**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

**DATE:** June 30, 2006

## ACTION MEMORANDUM

**SUBJECT:** Reassessment of One Exemption from the Requirement for Chlorobenzene (CAS Reg. No. 108-90-7)

**FROM:** Pauline Wagner, Chief Pauline Wagner 7/3/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

**TO:** Lois A. Rossi, Director
Registration Division (7505P)

## I. FQPA REASSESSMENT ACTION

**Action:** Reassessment of one exemption from the requirement of a tolerance. The reassessment decision is to maintain the exemption "as-is".

**Chemicals:** Chlorobenzene (CAS Reg. No. 108-90-7)

**Table 1. Exemption from the Requirement of a Tolerance**

| CFR Citation | | | | CAS Reg. No. 9CI Name |
|---|---|---|---|---|
| **40 CFR §** | **Inert Ingredients** | **Limits** | **Uses** | |
| 180.920* | Chlorobenzene | Contains not more than 1% impurities. Not for use after edible parts of the plant begin to form. Do not graze livestock in treated areas within 48 hours after application | Solvent, cosolvent | 108-90-7<br>Benzene, chloro- |

*Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

**Pesticide Use:** This chemical is used as a solvent, cosolvent in pesticide formulations applied to growing crops only. Its use limitations include: contains not more than 1% impurities; not for use after edible parts of the plant begin to form; and do not graze livestock in treated areas within 48 hours after application.

**List Reclassification Determination:** The current List Classification for chlorobenzene is 1. Because EPA has determined that there is a reasonable certainty of no harm to any population subgroup will result from aggregate exposure to chlorobenzene when used as an inert ingredient in pesticide formulations, the List Classification for this chlorobenzene will change from List 1 to List 4B.

## II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the exemption from the requirement of a tolerance for chlorobenzene (CAS Reg. No. 108-90-7), as well as the List reclassification determination described above.

I consider the one exemption from the requirement of a tolerance established in 40 CFR 180.920 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois Rossi

Lois A. Rossi, Director
Registration Division

July 7, 2006

Date

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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**MEMORANDUM**

SUBJECT: Reassessment of One Exemption from the Requirement of a Tolerance for Chlorobenzene (CAS Reg. No. 108-90-7)

FROM: Keri Grinstead
Inert Ingredient Assessment Branch
Registration Division (7505P)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505P)

## Background

Attached is the science assessment for chlorobenzene. Chlorobenzene has one exemption from the requirement of a tolerance under 40 CFR 180.920 for use as a solvent or cosolvent, containing not more than 1% impurities, in pesticide formulations applied to growing crops only before the edible parts of the plant begin to form and livestock are not grazed in treated areas within 48 hours of application. The exact CFR citation with limitations is listed in Table 1. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of chlorobenzene. The purpose of this document is to reassess the existing exemption from the requirement of a tolerance for residues of chlorobenzene when used as an inert ingredient in pesticide formulations as required under the Food Quality Protection Act (FQPA).

## Executive Summary

This report evaluates the existing exemption from the requirement of a tolerance under 40 CFR 180.920 for chlorobenzene (CAS Reg. No. 108-90-7) (containing not more than 1% impurities) when used as an inert ingredient in pesticide formulations applied to growing crops only before the edible parts of the plant begin to form and livestock are not grazed in treated areas within 48 hours of application.

Chlorobenzene is of low acute toxicity *via* the oral, dermal, and inhalation routes of exposure, but it is listed as a skin and mucous membrane irritant. The liver and kidney are target organs in rats, mice, rabbits, and dogs following subchronic and/or chronic exposure *via* oral and/or inhalation routes of exposure. The nervous system and bone

marrow have also been shown to be target tissues at high-dose levels via oral and inhalation exposure. No developmental or reproductive toxicity is observed following inhalation exposure. Predominantly negative results were found with chlorobenzene in short-term *in vitro* and *in vivo* genetic toxicity testing. Chlorobenzene is classified as a Group D carcinogen; not classifiable as to human carcinogenicity (USEPA).

Based on the physical/chemical properties of chlorobenzene, as well as the application restrictions of pesticide products containing this chemical, dietary (food and drinking water) and residential (inhalation and dermal) exposures of concern are unlikely from chlorobenzene when used as an inert ingredient in pesticide products applied to growing crops only before the edible parts of the plant begin to form.

Ecotox studies indicate that Chlorobenzene is moderately toxic to fish and slightly toxic to invertebrates on an acute basis. Chlorobenzene is moderately toxic to mammals on an acute oral basis. Quantitative risks estimates can not be determined for aquatic and terrestrial organisms.

Taking into consideration all available information, EPA has determined there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to chlorobenzene when used as an inert ingredient in pesticide formulations when considering the dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the one exemption from the requirement of a tolerance established for residues of chlorobenzene be maintained and considered reassessed as safe under section 408(q) of the FFDCA.

## I. Introduction

Chlorobenzene is a colorless, flammable liquid which readily evaporates into air. It does not occur naturally in the environment.

Chlorobenzene production in the United States has declined by more than 60% from its peak in 1960. Now chlorobenzene is used as a solvent for some pesticide formulations, to degrease automobile parts, and as a chemical intermediate to make several other chemicals.

This report provides a qualitative assessment for chlorobenzene, a chemical used as an inert ingredient in pesticide products. Chlorobenzene is exempted from the requirement of a tolerance under 40 CFR 180.920 when used as a solvent or cosolvent, containing not more than 1% impurities in pesticide formulations applied to growing crops only, before the edible parts of the plant begin to form, and livestock are not grazed in treated areas within 48 hours of application.

## II. Use Information

### A. Pesticide Uses

**Table 1. Pesticide Uses**

| CFR Citation | | | | CAS Reg. No. 9CI Name |
|---|---|---|---|---|
| **40 CFR §** | **Inert Ingredients** | **Limits** | **Uses** | |
| 180.920* | Chlorobenzene | Contains not more than 1% impurities. Not for use after edible parts of the plant begin to form. Do not graze livestock in treated areas within 48 hours after application | Solvent, cosolvent | 108-90-7<br>Benzene, chloro- |

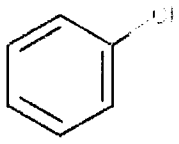
*Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

### B. Other Uses

According to the Agency's Chlorobenzene Chemical Fact Sheet: Support Document (USEPA 1995), chlorobenzene is used as a chemical intermediate in the production of ortho- and para-nitrochlorobenzenes. These chemicals are used as intermediates in the manufacture of rubber chemicals, agricultural chemicals, antioxidants, and dyes and pigments. Chlorobenzene has also been used in the production of phenol; the insecticide DDT; and aniline . Chlorobenzene is also used as a solvent in the manufacture of adhesives, paints, polishes, waxes, diisocyanates, pharmaceuticals, and natural rubber. Other applications include use as a fiber swelling agent and dye carrier in textile processing; as a tar and grease remover in cleaning and degreasing operations; as a solvent in surface coating and surface coating removers; and as a heat-transfer medium.

## III. Physical and Chemical Properties

**Table 2. Physical and Chemical Properties**

| | Chlorobenzene (CAS Reg. No. 108-90-7) | |
|---|---|---|
| Parameter | Value | Source |
| Structure |  | ChemID[1] |

| | Chlorobenzene (CAS Reg. No. 108-90-7) | |
|---|---|---|
| Parameter | Value | Source |
| Molecular formula | $C_6H_5Cl$ | |
| Molecular Wt. | 112.56 | ATSDR[2] 1990 (as cited in USEPA 1995) |
| Physical State | Colorless Liquid | ATSDR 1990 (as cited in USEPA 1995) |
| Melting Point | -45.6° C | ATSDR 1990 (as cited in USEPA 1995) |
| Boiling Point | 132° C | ATSDR 1990 (as cited in USEPA 1995) |
| Water solubility | 466.3 mg/L(25° C) | USEPA 1988 |
| Density (air=1) | 1.1058 @ 20° C | ATSDR 1990 (as cited in USEPA 1995) |
| $K_{oc}$ | 126 | USEPA 1988 |
| $K_{ow}$ | 692 (experimental) | USEPA 1988 |
| Vapor Pressure | 11.7 mm Hg (25° C) | USEPA 1988 |
| Reactivity | Flammable | Keith and Walters 1985 (as cited in USEPA 1995) |
| Flash Point | 29.4° C | ATSDR 1990 (as cited in USEPA 1995) |
| Henry's Law Constant | 3.58 x $10^{-3}$ atm-$m^3$/mol | ATSDR 1990 (as cited in USEPA 1995) |
| log P (Octanol-water) | 2.84 Experimental | ChemID, USEPA 1988 |
| Fish Bioconcentration factor | 45.7 (rainbow trout), 446.7 (fathead minnow) | USEPA, 1988 |

[1]ChemIDplus Advanced on TOXNET (http://www.toxnet.nlm.nih.gov/index.html)
[2]Agency for Toxic Substances and Disease Registry

## IV. Hazard Assessment

### A. Hazard Profile

A large body of data on chlorobenzene exists in the literature. The data and information presented in this evaluation of chlorobenzene is primarily from the following documents: Agency for Toxic Substances and Disease Registry (ATSDR 1990) Toxicological Profile for Chlorobenzene, IRIS database (2004), Environmental Health Criteria 128 (1991) by IPCS, Hazardous Substances Data Bank (HSDB), 2004, and a USEPA Chlorobenzene Chemical Fact Sheet: Support Document (USEPA 1995).

The available toxicity database for chlorobenzene consists of acute, subchronic, chronic, carcinogenicity, mutagenicity, developmental, and reproductive studies. No relevant neurotoxicity data have been identified for chlorobenzene, although chlorobenzene is recognized as a sedative from acute studies.

Chlorobenzene is of low acute toxicity *via* the oral, dermal, and inhalation routes of exposure, but it is listed as a skin and mucous membrane irritant. The liver and kidney are target organs in rats, mice, rabbits, and dogs following subchronic and/or chronic exposure *via* oral and/or inhalation routes of exposure. The nervous system and bone marrow have also been shown to be target tissues at high-dose levels via oral and inhalation exposure. No developmental or reproductive toxicity is observed following inhalation exposure. Predominantly negative results were found with chlorobenzene in short-term *in vitro* and *in vivo* genetic toxicity testing. Chlorobenzene is classified as a Group D carcinogen; not classifiable as to human carcinogenicity potential (USEPA 1995).

### B. Metabolism and Pharmacokinetics

The toxicokinetic profile of chlorobenzene is that of a lipid-soluble molecule that is readily absorbed in the gastrointestinal tract, has affinity for adipose tissue, but is not stored in tissues because of pulmonary exhalation and a relatively efficient transformation to oxidized metabolites by liver enzymes. One pathway of transformation, conversion of chlorobenzene to p-chlorophenol *via* the 3,4-arene oxide intermediate, may be associated with reactive compounds that produce toxicity to liver and kidney cells, but the precise identities of these reactants are not known.

Chlorobenzene is metabolized to an arene oxide as the first stage intermediate, the major urinary metabolites being 4-chlorocatechol (and conjugates) and 4-chloro-phenylmercapturic acid. The minor metabolites are three isomeric chlorophenols (2-, 3-, or 4-chlorophenol) and 3-chlorocatechol (IPCS, 1991). From inhalation studies in rats, it is known that exhalation of unchanged chlorobenzene is also a route of excretion (Sullivan, *et al.*, 1983). Azouz, *et al.* (1952) showed that 24% to 32% of an orally administered dose is exhaled in rabbits. Thus, the major portion of absorbed chlorobenzene that is not measured as urinary metabolites is most likely accounted for by exhalation.

Male Sprague-Dawley rats were exposed *via* inhalation to $^{14}$C-chlorobenzene at 100, 400, or 700 ppm (0.460, 1.840, or 3.220 mg/L) for 8 hours/day. The largest amounts of radiolabel were found in adipose tissue, followed by the liver and kidney. The radiolabel measurements did not distinguish between unchanged chlorobenzene and its metabolites (Sullivan, *et al.*, 1983).

### C. Toxicological Data (See Attachment 1 for toxicity study summaries)

Acute Toxicity

Chlorobenzene is not acutely toxic *via* the oral, dermal, or inhalation routes of exposure, as indicated in Table 3. In experimental animals, the manifestations of acute toxicity of chlorobenzene are consistent with irritant effects on mucous membranes (hyperemia, salivation, and lacrimation, submucosal hemorrhage of stomach lining) and anesthetic effects on the central nervous system (ataxia, decreased locomotor activity,

paralysis, and labored breathing). Death from ingestion or inhalation of large doses is due to severe respiratory depression (Willhite and Book, 1990; Hellman, 1993).

Deaths occurred within 2 to 3 days following a single gavage exposure to 4000 mg/kg (in corn oil) in Fischer 344 rats of both sexes and in B6C3F1 mice after a single gavage exposure to 1000 mg/kg (male) or 2000 mg/kg (female) (Kluwe, *et al.*, 1985). Acute oral exposure (rats and mice) results in hyperpnoea, ataxia, labored breathing, prostration, and death from respiratory paralysis. Effects on porphyrin metabolism occurred following acute gavage exposure to 1140 mg/kg/day for 5 days (Rimington and Ziegler, 1963). Acute inhalation exposure causes sensory irritation of the respiratory system after several minutes and narcosis and central nervous system depression, which can result in death, on longer exposure. Inhalation exposure of rabbits to 5 mg/L chlorobenzene (1090 ppm) or greater for 2 hours produces muscle spasms followed by narcosis (Rosenbaum, *et al.*, 1947). Respiratory irritation, as evidenced by a reduction of the respiratory rate by 50% ($RD_{50}$), is observed in Swiss $OF_1$ mice following inhalation exposure to 4796 mg/m$^3$ (1054 ppm) for 5 minutes (De Ceaurriz, *et al.*, 1981). Acute dermal toxicity is not observed. Topical application to the skin of rabbits caused slight reddening. Severe eye irritation with no permanent damage occurs in rabbits following direct application to the eye.

**Table 3. Summary of Acute Toxicity Data for Chlorobenzene**

| Parameter | Toxicity Value | Reference |
|---|---|---|
| Oral $LD_{50}$ | Rat 2.29 g/kg<br>Mouse 1.44 g/kg<br>Rabbit 2.25 g/kg<br>Guinea pig 5.06 g/kg | Technical Report Series No. 261; NIH Pub. No. 86-2517 (1985) |
| Oral $LD_{50}$ | Rat 1540 mg/kg<br>Mouse <1000 mg/kg | Kluwe, *et al.*, 1985; Monsanto, 1989; NTP, 1985 |
| Dermal $LD_{50}$ | Rabbit >7940 mg/kg] | TSCATS (Monsanto) |
| Inhalation $LC_{50}$<br>Inhalation $LC_{50}$ | male rat 13490 mg/m$^3$; 2965 ppm<br>female mouse 8581 mg/m$^3$; 1886 ppm | Cited in IPCS 1991<br>Bonnet, *et al.*, 1979, 1982 |
| Eye Irritation, rabbit | Pain; transient conjunctival irritation, clears within 48 hours | Patty's Industrial Hyg. Tox. 4$^{th}$ed. (1993-94) |
| Skin Irritation, rabbit | Slight reddening | Patty's Industrial Hyg. Tox. . 4$^{th}$ed Vol. 2, 1994 |

Subchronic Toxicity (See Attachment 1 for Toxicity Study Summaries)

*Oral Exposure*

**RAT:** In a subchronic oral toxicity study, Fischer 344 rats (10/sex/dose) were administered chlorobenzene *via* gavage at dose levels of 0, 60, 125, 250, 500, or 750 mg/kg/day, 5 days/week for 13 weeks. There was a dose-related increase in mortality in both sexes at dose levels of 500 (males 40%/females 30%) and 750 (males 90%/females 80%) mg/kg/day and an increased incidence of clinical signs (rough coat and lethargy). There was a dose-related decrease in body-weight gain and food consumption in both sexes. The liver (increase in liver weight, increased incidence of hepatocytic degeneration and necrosis) and kidney (degeneration or focal necrosis of the proximal tubules) are target organs. Other findings include thymic necrosis, lymphoid or myeloid

depletion of bone marrow, spleen, or thymus. At the two highest dose levels, significant increases in serum glutamic oxaloacetic transaminase (SGOT, gamma-glutamyl transpeptidase (GGTP), serum glutamin pyruvic transaminase (SGPT), and alkaline phosphatase (AP) were observed, mainly in females. Also at these two dose levels, increased urine volumes were observed in both sexes, which were accompanied by increased excretion of coproporphyrin, and elevated liver protoporphyrin levels. NOAEL=60 mg/kg/day, LOAEL=125 mg/kg/day (NTP, 1985; Kluwe, *et al.*, 1985).

**MOUSE:** In a subchronic oral toxicity study, B6C3F1 mice (10/sex/dose) were administered chlorobenzene (>99% purity) by gavage at dose levels of 0, 60, 125, 250, 500, or 750 mg/kg/day, 5 days/week for 13 weeks. Dose-related mortality was observed in both sexes. Deaths occurred at 250 (males 60%/females 40%), 500 (males 100%/females 70%), and 750 (both sexes 100%) mg/kg/day. Clinical signs (rough coat and lethargy) were observed at the three highest dose levels. Decreased body-weight gains were observed in both sexes of mice at 125 (males 27%/females 3%) and 250 (males 74%/females 50%) mg/kg/day and in females at 500 (63%) mg/kg/day. Food consumption, hematology parameters, and clinical chemistry parameters were comparable among the groups. Increased urine volumes were observed in both sexes at the 250 mg/kg/day and in females at 500 mg/kg/day. Urinary levels of coproporphyrin were increased in females at these two dose levels. Liver findings included increased liver weight and foci of hepatocytic necrosis/degenerative changes in these centrilobular hepatocytes. In the kidney, vacuolar degeneration and focal necrosis of the proximal tubules was observed at dose levels of 250 mg/kg/day and above. Other findings include thymic necrosis, lymphoid or myeloid depletion of bone marrow, spleen, or thymus. NOAEL=60 mg/kg/day, LOAEL=125 mg/kg/day (NTP, 1985; Kluwe, *et al.*, 1985).

**DOG:** Beagle dogs were administered chlorobenzene *via* capsule at doses of 0, 27.25, 54.5, or 272.5 mg/kg/day, 5 days/week, for 13 weeks. Four of the eight dogs at the high-dose level died within 3 weeks. Body-weight loss, changes in hematology (increase in immature leukocytes), clinical chemistry (decreased glucose, increased serum ALT and alkaline phosphatase, increased plasma total bilirubin and total cholesterol), and urine analysis and pathological changes in the liver (bile duct hyperplasia, cytologic alterations, leukocyte infiltration, centrilobular degeneration), kidney, gastrointestinal mucosa, and hematopoietic tissue were observed at this dose level also. At 54.5 mg/kg/day, slight bile duct proliferation, cytologic alterations, and leukocyte infiltration of the stroma of the liver were observed. The NOAEL was given as 27.25 mg/kg/day and the LOAEL as 54.5 mg/kg/day (IRIS 1993). NOTE: The available data on rats and mice indicate little potential for progressive liver toxicity with continued (long-term) exposure to chlorobenzene. Due to the minimal toxicity observed at the 54.5 mg/kg/day dose level in the subchronic dog study, this dose can be considered a LOEL (lowest observed effect level) rather than a LOAEL (lowest observed adverse effect level). This determination is consistent with the International Programme on Chemical Safety, Environmental Health Criteria 128 (1991). Therefore, the LOAEL would be considered 272.5 mg/kg/day.

*Inhalation Exposure*

**RAT:** Rats exposed to 0, 341, or 1138 mg/m$^3$ (0, 75, or 251 ppm) for 7 hours/day, 5 days/week for 24 weeks displayed a dose- and time-related increase in reticulocyte count, treatment-related congestion of the liver (males), and focal hemorrhages and foci of the perivascular lymphocytes. NOAEL<0.341 mg/L, LOAEL=0.341 mg/L (Dilley, 1977, cited in ATSDR 1990). The NOAEL reported for rats following repeated exposure *via* inhalation (32 exposures of 7 hours/day over 44 days) of 0.910 mg/L was approximately 910 mg/m$^3$ (Irish, 1963, cited in IPCS, 1991)

**MOUSE:** Following inhalation exposure at 1250 mg/m$^3$ for 7 hours/day, over 3 weeks, fatty degeneration of the liver and changes in blood counts indicative of bone marrow damage were reported in Swiss white mice (cited in IPCS, 1991 and ATSDR 1990; NOTE: compound purity unknown and detailed experimental data not available). The LOAEL was determined to be 1250 mg/m$^3$.

**RABBIT:** Rabbits exposed to 0, 341, or 1138 mg/m$^3$ (0, 75, or 251 ppm) for 7 hours/day, 5 days/week for 24 weeks displayed treatment-related congestion of the liver (males) and focal hemorrhages and foci of perivascular lymphocytes. Treatment-related congestion of the kidneys was noted at both dose levels in rabbits sacrificed at 5 weeks. NOAEL<0.341 mg/L, LOAEL 0.341 mg/L (Dilley, 1977; cited in ATSDR 1990).

**DOG:** Dogs (6/sex/group) were exposed to 0, 780, 1570, or 2080 mg/m$^3$ of chlorobenzene for 6 hours/day, 5 days/week, for 6 months. At the two higher concentrations, males displayed decreased adrenal weights. There was an increased incidence of emesis in both sexes and an increased frequency of abnormal stools in treated females. The NOAEL is 780 mg/m$^3$ (Hellman, 1993).

Chronic Oral Toxicity

**RAT:** Fischer 344 rats (50/sex/dose) were administered chlorobenzene (99%) *via* gavage (corn oil) at dose levels of 0, 60, or 120 mg/kg/day (5 days/week) for 103 weeks (Kluwe, *et al.*, 1985; NTP 1985). The animals were weighed regularly, observed for mortality, and at sacrifice, subjected to complete necropsies and histopathological examination. There were no overt clinical signs of toxicity, and body weights were comparable among the groups for both sexes. There was a significant decrease in the survival of the males at 120 mg/kg/day. NTP concluded that the evidence of mild hepatocellular necrosis was equivocal, and the absence of marked toxic lesions did not support a causal relationship with chlorobenzene. Since histopathological examination of the livers, kidney, and hematopoietic tissues did not reveal signs of organ toxicity, there is little potential for chlorobenzene to produce progressive non-neoplastic toxicity more severe than that observed in the subchronic oral toxicity study. NOAEL=60 mg/kg/day; (NTP, 1985).

**MOUSE:** B6C3F1 mice (50/sex/dose) were administered chlorobenzene (99%) by gavage (corn oil) at dose levels of 0, 30, or 60 mg/kg/day (males) and 0, 60, or 120

mg/kg/day (females), 5 days/week, for 103 weeks. The animals were weighed regularly, observed for mortality, and at sacrifice, subjected to complete necropsies and histopathological examination. There were no overt clinical signs of toxicity, and body weights were comparable among the groups for both sexes. No treatment-related adverse effects were observed in either sex. NOAEL= 60 mg/kg/day, neither sex displayed a tumorigenic response (Kluwe, *et al.*, 1985; NTP 1985).

Neurotoxicity

According to the Agency's Chlorobenzene Fact Sheet: Supporting Document (USEPA 1995), animals exhibited narcosis and muscle spasms following acute exposure to high concentrations, and neuromuscular disorders following continuous exposure to low concentrations. Rats and mice exposed to chlorobenzene concentrations of 5,850 ppm for 30 minutes by inhalation exhibited central nervous system depression, whereas animals exposed to 2,990 ppm were not sedated. Narcosis was observed in animals inhaling 1,200 ppm chlorobenzene for two hours, but narcosis was not observed in animals inhaling 220-660 ppm. Rabbits exposed by inhalation to ≥1,090 ppm chlorobenzene for two hours exhibited muscle spasms followed by narcosis.

Mutagenicity

Chlorobenzene was negative in the Ames test (NTP, 1985; *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1538) at doses of 3.3 to 333 μg/plate in DMSO with and without metabolic activation. Chlorobenzene did not induce specific locus forward mutations in mouse lymphoma L5178Y cells, either with or without metabolic activation (Monsanto, 1976), but at high-dose levels, was positive in 2 of 4 trials without S-9 and in 2 trials with S-9 [McGregor, *et al.*, 1988]. DNA damage was not induced in the reverse mutation assay in *E. Coli* strains WP2 uvr A+ rec A+ or WP100 uvr A- rec A- or S. Typhimurium strains TA1978 uvr B+ or TA1538 uvr B- (cited in IRIS; Monsanto, 1976; Lawlor, et al.; Simmon, et al.). Results of a chromosomal aberration assay in Chinese hamster ovary cells was negative (Sofuni, T, *et al.* 1985), but positive results were observed in the sister chromatid exchange (SCE) assay in Chinese hamster ovary cells (Loveday, *et al.* 1989). Results of *in vivo* cytogenicity tests in mice were negative (Shelby, *et al.*, 1993, 1995). Chlorobenzene induced reciprocal recombination in *Saccharomyces cerevisiae* strain D3; negative without metabolic activation in strain D4 (Simmons, *et al.*, 1979, Monsanto, 1976).

Carcinogenicity

**RAT:** Chlorobenzene was administered to F344/N rats (50/sex/group) at dose levels of 0 (corn oil), 60, or 120 mg/kg/day, 5 times/week for 103 weeks. At the high-dose level, male rats displayed a significant increase in the incidence of benign neoplastic liver nodules [untreated control (4/50), vehicle control (2/50), low dose (4/49), high dose (8/49)], which were deemed an equivocal response by the NTP. Female rats did not show a tumorigenic response (NTP, 1985).

**MOUSE:** Chlorobenzene was administered to B6C3F1 mice (50/sex/group) at dose levels of 0 (corn oil), 30 (males), 60 (both sexes), or 120 (females) mg/kg/day, 5 times/week for 103 weeks. There was no increase in the incidence of any tumor type in either sex (NTP, 1985).

In the two-year bioassays in rats and mice, chlorobenzene induced benign liver tumors (hepatocellular neoplastic nodules) in male rats but was without tumorigenic effects in female rats and male and female mice. The carcinogenicity of chlorobenzene is classified by the Agency as Group D, not classifiable as to human carcinogenicity, based on this limited and equivocal evidence of carcinogenicity in experimental animals and the marginal evidence of genotoxicity.

Developmental Toxicity

**RAT**: Pregnant Fischer 344 rats [32-33/group] exposed *via* inhalation to chlorobenzene at dose levels of 0, 75, 210, or 590 ppm (0, 0.341, 0.955, or 2.684 mg/L) for 6 hours/day on days 6 through 15 of gestation displayed a decrease in maternal body-weight gain and food consumption and increased absolute and relative maternal liver weight at 590 ppm. Maternal mortality, mean litter size, resorptions/implantations, fetal sex ratio, and body measurements, and incidence of major malformations were comparable among the groups. There was no convincing evidence of embryotoxic, fetotoxic, or teratogenic effects. Developmental NOAEL=590 ppm (2.684 mg/L), the highest dose tested. Maternal NOAEL=210 ppm (0.955 mg/L) [John, et al 1984].

**RABBIT:** Pregnant New Zealand white rabbits (30 pregnant rabbits/dose) were exposed *via* inhalation to chlorobenzene at dose levels of 0, 0.341, 0.955, or 2.684 mg/L (0, 75, 210, or 590 ppm) for 6 hours/day on days 6 through 18 of gestation. The developmental NOAEL was 2.684 mg/L. The maternal NOAEL was 0.341 mg/L and LOAEL was 2.684 mg/L. In a second study, Pregnant New Zealand white rabbits were exposed *via* inhalation to chlorobenzene at dose levels of 0, 0.045, 0.136, 0.341, or 2.684 mg/L (0, 10, 30, 75, or 590 ppm) for 6 hours/day on days 6 through 15 of gestation. The developmental NOAEL was 2.684 mg/L. The maternal NOAEL and LOAEL were 0.341 and 2.684 mg/L, respectively [John, *et al.*, 1984].

Reproductive Toxicity

**RAT:** In a 2-generation reproduction study, $F_0$ Sprague-Dawley CD rats [30/sex/group] were administered chlorobenzene *via* inhalation (whole body) at dose levels of 50, 150, or 450 ppm (0, 227.5, 682.5, or 2047.5 mg/m$^3$) for 6 hours/day, 7 days/week for 10 weeks prior to mating. Exposure to females continued through gestation and lactation, except from day 20 of gestation through day 4 of lactation. Some of the prodigy ($F_1$ generation) were continued on the same concentration as the parents and mated to non-siblings. Prodigy (F2 generation) were produced under the same regimen as the previous generation. In $F_1$ litters, pup and litter survival were comparable among the groups. In F2 litters, a slight decrease in pup survival index was observed at the highest dose level, which was attributed to excessive mortality in two high-dose

litters. There were no treatment-related adverse effects on mortality, body-weight gain, food consumption, clinical observations, reproductive performance, mating, or fertility of $F_0$ and $F_1$ adults, or mortality and growth of $F_1$ and F2 pups. Increased relative liver weights were observed in adult males (mid- and high-dose for $F_0$; all dose levels for $F_1$). $F_0$ and $F_1$ adults displayed hepatocellular hypertrophy and degenerative and inflammatory lesions in the kidney. A slight increase was observed in the incidence of bilateral degeneration of the germinal epithelium of the testes in the high-dose males ($F_0$ and $F_1$ generations) and the $F_1$ mid-dose males. The significance of this finding is unclear since the mean mating, pregnancy, and male fertility indices for both $F_0$ and $F_1$ generations were comparable for all groups, and the incidences of testicular lesions were identical in the $F_1$ and F2 animals. It is to be noted that the study did not provide histopathological data on other organs related to reproductive functions; *i.e.*, epididymides, vas deferens, accessory sex glands, pituitary. There was evidence of hepatotoxicity [hypertrophy and increased liver weight] and nephrotoxicity (tubular dilatation with eosinophilic material, interstitial nephritis and foci of regenerative epithelium) in male rats in the $F_0$ and $F_1$ generations. The NOAEL for reproductive toxicity is considered to be 450 ppm (2.0475 mg/L, the highest dose tested). The NOAEL for systemic toxicity is considered to be 50 ppm (0.2275 mg/L), based on increased liver weight, hepatocellular hypertrophy, and degenerative and inflammatory lesions in the kidney in males [cited in IRIS; Nair, *et al.* (1987)].

### D. Special Consideration for Infants and Children

Chlorobenzene is of low toxicity. A reproductive toxicity study shows no treatment-related adverse effects on mortality, body-weight gain, clinical observations, reproductive performance, fertility, gestation, lactation, or pup growth and survival following chlorobenzene exposure *via* inhalation. In the developmental toxicity studies in rats and rabbits, no compound-related effects were observed in the offspring, although maternal toxicity was demonstrated in both species.

Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to chlorobenzene when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

## V. Environmental Fate Characterization/Drinking Water Considerations

According to the Agency's Chlorobenzene Fact Sheet: Support Document (CAS No. 108-90-7) [USEPA 1995]:

Chlorobenzene is volatile (vapor pressure, 11.7 mm Hg) and slightly soluble in water (466.3 mg/L). Evaporation is an important transport processes for the chemical from water and soil. Chlorobenzene evaporated from an unaerated aqueous solution at the rate of 99% in 72 hours. The chemical may also adsorb moderately onto organic sediments ($K_{OC}$ of 126).

If released to moist soil, most of the chlorobenzene should volatilize to the atmosphere; if released to sandy soil, the chemical is mobile and is expected to leach into groundwater (due to its low Koc); it will biodegrade very slowly or not at all.

**Air** — One source estimated the half-life of chlorobenzene in air to be about 9 days; another source estimated the half-life to be 20 to 40 hours under simulated atmospheric conditions. The predominant removal mechanism for chlorobenzene in the atmosphere is the reaction with photochemically generated hydroxyl radicals. Chlorobenzene absorbs light in the 290-310 nm region, suggesting photolysis as an additional, but slow, mechanism of degradation, resulting in the production of monochlorobiphenyl. In the atmosphere, photolysis would occur over the course of a month.

**Water** — The main fate processes for chlorobenzene in water are vaporization and biodegradation. Reported half-lives of chlorobenzene in water are 0.3 days in a river; about 1 to 12 hours in a rapidly flowing stream; and 75 days in sediment in an estuarine river under near natural conditions. Biodegradation will occur in warm weather, particularly with acclimated microorganisms, proceeding more rapidly in fresh water than in estuarine and marine systems. The biodegradation half-life of chlorobenzene was 150 days in river water and 75 days in sediment. Direct photolysis is not a significant process for the removal of chlorobenzene from surface water (half-life, ~170 years in summer at 40 latitude).

**Soil** — Evaporation is expected to be the main removal process for chlorobenzene from the soil surface. Over the course of one day, chlorobenzene applied to soil at the concentration of 1 kg/ha at depths of 1 cm and 10 cm disappeared at the rate of 86.5 and 23.4%, respectively. Based on these data, the volatilization half-lives were estimated to be 0.3 and 12.6 days, respectively. Chlorobenzene may adsorb to organic matter in soil and, if retained long enough, may undergo biodegradation. Acclimation of the microorganisms is important in the biodegradation of chlorobenzene. Twenty percent mineralization in a week was reported in one study; the main products of biodegradation are 2- and 4-chlorophenol.

**Bioconcetration** — The bioconcentration factors for chlorobenzene (45.7, rainbow trout; 446.7, fathead minnow) and its octanol/water partition coefficient (692) suggest some potential for bioconcentration. However, little or no bioconcentration for chlorobenzene is predicted.

## VI. Exposure Assessment

As an inert ingredient in pesticide products, chlorobenzene can be applied to growing crops as a solvent or cosolvent, but applications are limited to only before the edible parts of the plant begin to form and livestock are not grazed in treated areas within 48 hours of application. This limitation effectively reduces the number of applications that can occur and significantly reduces the potential for dietary exposures (food and drinking water) from applications to growing crops and for residential exposures (inhalation and dermal) from home garden uses. In addition, livestock cannot graze in

treated areas within 48 hours of application. The volatile nature of chlorobenzene will further reduce the likelihood of dietary exposures. For these same reasons, chlorobenzene concentrations of concern in drinking water are not anticipated from the use of chlorobenzene as an inert ingredient in pesticide products.

## VII. Aggregate Exposure

In examining aggregate exposure, FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in garden, lawns, or buildings (residential and other indoor uses).

For chlorobenzene, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to chlorobenzene when used as an inert ingredient in pesticide formulations.

## VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism or toxicity, EPA has not made a common mechanism of toxicity safety finding as to chlorobenzene and any other substances, and chlorobenzene does not appear to produce toxic metabolites produced by other substances. For the purpose of these tolerance actions, therefore, EPA has not assumed that chlorobenzene has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

## IX. Human Health Risk Characterization

The acute toxicity of chlorobenzene is low *via* the oral, dermal, and inhalation routes of exposure. Chlorobenzene is not considered a dermal irritant. It causes severe discomfort when applied directly to the rabbit eye, but no permanent damage is observed. Dermal toxicity data on repeat exposure were not located on chlorobenzene. No published data were found on the magnitude of dermal absorption of chlorobenzene. Dermal sensitization is not reported. The liver and kidney are target organs in rats, mice, rabbits, and dogs following subchronic and/or chronic exposure *via* oral and/or inhalation

routes of exposure. Chronic oral toxicity studies of rats and mice administered chlorobenzene by gavage for 2 years resulted in a NOAEL of 60 mg/kg/day.

The developmental toxicity data in rats and rabbits indicate no adverse effects to the offspring following inhalation exposure of the maternal animal to dose levels that do not produce severe maternal effects. The reproductive toxicity data on chlorobenzene indicate no adverse reproductive effects following inhalation exposure. Although there was a slight increase in degeneration of germinal epithelium in the testes of $F_0$ and $F_1$ males, these changes are not considered biologically significant in light of the absence of any effects on reproduction and male fertility. Predominantly negative results were found with chlorobenzene in short-term *in vitro* and *in vivo* genetic toxicity testing. The majority of the mutagenicity data do not suggest a significant genotoxic risk from exposure to chlorobenzene, with mostly negative results with chlorobenzene in short-term tests of genetic toxicity [bacterial, yeast, and mammalian cells]. In *in vivo* assays, evidence of clastogenicity is noted at high dose levels. In the two-year bioassays in rats and mice, chlorobenzene induced benign liver tumors [hepatocellular neoplastic nodules] in male rats but was without tumorigenic effects in female rats and male and female mice. The carcinogenicity of chlorobenzene is classified by the Agency as Group D, not classifiable as to human carcinogenicity, based on this limited and equivocal evidence of carcinogenicity in experimental animals and the marginal evidence of genotoxicity.

Based on the physical/chemical properties of chlorobenzene, as well as the application restrictions of pesticide products containing this chemical, dietary (food and drinking water) and residential (inhalation and dermal) exposures of concern are unlikely from chlorobenzene when used as an inert ingredient in pesticide products applied to growing crops only before the edible parts of the plant begin to form.

Taking into consideration all available information, EPA has determined there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to chlorobenzene when used as an inert ingredient in pesticide formulations when considering the dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the one exemption from the requirement of a tolerance established for residues of chlorobenzene be maintained and considered reassessed as safe under section 408(q) of the FFDCA.

## X. Ecotoxicity and Ecological Risk Characterization

Studies in the Agency's Ecotox Database (http://www.epa.gov/ecotox) for Chlorobenzene contained acute fish and invertebrate studies. No terrestrial or aquatic plant studies were available in Ecotox appropriate for guideline studies.
No chronic fish or chronic invertebrate studies were available in Ecotox appropriate for guideline studies. The maximum label rates (lb ai/A) of Chlorobenzene were not provided therefore, quantitative risks estimates can not be determined for aquatic and terrestrial organisms.

### A. Toxicity to Aquatic Organisms

Ecotox studies indicate that Chlorobenzene is moderately toxic to fish and slightly toxic to invertebrates on an acute basis.
LC50's for fish ranged from 2.4 mg/L to 16 mg/L (Ecotox ref#563).
LC50's for invertebrates ranged from 10.7-15.4mg/L (Ecotox ref#12055).

LC50 values for Chlorobenzene in fish exposed for 96 hours are as follows: 7.7-16 mg/L for the fathead minnow (*Pimephales promelas*) (Ecotox ref#4343); 4.5 – 7.4 mg/L for the bluegill (*Lepomis macrochirus*) (Ecotox ref#7398); 4.7-7.4 mg/L rainbow trout (*Oncorhychus mykiss*) (Ecotox ref#15457, 10688) 2.4-3.5 mg/L for the goldfish (*Carassius auratus*) (Ecotox ref#563).
LC50 values for Chlorobenzene in invertebrates exposed for 48 hours are as follows: EC50 of 10.7-15.4 mg/L Daphnid (*Daphnia Magna)* (Ecotox ref#12055).

Threshold limit values for chlorobenzene in fish exposed for 24 to 96 hours are as follows: 29-39 mg/L for the fathead minnow (*Pimephales promelas*); 24 mg/L for the bluegill (*Lepomis macrochirus*); 51-73 mg/L for the goldfish (*Carassius auratus*); and 45 mg/L for the guppy (*Poecilia reticulata*). The 24-hour $LD_{50}$ is 1.8 mL/L for the rainbow trout and the 14-day $LC_{50}$ is 19 mg/L for the guppy. Toxicity threshold values for the cell multiplication inhibition test are as follows: 17 mg/L for bacteria (*Pseudomonas putida*); 120 mg/L for algae (*Microcystis aeruginosa*); and an EC3 >390 mg/L for green algae (*Scenedesmus quadricauda*); and >390 mg/L for protozoa (*Entosiphon sulcatum*). An algal 96-h EC50 of 8.9 mg/L is predicted for chlorobenzene using the neutral organic quantitative structure activity relationship (QSAR). In the absence of daphnid data, a 48-h EC50 daphnid value of 13.6 mg/L is predicted for chlorobenzene using the neutral organic QSAR.

### B. Toxicity to Terrestrial Organisms

Acute Effects Mammals: Mammalian data will be used as a surrogate for other terrestrial phase animals. No information was found in Ecotox on wild mammals, however, the acute toxicity values for laboratory rats [oral $LD_{50}$, 400 to 1600 mg/kg (ACGIH 1991) which classifies Chlorobenzene as moderately toxic to mammals on an acute oral basis.

Chronic Effects Mammals: In a 2-generation rat reproduction study, $F_0$ Sprague-Dawley CD rats [30/sex/group] were administered chlorobenzene *via* inhalation (whole body) at dose levels of 50, 150, or 450 ppm (0, 227.5, 682.5, or 2047.5 $mg/m^3$) for 6 hours/day, 7 days/week for 10 weeks prior to mating. The NOAEL for reproductive toxicity is considered to be 450 ppm (2.0475 mg/L, the highest dose tested) [cited in IRIS; Nair, *et al.* (1987)].

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# ATTACHMENT I
# TOXICITY STUDY SUMMARIES

| study/species/exposure characteristics | NOAEL/LOAEL | Effects observed at LOAEL and above | References |
|---|---|---|---|
| **Subchronic oral toxicity** | | | |
| Fischer 344 rat<br>gavage 13 weeks [5 days/week]<br>0, 60, 125, 250, 500, 750 mg/kg/day | 60 mg/kg/day<br>125 mg/kg/day | Increased liver weight and serum enzymes; at 250 mg/kg/day, increased liver weight; decreased spleen weight; minimal liver histopathology; at 500 and 750 mg/kg/day, increased mortality [7/20 and 17/20] and clinical signs [lethargy and rough coat]; histopathology in liver (degeneration, necrosis), kidney (degeneration, necrosis), bone marrow, increased SGOT, SGPT, GGTP, AP, mild porphyrinuria; diuresis (750); decreased leukocytes (750) | NTP, 1985 |
| B6C3F1 mouse<br>gavage 13 weeks [5 days/week]<br>0, 60, 125, 250, 500, 750 mg/kg/day | 60 mg/kg/day<br>125 mg/kg/day | Males displayed a 27% decrease in body-weight gain; increased liver weight; at 250 mg/kg/day, increased mortality [males 60%; females 40%] and clinical signs [lethargy and rough coat]; decreased body-weight gains [males 74%]; increased urine volume; degeneration and necrosis in liver and kidney; at 500 mg/kg/day, all males and 70% females died; at 750 mg/kg/day, all mice died. | NTP, 1985 |
| Beagle dog<br>Capsule, 5 days/week for 13 weeks<br>0, 27.25, 54.5, or 272.5 mg/kg/day | 54.5 mg/kg/day<br>272.5 mg/kg/day | 4/8 dogs died within 3 weeks, body-weight loss, changes in hematology, clinical chemistry, urine analysis parameters; histopathology in liver (degeneration), kidney, GIT mucosa, hematopoietic tissue NOTE: at 54.5 mg/kg/day, slight bile duct proliferation, cytologic alterations, and leukocyte infiltration of the stroma of the liver were observed. | cited in IRIS, 1993 |
| **Subchronic inhalation toxicity** | | | |
| Rat (strain unknown)<br>0, 0.341 or 1.138 mg/L (0, 75, 251 ppm) for 7 hours/day, 5 days/week for 24 weeks | < 0.341 mg/L<br>0.341 mg/L | Increased reticulocyte count, treatment-related congestion of liver (males), focal hemorrhages, foci of perivascular lymphocytes | Dilley, 1977 |
| rat (unknown strain)<br>0.910 mg/L<br>32 exposures; 7 hours/day over 44 days | 0.910 mg/L | No effects | Irish, 1963, cited in IPCS, 1991 |
| Rabbit<br>0, 0.341 or 1.138 mg/L (0, 75, 251 ppm) for 7 hours/day, 5 days/week for 24 weeks | <0.341 mg/L<br>0.341 mg/L | Liver congestion (males), focal hemorrhage, foci of perivascular lymphocytes; congestion of kidney at 5 weeks | Dilley, 1977 |
| Swiss white mouse<br>1.250 mg/L for 7 hours/day over 3 weeks | LOAEL 1.250 mg/L | Fatty degeneration of the liver, changes in blood counts indicative of bone marrow damage | Cited in IPCS, 1991 |
| Dog 6-month vapor exposure | NOEL 2.06 mg/L | No details | Cited in TSCATS, Monsanto Co., 1989 |

| study/species/exposure characteristics | NOAEL/LOAEL | Effects observed at LOAEL and above | References |
|---|---|---|---|
| **Chronic oral toxicity** | | | |
| Fischer 344 rat (gavage)<br>0, 60, 120 mg/kg/day, 5 days/week for 103 weeks | 60 mg/kg/day<br>120 mg/kg/day | Slight decrease in survival (males); equivocal evidence of mild hepatocellular necrosis (absence of marked toxic lesions) Males at 120 mg/kg/day displayed an increased incidence of benign neoplastic liver nodules [considered as equivocal response]; no increase in tumor incidence in females | Kluwe, *et al.*, 1985; NTP, 1985 |
| B6C3F1 mouse (gavage)<br>0, 60, 120 mg/kg/day, 5 days/week for 103 weeks | 60 mg/kg/day<br>120 mg/kg/day | Neither sex displayed a tumorigenic response | Kluwe, *et al.*, 1985; NTP, 1985 |
| **Developmental toxicity [inhalation]** | | | |
| Fischer 344 rat<br>0, 300, 1000, or 3000 ppm [0, 1.35, 4.51, or 13.5 mg/L] for 6 hours/day on days 6-15 of gestation | range-finding | 100% mortality at 3000 ppm; at 1000 ppm, decreased body weight, body-weight loss, increased liver and kidney weights, enlarged liver; 50% litters totally resorbed; all litters with resorptions; 29% fetuses dead; at 300 ppm, enlarged liver, accentuation of lobular pattern in liver | Dow Chemical, 1981 |
| Fischer 344 rat<br>0, 75, 210, or 590 ppm [0, 0.341, 0.955, or 2.684 mg/L] for 6 hours/day on days 6-15 of gestation | Maternal : NOAEL 0.955 mg/L<br>LOAEL 2.684 mg/L<br><br>Developmental: 2.684 mg/L | Maternal: decreased body-weight gain and food consumption, increased liver weight<br><br>Developmental: no convincing evidence of embryotoxic, fetotoxic, or teratogenic effect | John, *et al.*, 1984 |
| New Zealand rabbit<br>0, 300, 1000, or 3000 ppm for 6 hours/day on days 6-18 of gestation | range-finding | At 3000 ppm, 4 does died during exposure period; negative body-weight gain at 1000 ppm and 3000 ppm; % resorptions increased at 1000 ppm and 3000 ppm; hepatotoxicity at all dose levels | Dow Chemical, 1981 |
| New Zealand rabbit<br>0, 75, 210, or 590 ppm for 6 hours/day on days 6-18 of gestation | Maternal: 0.341 mg/L/2.684 mg/L<br><br>Developmental: 2.684 mg/L [see below] | Maternal: enlarged liver<br><br>Developmental: an increase in % of litters with resorption sites (indicating early embryonic deaths) | John, *et al.*, 1984 |
| New Zealand rabbit<br>0, 10, 30, 75, or 590 ppm for 6 hours/day on days 6-18 of gestation | Maternal: 0.341 mg/L/2.684 mg/L<br><br>Developmental: 2.684 mg/L [HDT] | Maternal: enlarged liver<br><br>Developmental: no structural malformations were noted in offspring; no increase in resorptions was observed | John, *et al.*, 1984 |

| study/species/exposure characteristics | NOAEL/LOAEL | Effects observed at LOAEL and above | References |
|---|---|---|---|
| **Reproductive toxicity [inhalation]** | | | |
| Sprague-Dawley rat<br>0, 50, 150, or 450 ppm [0, 0.228, 0.683, or 2.048 mg/L (whole body)] for 6 hours/day, 7 days/week for 10 weeks prior to mating; through gestation/lactation | Reproductive toxicity: 2.0475 mg/L<br><br>Offspring NOAEL: 0.683 mg/L<br>LOAEL: 2.0475 mg/L<br><br>Systemic toxicity: 0.2275 mg/L/ 0.6825 mg/L | No reproductive toxicity observed<br><br>Offspring: decreased pup survival (F2) at highest dose tested<br><br>Systemic toxicity: increased liver weight, hepatocellular hypertrophy, degenerative and inflammatory lesions in kidneys in males | Nair, *et al.*, 1987 |
| **Genotoxicity Studies [gene mutation]** | | | |
| Salmonella assay with and without rat or hamster S-9 [*S. typhimurium* strains TA1535, 1537, 1538, 98, 100]; doses 3.3 to 333 µg/plate | N/A | Negative | NTP (1985); Haworth, *et al.* (1983); Lawlor, *et al.*, 1979); Monsanto (1976a) |
| **Streptomyces griseus** | N/A | Negative | Bucholz,*et al.* (1992) |
| *Escherichia coli* strains WP2 uvr A+ rec A+ or WP100uve A-recA | N/A | Negative | Monsanto, (1976a); Lawlor, *et al.*, 1979); Simmon , *et al.*, (1979) |
| Reciprocal recombination in *Saccharomyces cerevisiae* | N/A | Positive with metabolic activation in strain D3; negative without metabolic activation in strain D4 | Simmon , *et al.*, (1979); Monsanto, (1976a) |
| Mouse cell lymphoma assay [L5178Y cells] for forward mutations | N/A | Positive in 2 out of 4 trials without S-9 and in 2 trials with S-9, lowest effective concentration 100 µg/mL | McGregor, *et al.*, (1988) |
| Mouse cell lymphoma assay [L5178Y cells] for forward mutations | N/A | negative | Monsanto, (1976b) |
| **Genotoxicity [clastogenic effects]** | | | |
| Sister chromatid exchanges [Chinese hamster ovary cells] | N/A | Positive in 1% DMSO with and without S-9 at 300 to 500 µg/mL | Loveday, *et al.* (1989) |
| Micronucleus tests; mouse *in vivo* [bone marrow cells] | N/A | Positive at 225 to 900 mg/kg i. p. | Mohtashamipur, *et al.* (1987) |
| Micronucleus (i.p.) B6C3F1 mouse | N/A | Negative | Shelby, *et al.* (1993, 1995) |
| Chromosome aberration with & without S-9; Chinese hamster ovary cells | N/A | Negative | Sofuni, *et al.* (1985) |