at 13°C had no effect on bluegills or larval sea lampreys, Petromyzon marinus. 2-Chlorophenol at this exposure concentration produced death in rainbow trout, Salmo gairdneri, after 13 hours.

4.1.2. Chronic Effects on Fauna.

4.1.2.1. TOXICITY -- An early life stage toxicity test was conducted on fathead minnows, P. promelas, by LeBlanc (1983). The eggs (and larvae after hatching) were exposed under flowthrough conditions to mean measured concentrations of 0.78, 1.1, 1.7, 2.6 and 4.0 mg/ℓ of 2-chlorophenol. Untreated and solvent controls were also included. Endpoints examined were percent hatch of eggs and percent survival, length and weight of larvae at 30 days post-hatch. No effects were reported at any concentration.

4.1.2.2. BIOACCUMULATION/BIOCONCENTRATION -- The tendency of 2-chlorophenol to bioconcentrate in fish was studied by Barrows et al. (1980). A total of 100 bluegill sunfish, L. macrochirus, were exposed to a mean measured concentration of 9.2 µg/ℓ of radiolabeled 2-chlorophenol for 28 days under flowthrough conditions. A 7-day depuration period followed. The equilibrium BCF measured at 28 days was 214. The half-life

for elimination of 2-chlorophenol from the tissues was <1 day. The relatively low BCF and short biological half-life indicate that this compound is not concentrated or retained significantly by bluegill.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- Two studies have investigated the toxicity of 2-chlorophenol to aquatic plants. Static 96-hour assays were conducted by Shigeoka et al. (1988) on two species of green algae, Selenastrum capricornutum and Chlorella vulgaris. Test algae were exposed to five nominal concentrations of 2-chlorophenol at 21°C. The $EC_{50}$ values for growth inhibition, calculated from measurements of cell density, were 70 ppm (mg/ℓ) for S. capricornutum and 170 ppm (mg/ℓ) for C. vulgaris. 2-Chlorophenol did not affect chlorophyll concentration or oxygen production in the green alga, Chlorella pyrenoidosa, at concentrations of ≤10 mg/ℓ, but oxygen production was reduced to 88% of control at 100 mg/ℓ and to 74% of control at 500 mg/ℓ (Huang and Gloyna, 1968). In this study, algal cultures were exposed to nominal concentrations of the test chemical for 72 hours under static conditions at 25°C.

4.1.3.2. BIOCONCENTRATION -- Pertinent data regarding the bioconcentration potential of 2-chlorophenol in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects on Bacteria. The effects of 2-chlorophenol on bacteria have been studied in several different ways. The most common assay that has been done is the Microtox test on Photobacterium phosphoreum, which measures the reduction in light emitted from this photoluminescent species following exposure to a chemical. $EC_{50}$ values reported by various authors range from 14.7-40 mg/ℓ for tests lasting 5-30 minutes (Bazin et al., 1987; Cunningham et al., 1986; Curtis et al., 1982; Ribo and Kaiser, 1983). A

second assay involved quantifying nitrification activity by Nitrobacter (Wang and Reed, 1984). Nitrite utilization was reduced 25-27% following 4-hour exposure to 50 mg/ℓ of 2-chlorophenol. Another study examined the effect of 2-chlorophenol exposure on ATP content in both the heterotrophic bacteria, Escherichia coli, and the nitrifying bacteria, Nitrosomonas europaea (Parker and Pribyl, 1984). The effect was greater on N. europaea; following 20-minute exposure, the percent reduction in ATP increased from 24-32% as the concentration of 2-chlorophenol increased from 100-400 mg/ℓ. The percent reduction in ATP content of E. coli increased from 6.5-23% as the exposure concentration increased from 100-1000 mg/ℓ. One study evaluated the ability of 2-chlorophenol to inhibit bacterial dehydrogenase activity in a mixed bacterial culture (Liu et al., 1982). The $EC_{50}$ for this effect was 700 mg/ℓ.

## 4.2. TERRESTRIAL TOXICOLOGY

4.2.1. Effects on Fauna. Only one study regarding the effects of exposure of terrestrial fauna to 2-chlorophenol was located in the available literature. Red-winged blackbirds trapped in the wild and held in captivity for 2-6 before testing were given single doses of 2-chlorophenol by gavage in propylene glycol (Schafer et al., 1983). The estimated $LD_{50}$ for 2-chlorophenol in red-winged blackbirds was >113 mg/kg.

4.2.2. Effects on Flora. Pertinent data regarding the effects of exposure of terrestrial flora to 2-chlorophenol were not located in the available literature cited in Appendix A.

## 4.3. FIELD STUDIES

Pertinent data regarding the effects of 2-chlorophenol 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 pertinent data regarding the effects of exposure of aquatic fauna and flora to 2-chlorophenol prevented the development of a freshwater criterion by the method of U.S. EPA/OWRS (1986). Available data are displayed in Figure 4-1. Additional data required for the development of a freshwater criterion include the results of acute assays with a salmonid fish species, a benthic crustacean, an insect, a nonarthropod and non-chordate species and an insect or species from a phylum not previously represented. The development of a freshwater criterion will also require data from an additional chronic toxicity test on either a fish or an invertebrate.

Pertinent data regarding the effects of exposure of marine fauna and flora to 2-chlorophenol were not located in the available literature. Acute studies with representatives from eight families of marine fauna and at least three chronic studies and one bioconcentration study with marine fauna and flora are needed to develop a saltwater criterion.

## 4.5. SUMMARY

The acute toxicity of 2-chlorophenol was similar in all species of freshwater fish examined, with $LC_{50}$ values ranging from 6.6-10.0 mg/ℓ in the bluegill, L. macrochirus (Buccafusco et al., 1981; Lammering and Burbank, 1961; Pickering and Henderson, 1966), 9.7-14.48 mg/ℓ in the fathead minnow, P. promelas (Phipps et al., 1981; Pickering and Henderson, 1966), 12.37-16 mg/ℓ in the goldfish, C. auratus (Kobayashi et al., 1979; Pickering and Henderson, 1966), and 7.06-20.17 mg/ℓ in the guppy, P. reticulata (Konemann and Musch, 1981; Pickering and Henderson, 1966). In a screening-type study, 5 mg/ℓ had no effect on bluegill or sea lamprey, P. marinus, but produced death in trout, S. gairdneri, within 13 hours

| Family | TEST TYPE | | |
|---|---|---|---|
| | GMAV[a] (mg/L) | GMCV[a] (mg/L) | BCF[a] |
| #1 Chordate (Salmonid-fish) | NA | NA | NA |
| #2 Chordate (warmwater fish) | 8.1[b] | NA | 214[c] |
| #3 Chordate (fish or amphibian) | 12[d] | ≥4[e] | NA |
| #4 Crustacean (planktonic) | 4.6[f] | NA | NA |
| #5 Crustacean (benthic) | NA | 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 | NA | 70[g] | NA |
| #10 Vascular plant | NA | NA | NA |

[a]NA=Not Available
[b]Acute value for bluegill sunfish, Lepomis macrochirus
[c]BCF for bluegill sunfish
[d]$LC_{50}$ for fathead minnow, Pimephales promelas
[e]Chronic value for fathead minnow
[f]Acute value for Daphnia magna
[g]$EC_{50}$ for growth inhibition in Selenastrum capricornutum

FIGURE 4-1

Organization Chart for Listing GMAVs, GMCVs, and BCFs Required to Derive Numerical Water Quality Criteria by the Method of U.S. EPA/OWRS (1986) for the Protection of Freshwater Aquatic Life from Exposure to 2-Chlorophenol

(Applegate et al., 1957). Exposure to concentrations ≤4 mg/ℓ for 30 days had no effect on eggs and larvae of fathead minnows in an early life stage toxicity test (LeBlanc, 1983). The BCF determined in bluegill was 214; the elimination half-life was <1 day (Barrows et al., 1980). Studies using freshwater invertebrates revealed that toxic effects occurred at concentrations similar to those found for fish. $LC_{50}$ and immobilization $EC_{50}$ values in Daphnia ranged from 2.6-23 mg/ℓ (Bazin et al., 1987; Devillers and Chambon, 1986; Keen and Baillod, 1985; Knie et al., 1983; Kopperman et al., 1974; LeBlanc, 1980; Randall and Knopp, 1980; Tissot et al., 1985; Trabalka and Burch, 1978). The lethal threshold was 5.3 mg/ℓ in the shrimp, C. septemspinosa, the only saltwater animal studied. Among freshwater algae, $EC_{50}$ values for growth inhibition were 70 mg/ℓ in S. capricornutum, and 170 mg/ℓ in C. vulgaris (Shigeoka et al., 1988). Effects in bacteria included 50% reduction in light emitted by P. phosphoreum at 14.7-40 mg/ℓ (Bazin et al., 1987; Cunningham et al., 1986; Curtis et al., 1982; Ribo and Kaiser, 1983), 25-27% reduction in nitrite utilization by Nitrobacter at 50 mg/ℓ (Wang and Reed, 1984), decreased ATP content in E. coli and N. europa at 100-1000 mg/ℓ (Parker and Pribyl, 1984) and 50% reduction in bacterial dehydrogenase activity in a mixed bacterial culture at 700 mg/ℓ. Among terrestrial organisms, the oral $LD_{50}$ in red-winged blackbirds was >113 mg/kg (Schafer et al., 1983).

# 5. PHARMACOKINETICS

## 5.1. ABSORPTION

Deichmann and Keplinger (1981) reported that the chlorophenols (not specifically 2-chlorophenol) are absorbed readily from the gastrointestinal tract and from sites of parenteral injection. Carpenter et al. (1985) reported that peak plasma levels of radioactivity were reached 2 hours after male rats were treated by gavage with 50 mg/kg $^{14}C$-labeled 2-chlorophenol in corn oil (plasma levels not reported). At 24 hours after treatment, urinary radioactivity accounted for 91% of the administered dose. Only 4% of the dose was recovered in the feces by 24 hours. Spencer and Williams (1950) administered 2-chlorophenol emulsified with water to chinchilla rabbits (gender not specified) and reported that 101.1% of the dose was accounted for as urinary metabolites. The duration of the urine collection period was not reported. Considered together, these data indicate that absorption of 2-chlorophenol from the gastrointestinal tract is rapid and virtually complete.

Roberts et al. (1977) performed an in vitro study of the permeability of human epidermis to various concentrations of phenolic compounds. A 2.5 $cm^2$ portion of the epidermal layer of abdominal skin obtained at autopsy was supported in a diffusion cell and exposed to reagent grade 2-chlorophenol in water. 2-Chlorophenol was absorbed by the epidermal membrane, with a permeability coefficient of $5.51 \times 10^{-4}$/cm/minute and a threshold concentration for tissue damage of 0.8% (w/v).

Permeation of 2-chlorophenol in saline through intact and denuded skin of hairless SKH-hr-1 mice (60-100 days old) was studied by Huq et al. (1986) using in vitro diffusion cell methods. The permeability coefficients for 2-chlorophenol at concentrations of 0.05, 0.19 and 0.50 g/100 mℓ through

whole skin were $107x10^{-3}$, $116x10^{-3}$ and $140x10^{-3}$/cm/hour, with an average lag times of 21.9, 10.3 and 6.3 minutes, respectively. The permeability coefficients of 2-chlorophenol in approximately the same concentrations through skin stripped of the stratum corneum were $253x10^{-3}$, $276x10^{-3}$ and $214x10^{-3}$/cm/hour, with lag times of 11.5, 5.5 and 8.5, respectively.

## 5.2. DISTRIBUTION

Liver and kidney tissues from weanling female Sprague-Dawley rats given drinking water containing 2-chlorophenol (97% pure) for 10 weeks, continuing through breeding, gestation and 3 weeks postparturition were analyzed for 2-chlorophenol content (Exon and Koller, 1982). Following exposure to 0, 5, 50 and 500 ppm, respectively, the levels in livers (from three pooled samples/group) were 0.16, 2.20, 3.20 and 0.08 ppm; the levels in the kidney (pooled tissues from five rats/group) were 0.26, 2.60, 2.40 and 2.00 ppm. The lower levels in the tissues of rats given higher doses were not explained.

Significant amounts of radioactivity were found in the gastrointestinal tracts and the fat of male rats treated by gavage with $^{14}C$-labeled 2-chlorophenol in corn oil at 50 mg/kg, but levels in fat decreased markedly by 4 hours after treatment (Carpenter et al., 1985). The compound was rapidly excreted in the urine and the feces, with little distribution to other (unspecified) tissues.

Radioactivity from radiolabeled 2-chlorophenol (probably orally administered, label not specified, dose not reported) bound to the livers and kidneys of Gunn rats >3-4 times in Sprague-Dawley rats (Houser, 1983).

## 5.3. METABOLISM

Following oral administration of 2-chlorophenol at 225 mg/kg to male Sprague-Dawley rats, the compound was recovered in the free form in the urine, along with the glucuronide and glucuronide and sulfate conjugates of 2-chlorohydroquinone (Houser, 1983). After pretreatment of the rats with B-naphthoflavone or Arochlor 1254, the proportion of metabolites recovered as 2-chlorohydroquinone derivatives increased (percent of dose not reported). In Gunn rats, oral administration of 300 mg/kg of 2-chlorophenol resulted in 24-hour recovery of the compound in the free form, as the glucuronide and sulfate and as the sulfate conjugate of 2-chlorohydroquinone (percent of dose not reported), in the urine (Houser, 1983). 2-Chlorohydroquinone derivatives were formed 8-9 times more in Gunn rats than in Sprague-Dawley rats.

In male rats treated by gavage with 50 mg/kg of $^{14}C$-labeled 2-chlorophenol in corn oil, 91% of the dose of radioactivity was recovered in the urine, with a small amount appearing in the feces (Carpenter et al., 1985). More than 90% of the urinary radioactivity was identified as glucuronide and sulfate conjugates of chlorophenol, with <2% recovered as parent compound.

In chinchilla rabbits (sex not reported) given 171.3 mg/kg of 2-chlorophenol emulsified with water by stomach tube (Spencer and Williams, 1950), 82.4% of the dose consisted of glucuronides, and 18.7% consisted of ethereal sulphates of 2-chlorophenol. No mercapturic acid was formed. Collectively, these data indicate that 2-chlorophenol is rapidly and extensively metabolized.

## 5.4. EXCRETION

The most meaningful excretion data were provided by Carpenter et al. (1985), who reported that rats treated by gavage with 50 mg/kg $^{14}C$-labeled

2-chlorophenol excreted 91% of the dose of radioactivity in the urine and 4% in the feces within 24 hours after dosing (Carpenter et al., 1985). In chinchilla rabbits treated with 171.3 mg/kg of 2-chlorophenol by stomach tube, 101.1% of the dose was recovered as metabolites in the urine (Spencer and Williams, 1950). The duration of the urine collection period was not specified.

## 5.5. SUMMARY

Chlorophenols (as a class) are readily absorbed from the gastrointestinal tract and from parenteral sites of injection (Deichmann and Keplinger, 1981). Orally administered 2-chlorophenol appears to be rapidly and almost completely absorbed from the gastrointestinal tracts of rats (Carpenter et al., 1985; Houser, 1983) and chinchilla rabbits (Spencer and Williams, 1950). In in vitro studies using human autopsy skin, 2-chlorophenol was absorbed by the epidermal membrane with a permeability coefficient of $5.51 \times 10^{-4}$/cm/min (Roberts et al., 1977).

Following oral administration of 2-chlorophenol to rats, the compound was found in the liver and kidney (Exon and Koller, 1982), but metabolism and excretion occurred so rapidly that there was little distribution to body tissues (Carpenter et al., 1985). Urinary excretion accounted for 91% of an oral dose in rats within 24 hours of treatment (Carpenter et al., 1985). Over 90% of the urinary excretion consisted of glucuronide and sulfate conjugates of the parent compound, and <2% consisted of unchanged parent compound (Carpenter et al., 1985). Other metabolites identified in the urine of treated rats include glucuronide and sulfate conjugates of 2-chlorohydroquinone (Houser, 1983), an oxidation product of 2-chlorophenol. Glucuronide and ethereal suflate conjugates of 2-chlorophenol in the urine of orally treated chinchilla rabbits accounted for virtually 100% of an oral dose (Spencer and Williams, 1950).

# 6. EFFECTS

## 6.1. SYSTEMIC TOXICITY

### 6.1.1. Inhalation Exposure.

6.1.1.1. SUBCHRONIC -- Pertinent data regarding toxicity from subchronic inhalation exposure to 2-chlorophenol were not located in the available literature cited in Appendix A.

6.1.1.2. CHRONIC -- Pertinent data regarding toxicity from chronic inhalation exposure to 2-chlorophenol were not located in the available literature cited in Appendix A.

### 6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC -- In a 3-week oral toxicity study, rats (number, strain and sex not given in translation) were given 65 or 130 mg/kg of 2-chlorophenol in olive oil. At both treatment levels, weight gain was significantly reduced, and liver weights were increased when compared with controls. By the third week, there were significant depressions in hemoglobin levels and hematocrit values. Histological examinations revealed degenerated liver tissue with congestion, atrophy, swelling, vacuolization, dilation of rough endoplasmic reticulum and mitrochondrial swelling and destruction of mitochondrial cristae (Chung, 1978).

6.1.2.2. CHRONIC -- As part of a cancer study (Sections 6.2.2. and 6.2.3.), Exon and Koller (1983b, 1985) exposed groups of 24-32 male and 24-28 female Sprague-Dawley rats to 2-chlorophenol (97% pure) in the drinking water at levels of 0, 5, 50 and 500 ppm from weaning to ~2 years of age. The dams (groups of 12-20) of these rats had been given the same treatments from 3 weeks of age through breeding (to untreated males) until weaning of their progeny. During gestation days 14-21, dams also received 0.318%

ethylurea in the diet and 1 ppm nitrite (precursors of the carcinogen ethylnitrosourea) in the drinking water. A negative control group (not exposed to any compounds) received normal food and water; a positive control group was administered just ENU precursors. Rats were checked daily for morbidity; moribund or tumor-bearing animals were sacrificed, and all tissues were examined grossly and microscopically. Body weights were recorded monthly for all rats, and hematological parameters were measured every 2 months or every 2 weeks (Exon and Koller, 1983b) on randomly selected animals (five males, five females) from each group.

At 7 months, mean body weights of female rats in most treated groups were significantly lower than those of controls, and the mean body weights of male rats were generally significantly higher than those of controls, but these data were not consistent or dose-related. At 24 months, Exon and Koller (1985) reported that treatment with 2-chlorophenol significantly elevated RBC, PCV and blood hemoglobin concentrations in both sexes of rats in the 500 ppm group. Noncancer histopathologic observations were not reported.

6.1.3. Other Relevant Information. All chlorophenols reportedly irritate the skin and eyes, and the dusts irritate the respiratory tract (Freiter, 1981). In humans, 2-chlorophenol is reportedly highly toxic, causing severe burns, some liver and kidney damage, narcosis and respiratory depression (Davis et al., 1959).

Houser (1983) reported that a single oral administration of 300 mg/kg of 2-chlorophenol to Gunn rats (sex not reported) resulted in centrilobular hepatic necrosis in 50% of the animals and renal necrosis in 75% of the animals. A dose of 225 mg/kg in male Sprague-Dawley rats was not renal- or hepatotoxic.

Deichmann (1943) reported $LD_{50}$s in rats (strain and sex not specified) of 670 mg/kg from an orally administered dose and 950 mg/kg from a subcutaneous dose. Oral $LD_{50}$ values of 670 mg/kg for the mouse (strain and sex not specified) and 440 mg/kg for the blue fox were reported (Bubnov et al., 1969).

The acute oral $LD_{50}$s, administered by gavage (98% pure, in deionized water), in 6-week-old male and female CD-1 ICR mice were 347 and 345 mg/kg, respectively (Borzelleca et al., 1985). Signs of toxicity included rapid respiration, tremors and convulsions leading to central nervous system depression. In other studies, Borzelleca (1983) found the $ED_{50}$ for motor impairment in CD-1 mice to be 63 mg/kg; maximum effect occurred 5 minutes after treatment and was reversible. The lowest dose that produced a behavioral change in the mice was 1 mg/kg, which resulted in a change in operant behavior after 2 days of treatment.

In a 14-day behavioral toxicity study, mice (strain and sex not specified) were gavaged with 2-chlorophenol in doses of 35, 69 and 175 mg/kg/day and compared to an untreated control group. There was 80% mortality in the group treated with 175 mg/kg/day; mortality in the control group was not reported. The 175 mg/kg/day group also showed a significant decrease in body weight before death. Hyperactivity was seen in the mice treated with 35 and 69 mg/kg from the fourth day of exposure until treatment was stopped (Kallman et al., 1982).

Farquharson et al. (1958) studied the toxicity of intraperitoneally administered 2-chlorophenol in fasted male albino rats. The median lethal dose of 230 mg/kg, injected in 10 mℓ of olive oil/kg body weight, caused excited behavior, running or vigorous nose-rubbing, followed within minutes

by tremors and convulsions. Rats that recovered remained sluggish and hypotonic for hours. The dose also produced a 2°C decrease in rectal temperature when compared with controls.

Intraperitoneally administered 2-chlorophenol (dissolved in 0.9% saline) produced clonic convulsions in 50% of anesthetized male Sheffield albino mice given 0.77 μmols/kg (~100 mg/kg).

Subcutaneous $LD_{50}$s of 800 and 950 mg/kg were reported for guinea pigs and rabbits (strain and sex not reported), respectively (Christensen and Luginbyhl, 1975).

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity from inhalation exposure to 2-chlorophenol were not located in the available literature cited in Appendix A.

6.2.2. Oral. In a study of the carcinogenic-cocarcinogenic potential of 2-chlorophenol, Exon and Koller (1983b, 1985) exposed groups of 24-32 male and 24-28 female Sprague-Dawley rats pre-, post- or pre- and postnatally to the compound mixed in the drinking water in concentrations of 0, 5, 50 and 500 ppm, along with prenatal exposure to ENU. ENU, a known carcinogen, was administered as the precursors; 0.316% ethyl urea in food and 1 ppm sodium nitrite in drinking water. In addition, a group of rats was exposed pre- and postnatally to 2-chlorophenol without prenatal exposure to ENU; a positive control group was treated with ENU alone.

Prenatal exposure to 2-chlorophenol consisted of exposing the dams to the levels in drinking water described above from weaning through mating at 90 days of age and through weaning to postpartum day 21. Postnatal exposure to 2-chlorophenol consisted of exposing the test animals to the levels in drinking water described above at weaning for 24 months. ENU was also

administered as above, with 3.18% ethylurea in the diet given concurrently with 1 ppm nitrite in the drinking water.

In the group prenatally exposed, the 2-chlorophenol did not produce consistent effects in survival to weaning. According to the authors, the weaning weight of males and females given 2-chlorophenol was generally decreased in comparison with controls, but the observation was not dose-dependent. Body weights of females remained decreased through 7 months, whereas male rats had generally increased body weights ($p \leq .1$). These differences were not observed after 24 months (Exon and Koller, 1985).

2-Chlorophenol alone did not increase the incidence of tumors, or decrease the time-to-tumor after ≤24 months of exposure in comparison with controls. Alternatively, male offspring of rats treated with ENU and 2-chlorophenol at all treatment levels, both pre- and postnatally, had significantly increased incidence of tumors when compared with the group given only ENU. Male progeny of rats treated with ENU and 2-chlorophenol given prenatally at 5 and 500 ppm (but not 50 ppm), and with ENU and 2-chloro- phenol given postnatally at 5 ppm, had significantly higher incidence of tumors compared with the ENU-treated group. Tumor incidence appeared to be higher in the lower dose groups, and females seemed to be less sensitive to ENU-induced tumors. Tumor latency was significantly decreased in rats exposed to ENU with both pre- and postnatal exposure to 2-chlorophenol at all treatment levels when compared with the ENU-only group. The investigators suggested that 2-chlorophenol may have enhanced the carcinogenicity of ENU (Table 6-1).

6.2.3. **Other Relevant Information.** Boutwell and Bosch (1959) conducted a study of the tumor-promoting ability of 2-chlorophenol applied dermally to 2- to 3-month-old female albino Sutter mice. When applied as a 20% solution

Table 6-1

Incidence of Tumors in Sprague-Dawley Rats Dosed With 2-Chlorophenol and/or Ethylurea and Nitrate (ENU)[a]

| Treatment[b] (ppm) | Days to Tumor Mean ± SE | Tumor Incidence (%) Total | Male | Female | No. Rats/Group Male | Female |
|---|---|---|---|---|---|---|
| Control | 422 ± 40 | 3[d] | 7[d] | 0[d] | 30 | 30 |
| Pre- and Postnatal (No. EUN) | | | | | | |
| 5 | 422 ± 60 | 2[d] | 4[d] | 0[d] | 24 | 24 |
| 50 | 420 ± 59 | 4[d] | 4[d] | 4[d] | 24 | 24 |
| 500 | 421 ± 61 | 5[d] | 4[d] | 7[d] | 28 | 28 |
| EUN Only | 302 ± 16 | 58 | 54 | 63 | 28 | 24 |
| Prenatal + EUN | | | | | | |
| 5 | 282 ± 15 | 69 | 75[d] | 63 | 24 | 24 |
| 50 | 268 ± 17 | 63 | 50 | 75 | 24 | 24 |
| 500 | 276 ± 17 | 57 | 75[d] | 39[d] | 28 | 28 |
| Postnatal + EUN | | | | | | |
| 5 | 282 ± 15 | 71[d] | 83[d] | 71 | 24 | 24 |
| 50 | 325 ± 17 | 54 | 63 | 46 | 24 | 24 |
| 500 | 300 ± 22 | 33[d] | 39 | 25[d] | 28 | 24 |
| Pre- and Postnatal + EUN | | | | | | |
| 5 | 245 ± 14[c] | 85[d] | 92[d] | 79 | 24 | 24 |
| 50 | 256 ± 17[c] | 63 | 85[d] | 50 | 24 | 24 |
| 500 | 259 ± 14[c] | 68 | 77[d] | 60 | 30 | 30 |

[a] From: Exon and Koller, 1983b

[b] 2-Chlorophenol was administered in the drinking water. Prenatal administration was done by dosing dams from weaning through parturition or postnatally from weaning (21 Days). ENU was administered as ethylurea in the feed (3.18%) and 1-ppm nitrate to the water.

[c] $\leq .10$ compared to ENU positive control by analysis of variance (lease-square means).

[d] $p \leq .10$ compared to ENU positive control by chi-square test.

in dioxane to the backs of the uninitiated mice twice weekly for 12 weeks, 28/30 mice survived; 46% of these mice developed papillomas, but none developed carcinomas. A dioxane-treated vehicle control group was not reported. When applied twice weekly for 15 weeks as a 20% solution in benzene following initiation with 0.3% DMBA in benzene, 31/35 mice survived compared with 15/20 similarly initiated vehicle control mice. A benzene-treated vehicle control group was not reported. Of the survivors, 61% had papillomas, compared with 7% of the controls; 10% had carcinomas, while none were seen in the controls (Table 6-2).

## 6.3. MUTAGENICITY

In a modification of the preincubation procedure of the Salmonella assay, concentrations of 10-1000 µg/plate of reagent grade 2-chlorophenol dissolved in dimethylsulfoxide (control plate was solvent only) were negative when tested in strains TA100, TA1535, TA1537 and TA98, with and without S-9 metabolic activation (Haworth et al., 1983).

Acute oral doses of 75-300 mg/kg in CD-1 mice did not induce SCE or affect DNA synthesis (Borzelleca, 1983).

Oral administration of 130 mg/kg of 2-chlorophenol to Sprague-Dawley rats every other day for 1 week resulted in a 5-fold increase in chromatid deletions in bone marrow cells (Chung, 1978). After exposures of 2-3 weeks, there was complete inhibition of mitosis in the cells.

## 6.4. DEVELOPMENTAL TOXICITY

Pertinent data regarding the teratogenicity of 2-chlorophenol from either oral or inhalation exposure were not located in the available literature cited in Appendix A.

Table 6-2

The Incidence of Tumors in Initiated and Uninitiated Mice Treated With 2-Chlorophenol[a]

| Treatment | No. Mice (Survivors/Treated) | No. with papillomas | No. with carcinomas |
|---|---|---|---|
| Control (No treatment) | 25/25 | 0 | 0 |
| No initiator; 20% chlorophenol in dioxane[b] | 28/30 | 13 (46%) | 0 |
| 3% DMBA in benzene; 20% chlorophenol in benzene[b] | 31/35 | 19 (61%)[c] | 3 (10%) |

[a]From: Boutwell and Bosch (1959)

[b]Benzene and dioxane vehicle control groups were not reported

[c]$p > .05$ compared with uninitiated mice by Fisher Exact Test

## 6.5. OTHER REPRODUCTIVE EFFECTS

Exon and Koller (1982, 1983b, 1985) performed several studies in which reproductive parameters were measured in groups of 12-20 female Sprague-Dawley rats exposed to 2-chlorophenol (97-98% pure) in drinking water at concentrations of 0, 5, 50 and 500 ppm. In all cases, dams were exposed from 3 weeks of age through breeding at 90 days (to untreated males); exposure continued until 3 weeks postparturition. Untreated negative controls were also included. Reproductive parameters evaluated were percent conception, litter size, number of stillbirths, birth and weaning weights and survival to weaning. Records of body weights and hematologic data were taken on the pups at weaning.

Results indicated that percent conception was greater in all treated groups (9/12, 9/12, 12/14 for 5, 50 and 500 ppm treated groups, respectively) than in the untreated control group (8/12), but these results were not statistically significant. Litter sizes (live and stillborn) were significantly decreased and percent of stillbirths was significantly greater in the dams given 500 ppm 2-chlorophenol. Birth weights (live pups only), body weights at weaning and survival to weaning (exclusive of stillborn pups) were not affected by the treatment. Body weight gains of the dams also were not affected. There were no statistically significant treatment-related effects on hematologic parameters. No effects were seen at <50 ppm.

In addition, Exon and Koller (1985) studied the immune function in another group of pups whose exposure was continued postnatally. These pups were weaned at 3 weeks; exposure to 2-chlorophenol was continued for a subsequent 12-15 weeks. The immunological status of each animal was evaluated by testing its ability to elicit three major types of immune

responses (humoral immunity, cell-mediated immunity and macrophage function). Each immune function test was performed on four male and four female offspring from each treatment group. Body, liver, spleen and thymus weights were also recorded at the time of sacrifice.

Rats treated with the 2-chlorophenol did not respond differently than their corresponding controls in any of the immune functions evaluated in these investigations. None of the treatment groups demonstrated any statistically significant alterations in either whole body or individual organ weights.

## 6.6. SUMMARY

No information was located concerning the subchronic or chronic inhalation toxicity of 2-chlorophenol.

In rats dosed by gavage with 2-chlorophenol at 65 or 130 mg/kg for 3 weeks, there were reductions in weight gains and increases in liver weights when compared with controls (Chung, 1978). Hematological effects and hepatic degeneration were also noted at both treatment levels.

In reports of a subchronic drinking water study (Exon and Koller, 1983a, 1985) in which rats were exposed to 2-chlorophenol pre-, post-, and pre- and postnatally through the dams and then in the drinking water at levels of 0, 5, 50 and 500 ppm for $\leq$15 weeks, no immunological effects were observed at any level.

In a chronic drinking water study (Exon and Koller, 1985) in which rats were exposed to 2-chlorophenol prenatally through their dams and then in the drinking water at levels of 0, 5, 50 and 500 ppm for $\leq$2 years, hemoglobin levels, RBC counts and PCV were all significantly higher in the groups exposed to 500 ppm than in controls.

Chlorophenols reportedly irritate the skin and eyes, and the dusts irritate the respiratory tract (Freiter, 1981). In humans, 2-chlorophenol

causes severe burns, liver and kidney damage, narcosis and respiratory depression (Davis et al., 1959).

Oral $LD_{50}$s of 670, 346-670 and 440 mg/kg have been reported for the rat (Deichmann, 1943), the mouse (Borzelleca et al., 1985; Bubnov, 1969) and the blue fox (Bubnov, 1969), respectively. A single oral dose of 300 mg/kg caused kidney and liver damage in Gunn rats, which appeared to be more sensitive to the compound than Sprague-Dawley rats (Houser, 1983). An oral dose of 63 mg/kg caused motor impairment in CD-1 mice within 5 minutes, and a dose of 1 mg/kg produced behavioral change after 2 days (Borzelleca, 1983). A gavaged dose of 175 mg/kg resulted in 80% mortality in mice, with a statistically significant weight loss before death; hyperactivity was seen at lower doses (Kallman et al., 1982). In rats, a median lethal intraperitoneal dose of 230 mg/kg caused excited behavior and convulsions, with a decrease in body temperature (Farquharson et al., 1958).

No information on carcinogenicity of 2-chlorophenol from inhalation exposures could be located. A carcinogenicity-cocarcinogenicity drinking water study (Exon and Koller, 1985) in which rats were exposed to 2-chlorophenol in utero and then in drinking water at concentrations ≤500 ppm was negative for carcinogenicity after 2 years of exposure. In the same study, 2-chlorophenol appeared to promote the carcinogenicity of ENU, increasing the tumor incidence and decreasing the time-to-tumor in male rats. Dermal application of 2-chlorophenol following initiation by DMBA promoted the formation of skin tumors in mice (Boutwell and Bosch, 1959).

Up to 1000 µg/plate 2-chlorophenol was negative for mutagenicity in four strains of Salmonella typhimurium, with and without metabolic activation (Haworth et al., 1983). It did not induce SCEs or affect DNA synthesis in mice dosed with 75-300 mg/kg (Borzelleca, 1983). Chromatid deletions

were reported in rat bone marrow cells from treatment with 130 mg/kg every other day for 1 week (Chung, 1978).

No information on the teratogenicity of 2-chlorophenol could be located. Reproductive effects were reported in rats exposed to 2-chlorophenol in drinking water from weaning through breeding and lactation (Exon and Koller, 1982; 1985). Reduced litter sizes and increased number of stillbirths were seen in rats exposed to 500 ppm 2-chlorophenol; these effects were not seen at $\leq$50 ppm.

# 7. EXISTING GUIDELINES AND STANDARDS

## 7.1. HUMAN

A verified RfD for 2-chlorophenol of 0.005 mg/kg/day (U.S. EPA, 1988) was based upon reproductive effects in the rat study by Exon and Koller (1982).

The U.S. EPA (1980b) established an ambient water quality criterion of 0.1 µg/ℓ for 2-chlorophenol, based upon organoleptic data from a report by Dietz and Traud (1978). WHO (1984) suggested a maximum level of 1 µg/ℓ for 2-chlorophenol in drinking water based on organoleptic considerations.

A DWEL of 0.175 mg/ℓ was determined by the U.S. EPA (1986b), based on the subchronic rat reproduction study by Exon and Koller (1982).

## 7.2. AQUATIC

Guidelines and standards for the protection of aquatic life from exposure to 2-chlorophenol were not located in the available literature cited in Appendix A.

# 8. RISK ASSESSMENT

## 8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of 2-chlorophenol to animals or humans from inhalation exposure were not located in the available literature cited in Appendix A.

8.1.2. Oral. Exon and Koller (1985) reported negative results in a carcinogenicity study of 2-chlorophenol in Sprague-Dawley rats. Rats were exposed to the compound in utero through lactation, and then in drinking water, at concentrations of 0, 5, 50 or 500 ppm for <24 months.

In the same study (Exon and Koller, 1985), the ability of 2-chlorophenol to potentiate the carcinogenicity of ENU, a known carcinogen, was examined. Rat dams were exposed to precursors of ENU during gestation. Offspring were exposed to 2-chlorophenol prenatally through the dams, postnatally in the drinking water or both. In all groups of 2-chlorophenol-exposed males, tumor incidence increased and time-to-tumor decreased when compared with rats exposed only to ENU.

8.1.3. Other Routes. Boutwell and Bosch (1959) found that dermal application of 2-chlorophenol to mice following initiation by DMBA promoted the formation of skin tumors.

8.1.4. Weight of Evidence. The only available carcinogenicity study of 2-chlorophenol is a negative drinking water study in which rats were exposed pre-, post- or both pre- and postnatally; exposure was continued through 2 years with drinking water containing 2-chlorophenol <500 ppm (Exon and Koller, 1985).

The U.S. EPA (1987) recommended that 2-chlorophenol be classified in U.S. EPA Group D (U.S. EPA, 1986d) (i.e., cannot be classified as to carcinogenicity in humans). More recent data were not located that would change this assessment.

8.1.5. Quantitative Risk Estimates.

8.1.5.1. INHALATION -- Lack of data precludes estimation of carcinogenic potency from inhalation exposure to 2-chlorophenol.

8.1.5.2. ORAL -- The only carcinogenicity data located regarding 2-chlorophenol were the negative drinking water studies in rats by Exon and Koller (1983b, 1985). The carcinogenic potency from oral exposure to 2-chlorophenol cannot be quantitatively estimated.

8.2. SYSTEMIC TOXICITY

The designation "Rec." in the following sections refers to data records compiled in Section C.2. of Appendix C for the generation of dose/duration-response graphs.

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME (SUBCHRONIC) -- Pertinent data regarding the subchronic inhalation toxicity of 2-chlorophenol were not located in the available literature cited in Appendix A; therefore, derivation of an RfD for subchronic inhalation exposure is not possible.

8.2.1.2. CHRONIC -- Pertinent data regarding subchronic or chronic inhalation toxicity of 2-chlorophenol were not located in the available literature cited in Appendix A; therefore, derivation of an RfD for chronic inhalation exposure is not possible.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME (SUBCHRONIC) -- Data from sufficiently comprehensive subchronic oral studies of 2-chlorophenol in which adequate parameters of toxicity were measured were not available. Chung (1978) reported decreased weight gain, liver and hematologic effects in rats treated by gavage at 65 or 130 mg/kg/day for 3 weeks. No immunological

effects were found in rats exposed both pre- and postnatally to 2-chlorophenol in the drinking water at levels <500 ppm (NOEL) (Rec. #11) for 12-15 weeks (Exon and Koller, 1983a, 1985). In a reproductive study, Exon and Koller (1982) found a decrease in litter sizes and an increase in stillbirths in rats given drinking water containing 500 ppm of 2-chlorophenol (Rec. #2) from 3 weeks of age through breeding and lactation. These effects were not observed at the next lower dose of 50 ppm, a NOAEL (Rec. #1).

The reproductive NOAEL of 50 ppm was used to derive a chronic RfD of 0.005 mg/kg/day or 0.4 mg/day for a 70 kg human (U.S. EPA, 1986b). Because the subchronic toxicity data base for 2-chlorophenol was judged to be inadequate to calculate an RfD, the chronic oral RfD (Section 8.2.2.2.) was adopted as the subchronic oral RfD (U.S. EPA, 1987). As discussed in Section 8.2.2.2., confidence in the key study, data base and the RfD are low.

8.2.2.2. CHRONIC -- Exon and Koller (1985) reported hematologic effects in rats provided drinking water containing 2-chlorophenol at 500 ppm (LOAEL) (Rec. #3) for <24 months. These effects were not observed in rats exposed to 50 ppm (NOAEL) (Rec. #4). Although the protocol stated that a complete histopathological examination was performed, noncancer results were not presented. In studies by Exon and Koller (1982, 1985), reproductive effects were noted in female rats exposed to 500 ppm 2-chlorophenol in drinking water from 3 weeks of age through breeding and parturition (Rec. #2). These effects were not seen in rats exposed to 50 ppm (NOAEL) (Rec. #1). The data from the 1982 study were used by the Office of Drinking Water as the basis for an oral RfD (U.S. EPA, 1986b). Based on the assumption that a rat drinks the equivalent of 10% of its body weight in water daily, 500 ppm was transformed to an estimated dosage of 50 mg/kg/day (LOAEL), and 50 ppm to 5 mg/kg/day (NOAEL). A verified RfD of 0.005 mg/kg/day was

derived using an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 to protect unusually sensitive individuals and 10 for use of data from a subchronic study). The assumption that rats drink water equivalent to 10% of their weight daily differs from the suggested water consumption guidelines for rats (U.S. EPA, 1986c) where water consumption = 0.049 ℓ/day with a reference body weight of 0.35 kg. These factors would result in a transformation of the NOAEL of 50 ppm to 7 mg/kg/day.

U.S. EPA (1988) considered confidence in the key study low because only reproductive and hematological endpoints were evaluated. Confidence in the data base is low because no other adequate subchronic, chronic or developmental toxicity data were available. Confidence in the RfD was low because of low confidence in the key study and data base.

Confidence in the RfD is further eroded by reports of altered behavior in mice treated with 2-chlorophenol by gavage. In a 14-day exposure study, Kallman et al. (1982) reported hyperactivity in mice treated with 35 or 69 mg/kg/day from day 4 until treatment was terminated. Because 35 mg/kg/day was the lowest level tested, a NOAEL for this effect was not determined. In another study from this laboratory, Borzelleca (1983) reported that 63 mg/kg administered as a single dose was the $ED_{50}$ for motor impairment, which peaked in intensity at 5 minutes after treatment. Alterations in operant behavior occurred after as few as two gavage doses $\geq$1 mg/kg/day. The testing protocol was not presented, however, and these data cannot be adequately evaluated.

# 9. REPORTABLE QUANTITIES

## 9.1. BASED ON SYSTEMIC TOXICITY

The U.S. EPA (1983) determined that the toxicity data for 2-chlorophenol were inadequate for deriving an RQ. However, more recent data on reproductive effects in rats (Exon and Koller, 1982) were deemed appropriate for RQ derivation (U.S. EPA, 1987). The RQ was derived from a dose of 500 ppm 2-chlorophenol in drinking water provided to rat dams from 3 weeks of age through lactation, which resulted in significantly reduced litter sizes. The equivalent human dose was 12 mg/kg/day, based on a daily water consumption conversion factor of 0.049 ℓ/day for rats (U.S. EPA, 1986c) and a transformed animal dose of 70 mg/kg/day. Multiplying the human body weight of 70 kg by the transformed human dose results in a human MED of 840 mg/day, which corresponds to an $RV_d$ of 1.1. With an $RV_e$ of 8 for the observed fetotoxicity, a CS of 9 was derived, which corresponds to an RQ of 1000. More recent toxicity data for 2-chlorophenol were not located, and the RQ of 1000 previously derived by U.S. EPA (1987) is presented in Table 9-1.

## 9.2. BASED ON CARCINOGENICITY

As reviewed in Chapter 6, carcinogenicity data for 2-chlorophenol are limited to the negative drinking water studies in rats by Exon and Koller (1983b, 1985). The U.S. EPA (1987) recommended that 2-chlorophenol be classified in U.S. EPA Group D (U.S. EPA, 1986d) -- i.e., cannot be classified as to carcinogenicity in humans. Since potency factors cannot be derived for the chemical, a hazard ranking based on carcinogenicity is not possible for this compound.

TABLE 9-1

2-Chlorophenol

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

| | |
|---|---|
| Route: | oral in drinking water |
| Species/sex: | rat/female |
| Dose*: | 840 mg/day |
| Duration: | from 3 weeks of age through parturition |
| Effect: | decreased litter size; increased number of stillbirths |
| $RV_d$: | 1.1 |
| $RV_e$: | 8 |
| CS: | 9 |
| RQ: | 1000 |
| Reference: | Exon and Koller, 1982 |

*Equivalent human dose

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# APPENDIX A

## LITERATURE SEARCHED

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

These searches were conducted in May, 1988, 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. p. 2879-3816.

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. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1984. 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., Littleton, MA. 575 p.

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

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 P884-243906. SRI International, Menlo Park, CA.

NTP (National Toxicology Program). 1987. 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 ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. Menlo Park, 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 (U.S. International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publ. 1892, Washington, DC.

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

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

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

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. U.S. 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 B

Summary Table for 2-Chlorophenol

| | 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 | ID | ID |
| Oral exposure | | | | | |
| Subchronic | rat | 50 ppm (5 mg/kg/day) from 3 weeks of age through parturition | NOAEL for decreased litter size, increased stillbirths | 0.005 mg/kg/day | Exon and Koller, 1982 |
| Chronic | rat | 50 ppm (5 mg/kg/day) from 3 weeks of age through parturition | NOAEL for decreased litter size, increased stillbirths | 0.005 mg/kg/day | Exon and Koller, 1982 |
| Carcinogenicity | ID | ID | ID | ID | ID |
| REPORTABLE QUANTITIES | | | | | |
| Based on chronic toxicity: | | 1000 | | | Exon and Koller, 1982 |
| Based on carcinogenicity: | | ID | | | ID |

ID = Insufficient data

# APPENDIX C

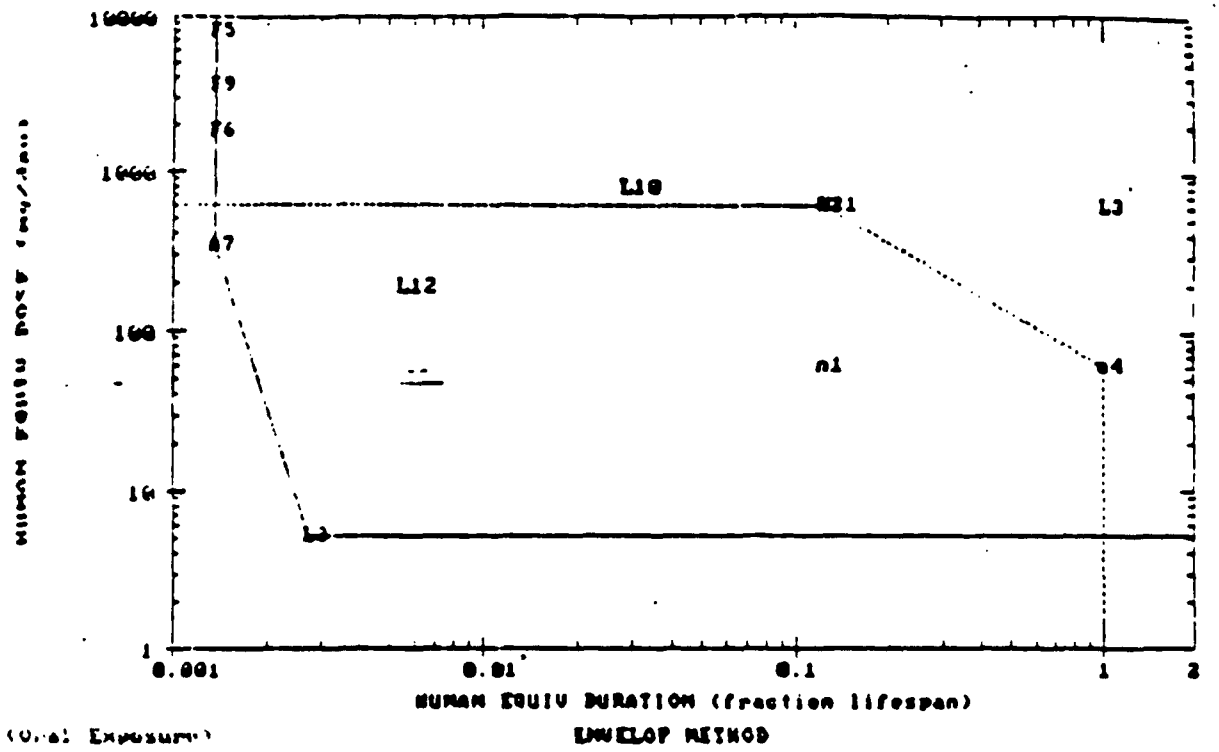
## DOSE/DURATION RESPONSE GRAPHS FOR EXPOSURE TO 2-CHLOROPHENOL

### C.1. DISCUSSION

A dose/duration-response graph for oral exposure to 2-chlorophenol generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1988) developed under contract to ECAO-Cinninnati is presented in Figure C-1. Data used to generate this graph are presented in Section C.2. In the generation of this figure, all responses are classified as adverse (FEL, AEL or LOAEL) or nonadverse (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 concentration. From this point, a line parallel to the duration axis is extended




Key: F = FEL
A = AEL
n = NOAEL
N = NOEL
Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-1

Dose/Duration - Response Graph for Oral Exposure
to 2-Chlorophenol: Envelope Method

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 effect 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.

Figure C-1 presents the dose-duration response graph generated by the envelope method. The adverse effects boundary is defined by five points, corresponding to an $LD_{50}$ in rats of 670 mg/kg (Deichmann, 1943) (Rec. #5), renal and hepatocellular necrosis in rats from an acute dose of 300 mg/kg (Houser, 1983) (Rec. #9), an oral $LD_{50}$ of 346 mg/kg in mice (Borzelleca et al., 1985) (Rec. #6), motor impairment in mice treated by gavage with a single dose of 63 mg/kg (Borzelleca, 1983) (Rec. #7) and a gavage dose of 1 mg/kg/day for 2 days, explained only as the lowest dose that caused behavioral effects in mice (Borzelleca, 1983) (Rec. #8). The no adverse effects boundary is defined by two points, representing no immunological effects observed in rats at dose levels <50 mg/kg (500 ppm in drinking water) administered prenatally and continued <15 weeks (Exon and Koller, 1983a, 1985) (Rec. #11), and the other representing a 2-year study by Exon and

Koller (1985) where no hematological effects were seen in rats at the 5 mg/kg dosage (50 ppm in drinking water) (Rec. #4). The region of contradiction is quite large and cannot be censored because of insufficient data.

C.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS

C.2.1. Inhalation Exposure. No inhalation toxicity data were located.

C.2.2. Oral Exposure.

Chemical Name: 2-Chlorophenol
CAS Number: 95-57-8
Document Title: Health and Environmental Effects Document on 2-Chlorophenol
Document Number: Pending
Document Date: Pending
Document Type: HEED

| | | | | |
|---|---|---|---|---|
| RECORD #1: | Species: | Rats | Dose: | 5.000 |
| | Sex: | Female | Duration Exposure: | 90.0 days |
| | Effect: | NOEL | Duration Observation: | 90.0 days |
| | Route: | Water | | |
| | Number Exposed: | 13 | | |
| | Number Responses: | 0 | | |
| | Type of Effect: | | | |
| | Site of Effect: | | | |
| | Severity Effect: | 8 | | |
| Comment: | 50 ppm (range 0, 5, 50, 500 ppm), assume water consumption factor of 0.1. Exposure from weaning through breeding, lactation. | | | |
| Citation: | Exon and Koller, 1982, 1985 | | | |

| | | | | |
|---|---|---|---|---|
| RECORD #2: | Species: | Rats | Dose: | 50.000 |
| | Sex: | Female | Duration Exposure: | 90.0 days |
| | Effect: | LOAEL | Duration Observation: | 90.0 days |
| | Route: | Water | | |
| | Number Exposed: | 13 | | |
| | Number Responses: | NR | | |
| | Type of Effect: | REPRO | | |
| | Site of Effect: | FETUS | | |
| | Severity Effect: | 8 | | |
| Comment: | 500 ppm (see previous record); effects were decreased litter size and increased numbers of stillborn. | | | |
| Citation: | Exon and Koller, 1982, 1985 | | | |

RECORD #3:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: | 50.000 |
| Sex: | Both | Duration Exposure: | 24.0 months |
| Effect: | LOAEL | Duration Observation: | 24.0 months |
| Route: | Water | | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | HEMAT |
| Site of Effect: | BLOOD |
| Severity Effect: | 1 |

Comment: 500 ppm (range 0, 5, 50, 500 ppm). Assumed water consumption factor of 0.1. No other noncancer endpoints evaluated.

Citation: Exon and Koller, 1985

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RECORD #4:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: | 5.000 |
| Sex: | Both | Duration Exposure; | 24.0 months |
| Effect: | NOEL | Duration Observation: | 24.0 months |
| Route: | Water | | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | 0 |
| Type of Effect: | |
| Site of Effect: | |
| Severity Effect: | 3 |

Comment: 50 ppm (see previous record).

Citation: Exon and Koller, 1985

---

RECORD #5:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: | 670.000 |
| Sex: | NS | Duration Exposure: | 1.0 days |
| Effect: | FEL | Duration Observation: | 1.0 days |
| Route: | Gavage | | |

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

Comment: $LD_{50}$ dose.

Citation: Deichmann, 1943

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RECORD #6:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: | 346.000 |
| Sex: | Both | Duration Exposure: | 1.0 days |
| Effect: | FEL | Duration Observation: | 14.0 days |
| Route: | Gavage | | |

| | |
|---|---|
| Number Exposed: | 20 |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: $LD_{50}$ dose.

Citation: Borzelleca et al., 1985

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RECORD #7:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: | 63.000 |
| Sex: | Both | Duration Exposure: | 1.0 days |
| Effect: | AEL | Duration Observation: | 14.0 days |
| Route: | Gavage | | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | MOTOR |
| Site of Effect: | MSKEL |
| Severity Effect: | 9 |

Comment: $ED_{50}$ dose for impaired motor function.

Citation: Borzelleca, 1983

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RECORD #8:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: | 1.000 |
| Sex: | NS | Duration Exposure: | 2.0 days |
| Effect: | LOAEL | Duration Observation: | 2.0 days |
| Route: | Gavage | | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | BEHAV |
| Site of Effect: | BODY |
| Severity Effect: | 7 |

Comment: Lowest dose producing behavioral changes after 2 days exposure

Citation: Borzelleca, 1983

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RECORD #9:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: | 300.000 |
| Sex: | NS | Duration Exposure: | 1.0 days |
| Effect: | FEL | Duration Observation: | 1.0 days |
| Route: | Oral, NOS | | |

| | | |
|---|---|---|
| Number Exposed: | NR | NR |
| Number Responses: | NR | NR |
| Type of Effect: | NECRO | NECRO |
| Site of Effect: | KIDNY | LIVER |
| Severity Effect: | 6 | 6 |

Comment: Metabolism study: centrilobular hepatic necrosis in 50% of rats; renal necrosis in 75% of rats.

Citation: Houser, 1983

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RECORD #10:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: | 65.000 |
| Sex: | NS | Duration Exposure: | 3.0 weeks |
| Effect: | LOAEL | Duration Observation: | 3.0 weeks |
| Route: | Oral, NOS | | |

| | | |
|---|---|---|
| Number Exposed: | NR | NR |
| Number Responses: | NR | NR |
| Type of Effect: | WGTDC | ATROP |
| Site of Effect: | BODY | LIVER |
| Severity Effect: | 4 | 4 |

Comment: Range 65 and 130 mg/kg/day

Citation: Chung, 1978

---

RECORD #11:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: | 50.000 |
| Sex: | Both | Duration Exposure: | 90.0 days |
| Effect: | NOEL | Duration Observation: | 90.0 days |
| Route: | Water | | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | 0 |
| Type of Effect: | |
| Site of Effect: | |
| Severity Effect: | 3 |

Comment: No immune effects seen at levels <500 ppm in drinking water (50 mg/kg/day); range 0, 5, 50, 500 ppm.

Citation: Exon and Koller, 1983a

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| | | | | |
|---|---|---|---|---|
| RECORD #12: | Species: | Mice | Dose: | 35.000 |
| | Sex: | NS | Duration Exposure: | 4.0 days |
| | Effect: | LOAEL | Duration Observation: | 4.0 days |
| | Route: | Gavage | | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | FUNS |
| Site of Effect: | BRAIN |
| Severity Effect: | 7 |

Comment: Hyperactivity that stopped when treatment ceased. Mortality occurred at 175 mg/kg/day.

Citation: Kallman et al., 1982

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NS = Not stated